# Statistical Analysis Plan

## Non-Interventional study (NIS) Collecting Experiences For IPF in Taiwan

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|---|---|
| **PROTOCOL NO.** | **1199-0303** |
| **SAP VERSION** | **V1.0** |
| **SAP DATE** | **Apr-21-2020** |
| **SPONSOR** | **Boehringer Ingelheim** |
| **PREPARED BY** | |

# 1 TITLE PAGE

**Non-Interventional study (NIS) Collecting Experiences For IPF in Taiwan**

| | |
|---|---|
| **PROTOCOL NO.** | 1199-0303 |
| **INVESTIGATIONAL DRUG** | Nintedanib (OFEV®) |
| **INDICATION** | Idiopathic Pulmonary Fibrosis |
| **SPONSOR** | Boehringer Ingelheim |
| **PRINCIPAL INVESTIGATOR(S)** | |

| | |
|---|---|
| **DATE OF FIRST ENROLLMENT** | Aug-31-2017 |
| **DATE OF STUDY COMPLETION (LAST PATIENT LAST VISIT):** | Feb-18-2020 |
| **DATE OF DATABASE LOCK** | Expected on Jun-26-2020 |
| **SAP VERSION/DATE:** | V1.0/ Apr-21-2020 |

This study was performed in compliance with Good Clinical Practices (GCP) including the archiving of essential documents.

# 2 SIGNATURE PAGE

## SIGNATURE PAGE

## SPONSOR'S REPRESENTATIVE

Non-Interventional study (NIS) Collecting Experiences For Idiopathic Pulmonary Fibrosis (IPF) in Taiwan

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| **SAP VERSION/ DATE** | V1.0/ Apr-21-2020 |
| **SPONSOR** | Boehringer Ingelheim Taiwan Ltd. |
| **SPONSOR REPRESENTATIVE** | / Associate Medical Advisor |

Signature Date

# 3 TABLE OF CONTENTS

# 4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| Ab | Antibody |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALAT | Latin American Thoracic Association |
| ATS | American Thoracic Society |
| BMI | Body Mass Index |
| c-ANCA | Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies |
| CAT | COPD Assessment Test |
| CK | Creatine Kinase |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| CVD | Cardio-Vascular Disease |
| DLco | Diffusing capacity of the Lungs for Carbon monoxide |
| DM | Diabetes Mellitus |
| DVP | Data Validation Plan |
| ERS | European Respiratory Society |
| FBC | |
| FGF | Fibroblast Growth Factor |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| Hb | Hemoglobin |
| Hct | Hematocrit |
| HRCT | High-Resolution Computed Tomography |
| IC | Inspiratory Capacity |

| | |
|---|---|
| ICH | International Conference on Harmonization |
| ILD | Interstitial Lung Disease |
| IPF | Idiopathic Pulmonary Fibrosis |
| IRB | Institutional Review Board |
| JRS | Japanese Respiratory Society |
| MDT | Multidisciplinary Team |
| MedDRA | Medical Dictionary for Regulatory Activities |
| p-ANCA | Perinuclear Anti-Neutrophil Cytoplasmic Antibody |
| PDGF | Platelet Derived Growth Factor |
| PI | Principal Investigator |
| PT | Preferred Term |
| RBC | Red Blood Cell |
| SAE | Serious Adverse Event |
| SAS | Statistical Analysis System® |
| SGRQ | St George's Respiratory Questionnaire |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| TLC | Total Lung Capacity |
| UIP | Usual Interstitial Pneumonia |
| VEGF | Vascular Endothelial Growth Factor |
| WBC | White Blood Cell |
| 6MWT | Six-Minutes Walking Test |

# 5 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final protocol 1199-0303 dated 10 April 2017 (version 5.0) and the protocol administrative memorandums that have been approved by Institutional Review Board (IRB). The SAP provides details on the planned statistical methodology for analysis of the study data, and also outlines the statistical programming specifications for the table. It describes the safety variables, anticipated data transformations, manipulations, coding, and other details of the analyses not provided in the study protocol. A detailed description of the planned table and figures to be presented in the clinical study report (CSR). This SAP only covers the planned analysis of all safety and efficacy data collected on paper CRFs.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports".

# 6 STUDY OBJECTIVES AND ENDPOINTS

## 6.1 Study Objectives

### 6.1.1 Primary Objective(s)

The primary objective is to characterize the IPF population in Taiwan with regard to their clinical course under clinical practice conditions in Taiwan.

### 6.1.2 Secondary Objectives

The secondary objectives are to understand the clinical characteristics and quality of life of IPF population in Taiwan.

## 6.2 Endpoints

Key study outcomes are to characterize lung function profile of IPF patients in clinical practice.

### 6.2.1 Primary Endpoint(s)

- Annual percentage of decline from baseline in FVC
- Annual decline from baseline in DLco
- Annual decline from baseline in resting and exercise SpO2
- Annual percentage of decline from baseline in TLC
- Annual percentage of decline from baseline in IC

### 6.2.2 Secondary Endpoints

- Time to first acute exacerbation of IPF after enrolment
- Annual change from baseline in SGRQ
- Annual change from baseline in CAT
- Annual change from baseline in 6MWT
- Mortality (with cause of death) and time to death

### 6.2.3 Safety Endpoints

- Frequency of adverse events and serious adverse events.

# 7 STUDY METHOD

## 7.1 Overall Study Design and Plan

This is a non-interventional, multi-center study to collect data from patients with idiopathic pulmonary fibrosis (IPF) in clinical practice in Taiwan. The study will be carried out at 10 medical centers, the expert centers where IPF patients are mainly managed in Taiwan. A total of 100 IPF patients are planned to be included. Only patients who meet all study criteria will be enrolled.

The study duration consists of a 1-year enrolment period and a 2-year follow-up period. IPF patients will be enrolled in a consecutive manner. The observation period was from study inclusion until death, lung transplantation, end of data collection at 2-years, or loss to follow-up. Data collection will be started at the initial screening assessment based on the medical records, and prospectively thereafter if patients are eligible for inclusion.

The study will not interfere with the management of patients by their physician. Visits will be in accordance with clinical needs judged by physicians. All the data will be collected in line with real-world clinical practice (baseline [study enrolment], the first month, and every 3 months afterward).

### 7.1.1 Schedule of Assessments

The collection of patient data should be managed during routine clinical practice visits, which is approximately every 3 month in Taiwan Information on pre-specified variables of interest will be collected at inclusion (baseline visit) and captured at pre-defined intervals during the follow-up period (e.g. at 3, 6 months (time window: ± 1 month) and then every 6 months (time window: ± 2 month) intervals until finalization of the study).

| Variables \ Week# / Visit | Baseline | Wk 4 | Wk 16 | Wk 28 | Wk 40 | Wk 52 | Wk 64 | Wk 76 | Wk 88 | Wk 100 |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | | | ← 3-month interval → | | | | | | | |
| Allowed window | | ± 14 days | ← ± 1 month → | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Inclusion/exclusion | X | | | | | | | | | |
| Demographics[1] | X | | | | | | | | | |

| Variables \ Week# / Visit | Baseline | Wk 4 | Wk 16 | Wk 28 | Wk 40 | Wk 52 | Wk 64 | Wk 76 | Wk 88 | Wk 100 |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | | | ← 3-month interval → | | | | | | | |
| Allowed window | | ± 14 days | ← ± 1 month → | | | | | | | |
| IPF characteristics (diagnosis)*,[2] | X | | | | | | | | | |
| IPF symptoms[3] | X | X | X | X | X | X | X | X | X | X |
| Smoking status | X | | | | | | | | | |
| Comorbidities | X | | | | | | | | | |
| - STOP-Bang Scoring Model[4] | X& | | | | | | | | | |
| - Berlin Questionnaire-obstructive sleep apnea[4] | X& | | | X | | X | | X | | X |
| - Echocardiography data-PH | X& | | | X | | X | | X | | X |
| Concomitant medications[5] | X | X | X | X | x | x | X | X | X | X |
| Record of anti-fibrotic drugs* | X[6] | X | X | X | X | X | X | X | X | X |
| Lung function*,[7] | X& | X | X | X | X | X | X | X | X | X |
| 6MWT* | X& | | | | | X | | | | X |
| SGRQ* | X& | X | X | X | X | X | X | X | X | X |
| CAT* | X& | X | X | X | X | X | X | X | X | X |
| Acute exacerbation | X | X | X | X | X | X | X | X | X | X |
| Safety reporting[8] | ← | | | | | | | | | → |
| Serological tests*,[9] | X& | | X | | | X | | X | | X |
| Biomarkers*,[10] | X | | | | | X | | | | X |
| Gene test*,[11] | X | | | | | | | | | |

*Data will be collected, if applicable. All examinations and managements will be based on the discretion of the physician and regular practice.

#Data collection time points will follow visit schedule in clinical practice.

&Since this is an observational study, examinations and tests will be performed as judged appropriately by the treating physician according to local medical standards, and the results of interest that closest to the baseline will be registered only if

| Variables \ Week# / Visit | Baseline | Wk 4 | Wk 16 | Wk 28 | Wk 40 | Wk 52 | Wk 64 | Wk 76 | Wk 88 | Wk 100 |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | | | ← 3-month interval → | | | | | | | |
| Allowed window | | ± 14 days | ← ± 1 month → | | | | | | | |

those are available prior to baseline visit.

1. Age, gender, race, education level, environmental/occupation exposures, height, weight, and BMI.
2. HRCT, surgical lung biopsy, multidisciplinary team (MDT) diagnosis, and UIP pattern.
3. Cough, dyspnea, fatigue, weight loss, dizziness, chest pain, anxiety, aching muscles and joints, clubbed fingers, require oxygen therapy (device), or others (according to physicians' judgment and should be specified on the CRF)
4. STOP-Bang Scoring Model data will be collected to assess if patients have obstructive sleep apnea, and Berlin questionnaire results will only be collected from those with suspected/confirmed obstructive sleep apnea according to STOP-Bang Scoring Model.
5. Concomitant medications used for treating comorbidities within 6 months prior to enrolment will be collected.
6. Anti-fibrotic drugs (i.e., nintedanib and pirfenidone) used within 6 months before baseline will be recorded.
7. Spirometry data include FVC, DLCO, $SpO_2$, TLC, IC, etc.
8. OFEV relevant ADR (serious and non-serious), fatal AEs, and pregnancies.
9. Hct, Hb, platelets, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, CRP, CK, rheumatoid factor, antinuclear Ab, anti-Jo1 Ab, Sjogrens SS-A or SS-B Ab, seleroderma-70 Ab, c-ANCA, and p-ANCA, etc..
10. PDGF, VEGF, FGF, etc..
11. MUC5B, etc..

## 7.2 Selection of Population and Inclusion/Exclusion Criteria

### 7.2.1 Inclusion Criteria

1. Newly diagnosed IPF within 6 months based upon recent ATS/ERS/JRS/ALAT IPF guideline (Ref 1, Raghu G, et al. 2011)

- Exclusion of other known causes of ILD (e.g. domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) which needs serological test.
- Assessment of IPF based on HRCT or HRCT and surgical lung biopsy, if available.

2. Patient ≥ 20 years of age
3. Written informed consent prior to participation

4. Patients with further follow-up possible with participating physician during planned study period

5. Ability to read and write in the local language

### 7.2.2 Exclusion Criteria

1. Lung transplantation expected within next 6 months.

2. Inclusion in ongoing clinical trials

## 7.3 Randomization and Blinding

This is a non-interventional and observational study. No randomization and blinding in this study.

## 7.4 Sample Size

Approximately 100 patients are planned to be enrolled based on the recruitment timeframe and patient pool in 10 medical centers, the expert centers where patients are mainly managed in Taiwan. Since most outcomes are continuous, this number should be sufficient in order to get insights into Taiwanese IPF patients.

# 8 GENERAL CONSIDERATIONS

## 8.1 Relevant SOPs and Policies

The data will be managed with data verification, data validation, data clarification, data clean, and data lock processes. The statistical analysis method should follow the statistical analysis plan before implementing the data lock procedure. All processes will follow the SOPs below:

| | |
|---|---|
| DM 1709 | Data Entry Procedure |
| DM 1710 | Data Verification Procedure |
| DM 1711 | Data Validation Procedure |
| DM 1712 | Data Clarification Procedure |
| DM 1713 | Data Lock Procedure |
| DM 1719 | Statistical Analysis Plan Procedure |
| DM 1720 | Statistical Analysis Report Procedure |

## 8.2 Timing of Analyses

The final analysis will take place when all enrolled patients complete the study or permanently discontinued from the study. After the relevant data management processes are completed and data clean status is claimed, the database will be locked. The final analysis will be conducted based on the lock data.

## 8.3 Analysis Populations

The main analysis population will consist of all eligible patients (i.e. all patients who have signed the informed consent and fulfilled all inclusion criteria and no exclusion criteria)

## 8.4 Covariates and Subgroups

Subgroup analysis will be conducted based on the prescription of nintedanib and pirfenidone. All enrolled subjects will be grouped as “no anti-fibrotic drugs” and “with anti-fibrotic drugs”. Subject had no record of anti-fibrotic drugs during the observation will be categorized as “no anti-fibrotic drug”. In contrast, the subjects with at least one record of anti-fibrotic drugs will be categorized as “with anti-fibrotic drugs”.

## 8.5 Missing Data

For the subjects who have missing value of lung function at the visit, the missing value will be imputed by the mean value calculated based on the subjects with valid observations at the visits, assuming a similar rate of FVC decline with the other subjects. The lung function at baseline will not be imputed. The missing value will be imputed from the first follow-up visit to the last follow-up visit of the subjects.

## 8.6 Interim Analyses and Data Monitoring

There is no planned interim analysis in protocol.

## 8.7 Adjustments for Multiplicity

The study was not aimed to show significant difference between treatment groups and no hypothesis testing will be performed. Hence there is no need to adjust for multiplicity.

## 8.8 Multi-center Studies

Approximately 100 patients will be enrolled from 10 medical centers in Taiwan. With the intention of pooling the data for analysis, all the investigators from participating institutions will follow the study protocol and conduct the clinical trial to improve the consistency across centers. All the data defined on CRF will be collected and managed via a centralized process. A data validation plan will be developed to define the validation rules to check the data. All data from the 10 sites will be examined based on the data validation plan. If any discrepancy or illogic data is found, data query will be sent for clarification. All collected clinical data will be summarized with respect to demographic characteristics, efficacy and safety observations.

## 8.9 Data Management System and Analysis Software

The data collected will be entered into the study database against the paper CRF. Database backup is exhibited by data management personnel. The data will be exported to the Statistical Analysis System® (SAS) for Windows (Version 9.4 or higher, SAS Institute, Cary, North Carolina, USA) to generate the subject listings, tabulations, and statistical analyses.

## 8.10 Coding Dictionary

The system of variable coding will follow rules of SOPs. During the study, Data manager will follow the SOP to enter and manage the CRFs. In order to create a

standard language that is comparable across all therapeutic teams and provide standardization for statistical analysis, adverse events recorded on the paper CRF will be coded by medical dictionaries/thesaurus. In this study, the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher will be used to map adverse events verbatim to Preferred Terms (PT) and System Organ Class (SOC)

## 8.11 Data Handling and Transfer

All collected clinical data will be collected via paper CRF by study coordinator, and will be managed centralized and stored in the clinical data management systems. No external data will be imported to the system. The system of variable coding will follow rules of SOPs. During the study, Data manager will follow the SOP to enter and manage the CRFs. After data clean and data lock process, all the clinical data will be exported as SAS datasets and stored in a read-only space. Statistician will perform the statistical analysis based on the SAS datasets.

## 8.12 Programming Specifications

The summary statistics for continuous variables will be entitled as Number, Mean±SD, Median, Range and 95% C.I. in the table, which represent the number of observations, mean value plus/minus standard deviation, median value of observations, minimum and maximum, lower bound and upper bound of the 95% confidence interval. Range (minimum and maximum) and 95% confidence interval (lower and upper bound) are given in parentheses.

Unless otherwise noted, the summary statistics for continuous variables will be printed out to one decimal place except for the standard deviation and confidence interval. The standard deviation and confidence interval will be expressed to 2 decimal places. If the summary statistics cannot be obtained, it will be printed as "--"

For categorical variables, number and percentage will be presented as summary statistics. All table percentages will be reported with one decimal point unless otherwise specified.

The p-value will be reported to 3 decimal places. An asterisk indicates the statistical significance. P-value less than 0.001 will be reported as "<0.001*" and p-value greater than 0.999 will be expressed as ">0.999". If the p-value cannot be computed, p-value will be printed as '--'.

# 9 SUMMARY OF STUDY DATA

All the statistical analysis will be performed and categorized by the subgroup of with anti-fibrotic drug and no anti-fibrotic drug. The summary tables will be tabulated with columns of the two subgroups. The relevant population size will be annotated in the tables.

Continuous variables will be summarized by descriptive statistics: number of observations, mean, median, standard deviation, range, and 95% confidence interval. Frequency counts and percentages of observed levels will be reported for categorical variables. The denominator of percentages will be the number of subjects with valid assessment results. Subjects with missing data will not be included in the number of denominator.

## 9.1 Disposition of Subjects

The number of eligible subjects and number of subject reached study completion will be counted and summarized. The denominator of percentage of number of eligible subjects will be the number of subject screened. The denominator of percentage of number of subject complete the study will be the number of eligible subjects. The summary of reason for early termination will be provided as well. The denominator of the reason will be the number of subjects not complete the study.

## 9.2 Protocol Violations and Deviations

This is an observational study. Investigator could follow their practice and judgment. No protocol violation and deviation will be defined.

## 9.3 Demographic and Baseline Characteristics

The following demographics and baseline characteristics will be collected at visit 1: age, gender, race, education level, environmental/ occupation exposures, smoking status, height, weight, IPF characteristics, and comorbidity. Age will be calculated as (date of informed consent – date of birth)/365.25. Age, weight, and height will be summarized as continuous. While the other demographics will be presented as categorical.

IPF characteristics including the duration of IPF from initial diagnosis to the date of informed consent, HRCT pattern, UIP pattern, surgical lung biopsy, and multidisciplinary term diagnosis. duration of IPF will be summarized as continuous and the other IPF characteristics will be summarized as category.

## 9.4 Current Concomitant Medications

Concomitant medications will be collected at visit 1. The concomitant medications will be grouped per the indications into DM, Hypertension, Hyperlipidemia, CVD/cerebral artery occlusion, Respiratory, and other medication. The number of medication and number of subjects with the medication will be presented by the group of medication.

# 10 DEFINITION AND DETERMINATION OF ANALYSIS VARIABLES

## 10.1 Treatment Exposure and Compliance

Treatment exposure will be counted as total days of using anti-fibrotic drugs during the study. The summary of treatment exposure will be presented by the treatment of nintedaninb and pirfenidone. If the subjects ongoing use anti-fibrotic drug in the end of study, the duration will be counted to the last known date subject took anti-fibrotic drug.

Due to this study is an observational study. Investigator will give prescription per the judgement of medical practice. Hence, treatment compliance is not applicable and will not be computed.

## 10.2 Primary Endpoint(s)

- Annual percentage of decline from baseline in FVC

  Values of FVC (% pred.) will be used for this endpoint. The FVC(% pred.) collected at visit 1 will be served as baseline.

- Annual decline from baseline in DLco

  Values of DLco (% pred.) will be used for this endpoint. The DLco (% pred.) collected at visit 1 will be served as baseline.

- Annual decline from baseline in resting and exercise $SpO_2$

  Values of $SpO_2$ (%) will be used for this endpoint. The $SpO_2$ (%) collected at visit 1 will be served as baseline.

- Annual percentage of decline from baseline in TLC

  Values of TLC (% pred.) will be used for this endpoint. The TLC (% pred.) collected at visit 1 will be served as baseline.

- Annual percentage of decline from baseline in IC

  Values of IC (% pred.) will be used for this endpoint. The IC (% pred.) collected at visit 1 will be served as baseline.

Annual percentage of decline and annual decline from baseline will be calculated as

$$\text{Annual decline} = \frac{\text{Value}_{\text{follow-up}} - \text{Value}_{\text{baseline}}}{\text{Days of follow - up}} \times 365.25$$

In addition to the annual decline, the mean value and mean change from baseline will also be presented for the lung functions. Descriptive statistics including Number, Mean±SD, Median, Range and 95% C.I. of mean value and mean change from baseline at each visit will be calculated and listed.

## 10.3 Secondary Endpoints

- Time to first acute exacerbation of IPF after enrolment

  Time to first acute exacerbation starts from the date of informed consent to the date of first acute exacerbation recorded on the CRF. Subject with exacerbation free at the time of the last contact will be censored. The time of censored is from the date of consent to the last valid date of last known date subject took anti-fibrotic drugs, date of last contact, and last visit date.

- Annual change from baseline in SGRQ

  Descriptive statistics including Number, Mean±SD, Median, Range and 95% C.I. will be presented. Annual change from baseline in SGRQ will be calculated as

  $$\text{Annual change from baseline} = \frac{\text{SGRQ}_{\text{follow-up}} - \text{SGRQ}_{\text{baseline}}}{\text{Days of follow - up}} \times 365.25$$

  In addition to the annual change from baseline, the mean value and mean change from baseline will also be calculated.

- Annual change from baseline in CAT

  Descriptive statistics including Number, Mean±SD, Median, Range and 95% C.I. will be presented. Annual change from baseline in CAT will be calculated as

  $$\text{Annual change from baseline} = \frac{\text{CAT}_{\text{follow-up}} - \text{CAT}_{\text{baseline}}}{\text{Days of follow - up}} \times 365.25$$

  In addition to the annual change from baseline, the mean value and mean change from baseline will also be calculated.

- Annual change from baseline in 6MWT

  Descriptive statistics including Number, Mean±SD, Median, Range and 95% C.I. will be presented. Annual change from baseline in 6MWT will be calculated as

$$\text{Annual change from baseline} = \frac{6\text{MWT}_{\text{follow-up}} - 6\text{MWT}_{\text{baseline}}}{\text{Days of follow - up}} \times 365.25$$

In addition to the annual change from baseline, the mean value and mean change from baseline will also be calculated.

- Mortality (with cause of death) and time to death

  Time to death is calculated from the date of consent to the date of death from any cause. Subjects with no documented death will be censored. The time of censored is from the date of consent to the last valid date of last known date subject took anti-fibrotic drugs, date of last contact, and last visit date.

## 10.4 Safety Endpoints

- Frequency of adverse events and serious adverse events.

  All adverse events will be summarized with the coding term, severity, and relationship to nintedanib by frequency tables with the counts and percentage.

# 11 STATISTICAL METHODS

## 11.1 Primary Hypothesis

The hypothesis for the analysis of the primary outcome is

$$H_0 : \text{Annual Decline} = 0 \text{ vs. } H_a : \text{Annual Decline} \neq 0$$

## 11.2 Test of Assumptions

The primary outcomes will be tested by paired t-test. The assumption of normality will be tested by Shapiro-Wilk test. Wilcoxon sign rank test will be used if the assumption of normally distributed is violated.

## 11.3 Primary Endpoint Analysis

Annual declines will be summarized with descriptive statistics including Number, Mean±SD, Median, Range and 95% C.I. Annual decline will be tested by paired t-test to show if significant change. The Wilcoxon sign rank test will be used if the normally distributed assumption is violated. The test is two sided and the significant level is set as 0.05. The sas procedure used for the tests is listed as follow.

| Statistical Test | SAS procedures and option |
|---|---|
| Shapiro-Wilk test | PROC UNIVARIATE NORMALTEST |
| T-test | PROC UNIVARIATE MU0=0 ALPHA=0.05 |
| Wilcoxon sign rank test | PROC UNIVARIATE MU0=0 ALPHA=0.025 |

## 11.4 Secondary Endpoint Analyses

Time to first acute exacerbation of IPF, and time to death will be analyzed by Kaplan-Meier survival method. The graph of KM curve will be reported and summary statistics including survival estimate (25%, 50%, 75%) and 95% CI for the estimate will be tabulated.

The same analysis procedure of primary endpoints will be applied to the secondary outcomes of annual change, from baseline in SGRQ, CAT and 6MWT. The shapiro-wilk test will be performed to test the normality. Paired t-test will be used if normally distributed. Otherwise, Wilcoxon sign rank test will be adopted to conduct

the test. The sas procedure used for the tests is listed as follow.

| Statistical Test | SAS procedures and option |
|---|---|
| Shapiro-Wilk test | PROC UNIVARIATE NORMALTEST |
| T-test | PROC UNIVARIATE MU0=0 ALPHA=0.05 |
| Wilcoxon sign rank test | PROC UNIVARIATE MU0=0 ALPHA=0.05 |

## 11.5 Safety Analyses

- Frequency of adverse events and serious adverse events.
  - AEs and SAEs will be summarized as number of AEs, number of subjects with AEs and percentage of subjects with AEs. The summary will be further categorized by the seriousness, severity, causality, and outcome.
  - AE will be coded using the MedDRA dictionary. All adverse events will be classified using MedDRA terminology. The number of subjects and percentage of subjects will be computed by System Organ Class and Preferred Term to show the incidence of AE. The incidence of AE will be categorized by the severity. The incidence of AE by the severity will be presented as a separate table. Number of events and number of subject with events will be included in the summary table.
  - The incidence of AEs suspected related to nintedanib will be computed per the MedDRA terms. Number of suspected events and the number of subjects with suspected event with the corresponding percentage will be listed. The incidence of AEs suspected related to nintedanib will also be categorized by the severity.

## 11.6 Interpretation and Conclusion

The change from baseline endpoints will be assessed by two-sided paired T-test or Wilcoxon signed rank test under significance level 0.05. Once the p-value is lower than the significance level, the significant change could be claimed.

# 12 SUMMARY OF CHANGES TO THE PROTOCOL

The initial statistical analysis plan will follow the protocol design and no changes or differences will be planned in the initial statistical analysis plan.

# 13 APPENDIX

## 13.1 Mock-up Tables

Refer to the mock-up tables.