STATISTICAL ANALYSIS PLAN

Study Title

A regulatory required non-interventional study to monitor the safety and effectiveness of Ofev (Nintedanib 150mg/100mg BID) in Korean patients

Protocol No./Version

1199-0417/3.1

Sponsor

[redacted]

Version No.

1.0

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STATISTICAL ANALYSIS PLAN

SIGNATURE PAGE

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VERSION INFORMATION (DOCUMENT REVISION HISTORY)

Version	Date	Prepared by	Details
1.0	04-MAY-2022	[redacted]	First Version

[redacted]

STATISTICAL ANALYSIS PLAN

ABBREVIATION

Term	Definition
ADR	Adverse drug reaction
AE	Adverse events
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
DB	Database
FVC	Forced vital capacity
HRCT	High resolution computed tomography
IPF	Idiopathic pulmonary fibrosis
MFDS	Ministry of food and drug safety
PF-ILD	Progressive fibrosing interstitial lung disease
PT	Preferred term
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Supporting document
SOC	System organ class
SOP	Standard operating procedure
SS	Safety set
SSc-ILD	Systemic sclerosis associated interstitial lung disease
UADR	Unexpected adverse drug reaction
UAE	Unexpected adverse events
ULN	Upper limits of normal
VIF	Variance Inflation factor
WHO ATC index	World health organization anatomical therapeutic chemical index

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1. STUDY OVERVIEW

1.1 STUDY OBJECTIVES

1.1.1 Primary objective

The primary objective is to monitor the safety profile of Ofev in Korean patients in a routine clinical setting.

1.1.2 Secondary objective

The secondary objective is to monitor the effectiveness of Ofev by evaluating the change from baseline after 12 and/or 24 weeks in the FVC (mL), % predicted FVC and overall evaluation of Korean patients.

1.2 STUDY SIZE

Sample size of 3,000 patients initiating Ofev, based on the requirement of the local regulatory authority (Ministry of Food and Drug Safety, MFDS). Since IPF, SSc-ILD and PF-ILD are chronic diseases it might be restrictive to collect safety and effectiveness data in short-term (12weeks) period, all patients will be enrolled for long-term (24weeks) surveillance for maintaining approved indication. Thus, all patients will be enrolled for long-term(24weeks) surveillance, basically.

Considering total surveillance size of 3,000 cases, at least 20% (600 cases) of total would be enrolled for long-term(24weeks) surveillance, even considering follow up loss in real world clinical practice.

1.3 MILESTONES

MFDS sets Ofev re-examination period from 21 Oct 2016 to 20 Oct 2022. Interim report planned biannually for the initial two years and annually thereafter by Jan 2023.

Table 1 Milestones

Milestone	Planned Date
Start of data collection	21 Oct 2016 (HA's approval date)
End of data collection	20 Oct 2022
Interim report 1-1	20 June 2017
Interim report 1-2	20 Dec 2017

Milestone	Planned Date
Interim report 2-1	20 June 2018
Interim report 2-2	20 Dec 2018
Third-year report	20 Dec 2019
Fourth-year report	20 Dec 2020
Fifth-year report	20 Dec 2021
Final report of study results:	20 Jan 2023

2. STUDY POPULATION

A total of 3,000 patients will be enrolled at approximately 60 sites by as many as 60 or more NIS physicians. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals which has own IRB for study. The treating physicians will mainly be internists. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

2.1 MAIN DIAGOSIS FOR STUDY ENTRY

- Patients diagnosed with idiopathic pulmonary fibrosis
- (or) Patients diagnosed with systemic sclerosis associated interstitial lung disease
- (or) patients diagnosed with chronic fibrosing ILD with a progressive phenotype

2.2 INCLUSION CRITERIA

- Patients who have been started on Ofev in accordance with the approved label in Korea
- Patients who have signed on the data release consent form

2.3 EXCLUSION CRITERIA

- Patients for whom Ofev is contraindicated according to local label of Ofev
  - i. Patients with known hypersensitivity to Ofev, peanut or soya, or to any of the excipients
  - ii. Women who are pregnant or nursing
  - iii. Patients with moderate (Child pugh B) and severe (Child Pugh c) hepatic impairment

3. COMPOSITION OF SUBJECTS

3.1 SUBJECTS WHOSE CRF WAS RETRIEVED

The Subjects whose CRF was retrieved will include those whose CRF was retrieved in the relevant year.

3.2 SAFETY SET

The safety set will include all subjects who signed the data release consent form to participate in this study, took Ofev once at least, and were followed up by the physician once or more. The situations excluded from the safety set are as follows.

- Cases administered prior to the conclusion of an investigation contract
- Cases administered prior to signing the consent form
- Failure of follow-up
- Violation of efficacy·effectiveness, Dosage
- Didn't take at any one time with Ofev
- Dual registration
- Violation of Inclusion/Exclusion criteria

3.3 EFFECTIVENESS SET

The effectiveness set will include safety set who were evaluated for the effectiveness including overall effectiveness evaluation. The situations excluded from the effectiveness set are as follows

- Exclusion from safety evaluation
- Omission of effectiveness evaluation
- Overall effectiveness assessed as 'unassessable'

3.4 LONG-TERM SAFETY SET

The long-term safety set will include safety set who took Ofev for more than 24 weeks and were followed up by the physician 24 weeks after the date of first Ofev administration.

3.5 LONG-TERM EFFECTIVENESS SET

The long-term effectiveness set will include long-term safety set and effectiveness set who were evaluated for the effectiveness including overall effectiveness evaluation 24 weeks after the date of first Ofev administration.

3.6 DROPOUT

Dropout include those who signed the data release consent from to participate in this study as subject but did not meet any of the inclusion criteria, do not have any prescription record of Ofev, have prescription record but have not been followed up by the physician following prescription, and started administration prior to the signed date.

3.7 SUBJECTS OF SPECIAL INVESTIGATION

The subjects of special investigation will include Pediatric population(<18y old), Geriatric population(≥65y old), Pregnant women, Lactating women, Hepatic impairment, Renal impairment.

4. GENERAL ANALYSIS CONSIDERATIONS

4.1 STATISTICAL ANALYSIS SOFTWARE

Statistical analyses will be performed using SAS® Version 9.4 64bit (SAS Institute, Cary, NC, USA) or higher.

4.2 GENERAL CONSIDERATIONS

Continuous variables will be summarized with number of subjects, means, standard deviation (SD), median, minimum, and maximum, IQR. Categorical variables will be summarized with frequency and percentage. Unless otherwise specified, statistical tests will be performed at two-sided significance level of 5% for baseline characteristics.

P-values will be presented up to four decimal places (rounded from the 5th decimal place). The values that contain decimals such as, means, standard deviation (SD), percentages will be presented up to two decimal places (rounded up from the 3rd decimal place).

5. DATA HANDLING CONVENTIONS

5.1 HANDING OF MISSING DATA

All endpoints will be analyzed for OC (observed case) method. In other words, missing data is not replaced.

5.2 HANDLING OF MISSING DATES

If there are missing dates and are used in calculations, they will be imputed as the following:

Table 2 Handling of Missing Dates

Types of Dates	Missing	Imputation	Examples
1. Date of the diagnosis (IPF or SSc-ILD or PF-ILD) 2. Prior/ Concomitant medication start date	MM-DD	01-01	Collected date: 2021-UK-UK Imputed date: 2021-01-01
	DD	01	Collected date: 2021-12-UK Imputed date: 2021-12-01
Prior/ Concomitant medication end date	MM-DD	12-31	Collected date: 2021-UK-UK Imputed date: 2021-12-31
	DD	Last day of the month [day]	Collected date: 2021-12-UK Imputed date: 2021-12-31
AE onset date	DD	Step 1. For each missing/incomplete AE onset date, an interval [INT_START, INT_END] is defined. • INT_START: Min (AE end date, 01 of the reported month) • INT_END: Min (AE end date, Last date of the reported month) Step 2. 1. Date of first Ofev administration is within the interval [INT_START, INT_END]: date of first Ofev administration 2. Date of first Ofev administration is before INT_START: INT_START 3. Date of first Ofev administration is after INT_END or missing: INT_END	Step 1. AE end date: 2020-12-05 Collected date: 2020-11-UK interval: [2020-11-01, 2020-11-30] Step 2. 1. Date of first Ofev administration: 2020-11-23 Imputed date: 2020-11-23 2. Date of first Ofev administration: 2020-10-30 Imputed date: 2020-11-01 3. Date of first Ofev administration:

Types of Dates	Missing	Imputation	Examples
			2020-12-15 Imputed date: 2020-11-30
AE end date	YYYY-MM-DD	Date of safety assessment	Date of safety assessment: 2020-12-30 Collected date: UK-UK-UK Imputed date: 2020-12-30
	MM-DD	12-31	Collected date: 2021-UK-UK Imputed date: 2021-12-31
	DD	Last day of the month [day]	Collected date: 2021-05-UK Imputed date: 2021-05-31

5.3 HANDLING OF DERIVED VARIABLES

Derived Variables will be imputed as the following.

Table 3 Derived Variables

Variable	Derivation Method
Change from baseline	Post-baseline value – Baseline value
rate of change (%)	$\frac{\text{Post} - \text{baseline value} - \text{Baseline value}}{\text{Baseline value}} \times 100$
Age group	age ≥ 18y old and age < 30y old age ≥ 30y old and age < 40y old age ≥ 40y old and age < 50y old age ≥ 50y old and age < 60y old age ≥ 60y old
Duration of disease (years)	(Date of data release consent – Date of first diagnosis)/365.25
Pediatric population	<18y old, ≥18y old
Geriatric population	<65 old, ≥65 old
Duration of AE (Days)	AE end date* – AE onset date +1 *if the end date is ongoing, then the end date will be replaced with Date of safety assessment duration will be displayed including the '≥' symbol (e.g. ≥15). If the Date of safety assessment is missing, then the end date will be replaced with Date of last visit.
Onset duration of AE	AE onset date – Date of first Ofev administration

5.4 HOW TO HANDLE DATA ERRORS AFTER DB LOCK

If an 'Error List After DB Lock' (SD 0314 D) document according to 'SOP 0314' Database Lock is created after DB lock, the related content is not reflected in the analysis and written in the comments.

6. SUBJECT INFORMATION

6.1 STUDY PERIOD AND NUMBER OF SUBJECTS

The study year and study period will be presented. The number of subjects whose CRF was retrieved, safety set, effectiveness set, long-term safety set, long-term effectiveness set by year of the study will be presented.

6.2 POST-MARKET SURVEILLANCE TABLES

The study sites and study Principal Investigator will be presented. The number of subjects whose CRF was retrieved, safety set, effectiveness set, long-term safety set, long-term effectiveness set by year of the study will be presented.

6.3 SUBJECT CHARACTERISTICS

Subject characteristics will be performed on safety set.

6.3.1 Demographics

For the following variables, the continuous variables will be summarized using number of subjects, mean, SD,
median, minimum, and maximum, IQR, and the categorical variables will be summarized using number of subjects and percentages.

- Continuous variables: Age (years), Height (cm), Weight (kg), Occupation or exposure period
- Categorical variables: Age group, Gender, Smoking status, Alcohol consumption, Occupation or exposure status

6.3.2 Disease information

For the following variables, the continuous variables will be summarized using number of subjects, mean, SD,
median, minimum, and maximum, IQR, and the categorical variables will be summarized using number of subjects and percentages.

- Continuous variables: Duration of disease (years)
- Categorical variables: Diagnosed disease, Allergy, Child Pugh Score Class, Family history of pulmonary fibrosis/SSc-ILD, Chest HRCT evaluation, Result of lung biopsy, Medical History, Comorbidities, Prior medication, Concomitant medication

6.3.3 Subjects of special investigation

The following variables will be summarized using number of subjects and percentages.

- Pediatric population (<18y old, ≥18y old)
- Geriatric population (<65 old, ≥65 old)
- Pregnant women (Yes, No)
- Lactating women (Yes, No)
- Hepatic impairment (Yes, No)
- Renal impairment (Yes, No)

6.3.4 Medical history and comorbidities

Previous medical history is defined as those that are checked "1" for the question "Ongoing" under [Medical History] page of the CRF, and comorbidities are defined as those that are blanked for the same question.

Medical history and comorbidities will be summarized with number of subjects, percentages and cases. Medical history and comorbidities will be coded with Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 and will be summarized with system organ class (SOC) and preferred term (PT) using number of subjects, percentages and cases.

6.3.5 Prior and concomitant medications

Prior medication is defined as any medication that the subjects took before the first dose of Ofev.

Concomitant medication is defined as any medication that the subjects took on or after the first dose of Ofev. Specifically, medications will be classified as the following:

Prior medication is any medication that can be classified into any of the following categories:

- Medication start date $<$ Date of first Ofev administration OR
- Medication end date $\leq$ Date of first Ofev administration

Concomitant medication is any medication that can be classified into any of the following categories:

- Medication start date ≥ Date of first Ofev administration OR
- Medication end date ≥ Date of first Ofev administration OR
- Ongoing

Table 4 Examples of Categorization

Medication start date	Medication end date	Date of first Ofev administration	Prior medication	Concomitant medication
2020-01-01	2020-01-14	2020-01-15	Y	
2020-01-01	2020-01-15	2020-01-15	Y	Y
2020-01-01	2020-01-20	2020-01-15	Y	Y
2020-01-01	Ongoing	2020-01-15	Y	Y
2020-01-15	2020-01-15	2020-01-15		Y
2020-01-15	2020-01-20	2020-01-15		Y
2020-01-15	Ongoing	2020-01-15		Y
2020-01-20	2020-01-25	2020-01-15		Y
2020-01-20	Ongoing	2020-01-15		Y

In the case of [Date of first Ofev administration = medication start date = medication end date], it is included only as the concomitant medication. If it is clearly possible to classify as Prior medication*, it is classified only as Prior medication.

* (In clinical trials comparing laparoscopic procedures, preoperative medication) lidocaine

If there is a missing date, Prior/concomitant medication is classified according to [5.2 Handling of Missing Dates].

Prior and concomitant medications will be summarized with number of subjects, percentages and cases. Prior and concomitant medications will be coded using the World Health Organization Anatomical Therapeutic Chemical index (WHO ATC index) version 2022 and will be summarized with Level1(anatomical main group) and Level 5 (chemical substance) using number of subjects, percentages and cases. However, if level 5 (chemical substance) doesn't exist or 'Combinations', 'Various' then level 4 (chemical subgroup) will be used instead. (If level 5 doesn't exist then a higher level will be used.)

6.4 OFEV ADMINISTRATION STATUS

Total duration of administration (day), Total administered dose (mg), and Average daily dose (mg) will be summarized using number of subjects, mean, SD, median, minimum, and maximum.

If the date of last administration is missing or Ofev administration status is "continuing", then the date of last administration will be replaced with date of overall effectiveness evaluation. If the date of overall effectiveness evaluation is missing, then the date of last administration will be replaced with date of last efficacy assessment of efficacy endpoints.

Each variable is defined as follows.

- Total duration of administration (day): Date of last administration – Date of first administration + 1
- Total number of days administered (day): Sum of number of days administered by timepoint (Date of last administration by timepoint - Date of first administration by timepoint + 1)
- Total administered dose (mg): Sum of administered dose by timepoint (Single dose × Frequency per Day × number of days administered by timepoint)
- Average daily dose (mg): Total administered dose (mg) / Total number of days administered (day)

7. SAFETY ANALYSES

Safety analyses will be performed on Safety set.

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR) refers to any harmful, unintended reaction to the medicinal product of any dose at which a causal relationship with the medicinal product cannot be ruled out. In the case of voluntarily reported AEs, if the causal relationship with the medicinal

product of any dose is not known, it is regarded as ADR. However, if both the reporter and the manufacturer/sponsor determine that it is not related to the medicinal product of any dose, it is excluded from ADR.

The following relationship categories will be considered as ADR:

- certain
- probable/likely
- possible
- conditional/unclassified
- unassessable/unclassifiable

Serious adverse event (SAE) is AE occurring at random doses of Ofev from this study that results in one of the following outcomes:

- Results in death
- Immediately life-threatening
- Persistent or significant disability/incapacity
- Requires patient hospitalization, Prolongs patient hospitalization
- Congenital anomaly/birth defect
- Other comparable medical criteria

Unexpected adverse event (UAE) is AE not listed in the permit.

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.

The following are considered as AESIs:

- Hepatic injury defined by the following alterations of liver parameters:
  1) AST or ALT ≥ 3 fold ULN AND total bilirubin ≥ 2 fold ULN measured in the same blood draw sample
  2) AST or ALT ≥ 8 fold ULN
- Adverse events relating to gastrointestinal perforation.

Adverse events leading to discontinuation refer to a case where the action taken with trial drug due to AE is discontinued or discontinuation and reintroduction.

7.1 SUMMARY OF ADVERSE EVENTS

The following types of AEs will be summarized with number and cases of AEs, incidence rate and exact 95% confidence intervals.

- Adverse event (AE)
- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)
- Unexpected adverse drug reaction (UADR)
- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Adverse events leading to discontinuation and reintroduction

7.2 ANALYSES OF ADVERSE EVENTS

The following types of AEs will be coded with MedDRA version 25.0 and will be summarized with SOC and PT using number and cases of AEs, incidence rate. The details of SAEs will also be presented in a listing.

- AE/ADR
- SAE/SADR
- UAE/UADR
- AESI
- AE leading to discontinuation
- AE classified by Intensity
- AE classified by Outcome of the event
- AE classified by Causal Relationship
- AE classified by Action taken with Ofev
- AE classified by Therapy for the event
-

The following AEs of rare (less than 0.1%) or Occasional (less than 0.1%~5%) occurrent will be coded with MedDRA version 25.0 and will be summarized with SOC and PT using number

and cases of AEs, incidence rate.

- SAE/SADR
- UAE/UADR

7.3 SAFETY ANALYSES BY FACTORS

7.3.1 Univariate analysis

The following categorical variables will be summarized using number of subjects, number and cases of AEs, incidence rate and 95% confidence interval. AE Occurrence will be analyzed using Pearson's chi-square test or Fisher's exact test to determine if statistically significant differences exist. (However, if [Family history of pulmonary fibrosis/SSc-ILD], [Alcohol consumption], [Occupation or exposure status], [Chest HRCT evaluation] and [Result of lung biopsy] responds with [Unknown], it is excluded from Pearson's chi-square test or Fisher's exact test.)

- Diagnosed disease (IPF, SSc-ILD, PF-ILD)
- Gender (Male, Female)
- Allergy (Yes, No)
- Child Pugh Score Class (Class A, Class B, Class C, Not Applicable)
- Family history of pulmonary fibrosis/SSc-ILD (Yes, no, Unknown)
- Smoking status (Never smoked, EX-smoker, Current smoker)
- Alcohol consumption (Never, Former, Current, Unknown)
- Occupation or exposure status (Yes, no, Unknown)
- Chest HRCT evaluation (UIP pattern, probable UIP pattern, inconsistent UIP pattern, emphysema, Normal, Unknown)
- Result of lung biopsy (UIP pattern, probable UIP pattern, possible UIP pattern, inconsistent with UIP, Normal, Unknown)
- Medical History (Yes, No)
- Comorbidities (Yes, No)
- Prior medication (Yes, No)
- Concomitant medication (Yes, No)

The following continuous variables will be summarized using number of subjects. AE Occurrence will be summarized using odds ratio and 95% confidence interval by using simple logistic regression.

- Age (years)
- Height (cm)
- Weight (kg)
- Occupation or exposure period
- Duration of disease (years)
- Average daily dose (mg)

Subjects of special investigation will be summarized using number of subjects, number and cases of AEs, incidence rate and 95% confidence interval. AE Occurrence will be analyzed by using Pearson's chi-squire test or Fisher's exact test to confirm statistically significant differences.

- Pediatric population (<18y old, ≥18y old)
- Geriatric population (<65 old, ≥65 old)
- Pregnant women (Yes, No)
- Lactating women (Yes, No)
- Hepatic impairment (Yes, No)
- Renal impairment (Yes, No)

7.3.2 Multivariable analysis

As a result of simple logistic regression, statistically significant variables will be summarized using odds ratio and 95% confidence interval by using multiple logistic regression. (However, Variables with the Variance Inflating Factor (VIF) exceeding 10 can be excluded from the model.) The complete case analysis will be used to handle missing values of variables in the multivariate logistic regression model.

7.4 SUMMARY OF ADVERSE EVENTS FOR SUBJECTS OF SPECIAL INVESTIGATION

The following types of AEs for each subject of special investigation will be summarized with number and cases of AEs, incidence rate and exact 95% confidence intervals. The details of AEs for each subject of special investigation will also be presented in a listing.

- Adverse event (AE)

- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)
- Unexpected adverse drug reaction (UADR)
- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Adverse events leading to discontinuation and reintroduction

7.5 SUMMARY OF ADVERSE EVENTS FOR SUBJECTS WHO ARE NOT ELIGIBLE

The following types of AEs for each subject who are not eligible will be summarized with number and cases of AEs, incidence rate and exact 95% confidence intervals. The details of AEs for each subject who are not eligible will also be presented in a listing.

- Adverse event (AE)
- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)
- Unexpected adverse drug reaction (UADR)
- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Adverse events leading to discontinuation and reintroduction

7.6 SUMMARY OF ADVERSE EVENTS FOR LONG-TERM SAFETY SET

The following types of AEs for long-term safety set will be summarized with number and cases of AEs, incidence rate and exact 95% confidence intervals. The details of AEs for long-term safety set will also be presented in a listing.

- Adverse event (AE)
- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)
- Unexpected adverse drug reaction (UADR)

- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Adverse events leading to discontinuation and reintroduction

8. EFFICACY ANALYSIS

Efficacy analyses will be performed on Effectiveness set.

8.1 MAIN OUTCOME

For FVC (mL), the changes from baseline to 12 and 24 weeks will be summarized using number of subjects, mean, SD, median, minimum, maximum and will be compared using paired t-test depending on whether the normality assumption is met.

8.2 OTHER OUTCOMES

1) For % predicted of FVC, the changes from baseline to 12 and 24 weeks will be summarized using number of subjects, mean, SD, median, minimum, maximum and will be compared using paired t-test depending on whether the normality assumption is met.
2) For overall effectiveness evaluation, the three items ([Improved, Unchanged, Aggravated]) at the time of week 12 and week 24 will be summarized using number of subjects, percentage, 95% confidence intervals. In addition, if overall effectiveness is evaluated as [Improved], it is classified as [Efficacy]. And If overall effectiveness is evaluated as [Unchanged, Aggravated], it is classified as [Inefficacy]. [Efficacy], [Inefficacy] will be summarized using number of subjects, percentage, 95% confidence intervals. The analysis of the overall effectiveness evaluation results also will be performed on long-term effectiveness set.

8.3 UNIVARIATE ANALYSIS

The following categorical variables will be summarized using number of subjects, number and cases of efficacy, efficacy rate and 95% confidence interval. Efficacy will be analyzed by using Pearson's chi-squire test or Fisher's exact test to determine if statistically significant differences exist. (However, if [Family history of pulmonary fibrosis/SSc-ILD], [Alcohol consumption], [Occupation or exposure status], [Chest HRCT evaluation] and [Result of lung biopsy] responds with [Unknown], it is excluded from Pearson's chi-squire test or Fisher's exact test.)

- Diagnosed disease (IPF, SSc-ILD, PF-ILD)
- Gender (Male, Female)
- Allergy (Yes, No)
- Child Pugh Score Class (Class A, Class B, Class C, Not Applicable)
- Family history of pulmonary fibrosis/SSc-ILD (Yes, no, Unknown)
- Smoking status (Never smoked, EX-smoker, Current smoker)
- Alcohol consumption (Never, Former, Current, Unknown)
- Occupation or exposure status (Yes, No, Unknown)
- Chest HRCT evaluation (UIP pattern, probable UIP pattern, inconsistent UIP pattern, emphysema, Normal, Unknown)
- Result of lung biopsy (UIP pattern, probable UIP pattern, possible UIP pattern, inconsistent with UIP, Normal, Unknown)
- Medical History (Yes, No)
- Comorbidities (Yes, No)
- Prior medication (Yes, No)
- Concomitant medication (Yes, No)

The following continuous variables will be summarized using number of subjects. Efficacy will be summarized using odds ratio and 95% confidence interval by using simple logistic regression.

- Age (years)
- Height (cm)
- Weight (kg)
- Occupation or exposure period
- Duration of disease (years)
- Average daily dose (mg)

Subjects of special investigation will be summarized using number of subjects, number and cases of efficacy, efficacy rate and 95% confidence interval. Efficacy will be analyzed by using Pearson's chi-square test or Fisher's exact test to determine if statistically significant differences exist.

- Pediatric population (<18y old, ≥18y old)

- Geriatric population (<65y old, ≥65y old)
- Pregnant women (Yes, No)
- Lactating women (Yes, No)
- Hepatic impairment (Yes, No)
- Renal impairment (Yes, No)

8.4 MULTIVARIABLE ANALYSIS

As a result of simple logistic regression, statistically significant variables will be summarized using odds ratio and 95% confidence interval by using multiple logistic regression. (However, Variables with the VIF exceeding 10 can be excluded from the model.) The complete case analysis will be used to handle missing values of variables in the multivariate logistic regression model.

9. APPENDIX

9.1 APPENDIX 2

Appendix 2 will be prepared for the Use Result Surveillance. The number of subjects whose CRF was retrieved, safety set, effectiveness set, long-term safety set, long-term effectiveness set by year of the study will be presented. The number of subjects excluded from the safety evaluation, efficacy evaluation, long-term safety evaluation, long-term efficacy evaluation and their specific reasons will be presented.

9.2 APPENDIX 3

ADR collected in use result surveillance will be summarized using number of study sites, number of safety set, number and cases of ADRs, incidence rate of ADRs according to the appendix format. AEs, SADRs, Not SAEs, Not SADRs collected from use result surveillance, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will be coded with Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized with system organ class (SOC) and preferred term (PT) using number and cases, incidence rate, percentage of cases (only use result surveillance).

9.3 APPENDIX 5

AEs, SADRs, UADRs collected from use result surveillance, special study(Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will only be presented for Re-examination according to the format

9.4 DETAILS OF SAES LEADING TO DEATH

The details of SAEs leading to death collected from use result surveillance, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will be presented in a listing.

9.5 DETAILS OF SERIOUS UNEXPECTED AES

The details of Serious Unexpected AEs leading to death collected from use result surveillance, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will be presented in a listing.

10. ROLE AND RESPONSIBILITY

Roles and responsibilities of this study are as following.

Table 5 Role and Responsibility

Role	Name	Responsibility
Biostatistician	[redacted]	Statistical analysis
Senior Biostatistician	[redacted]	Quality control for the statistical analysis process, Approval for SAP

11. APPLIED SOPS

The following SOPs of [redacted] will be applied in this study.

Table 6 Applied SOPs

SOP No.	SOP Version	SOP Name
0400	V 3.0	Statistical Analysis Plan
0401	V 4.1	Statistical Analysis Process
0406	V 4.0	Definition of Analysis Population
0408	V 3.0	Statistical Analysis Document Management

12. APPLIED SOP SDS

The following Supporting Documents of [redacted] will be used in this study.

Table 7 Applied SOP SDs

SD No.	SD Version	SD Title
SD 0400 A	V 3.0	Statistical Analysis Plan
SD 0401 A	V 3.0	Statistical Analysis QC Report
SD 0406 A	V 5.0	Definition of Analysis Population
SD 0408 A	V 4.0	STAT Master File Index

13. SAS PROGRAM CODE

The following SAS program codes will be used.

Table 8 SAS program code

Analysis method	SAS program code
Pearson's chi-square test or Fisher's exact test	PROC FREQ DATA=dataset; TABLE ae*factor/CHISQ EXACT; RUN;
Simple logistic regression	PROC LOGISTIC DATA=dataset; CLASS factor; MODEL ae=factor; RUN;
Multiple logistic regression	PROC LOGISTIC DATA=dataset; CLASS factor1 factor2 factor3; MODEL ae= factor1 factor2 factor3 factor4; RUN;

14. TABLE SELLS

The following are the lists of tables for this study.

Table 9 List of Tables

Table Number	Table Description
A1	Study period and number of subjects
A2	Post-Market Surveillance tables

[redacted]

STATISTICAL ANALYSIS PLAN

Table Number	Table Description
B1	Demographics
B2	Disease information
B3	subjects of special investigation
B4	Medical history
B5	comorbidities
B6	Prior medication
B7	Concomitant medication
B8	Ofev administration status
C1	Summary of AEs
C2	Status of AEs and ADRs
C3	Status of SAEs and SADRs
C4	Status of UAEs and UADRs
C5	Status of AESI
C6	Status of AEs leading to discontinuation
C7	Status of AEs leading to discontinuation and reintroduction
C8	Details of SAEs
C9	AE classified by intensity
C10	AE classified by outcome of the event
C11	AE classified by causal relationship
C12	AE classified by action taken with Ofev
C13	AE classified by therapy for the event
C14	Status of SAEs and SADRs by frequency of occurrence
C15	Status of UAEs and UADRs by frequency of occurrence
C16	Status of AEs by subject characteristics - categorical variables
C17	Status of AEs by subject characteristics - continuous variables
C18	Status of AEs for subjects of special investigation
C19	Status of AEs by subject characteristics - multivariable analysis
C20	Summary of AEs for subjects of special investigation
C21	Details of AEs for subjects of special investigation
C22	Summary of AEs for subjects who are not eligible
C23	Details of AEs for subjects who are not eligible
C24	Summary of AEs for Long-term Safety Set
C25	Details of AEs for Long-term Safety Set

[redacted]

STATISTICAL ANALYSIS PLAN

Table Number	Table Description
D1	Outcome– FVC(mL)
D2	Outcome – % predicted of FVC
D3	Overall effectiveness evaluation
D4	Result of effectiveness evaluation by subject characteristics - categorical variables
D5	Result of effectiveness evaluation by subject characteristics - continuous variables
D6	Effectiveness evaluation for subjects of special investigation
D7	Result of effectiveness evaluation by subject characteristics - multivariable Analysis
D8	Overall effectiveness evaluation for Long-term Effectiveness set

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	30 May 2022 01:24 CEST
Approval-Project Statistician		30 May 2022 08:58 CEST
Approval		30 May 2022 16:14 CEST
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