Non-Interventional Study (NIS) Protocol

Document Number:	***NA***
BI Study Number:	1199-0523
BI Investigational Product(s):	Not applicable
Title:	Incidence probability of progression to progressive fibrosing interstitial lung diseases and status of management and treatments in patients with fibrosing interstitial lung diseases other than idiopathic pulmonary fibrosis in Japan
Brief lay title:	Study of progression to PF-ILD incidence/management and treatment
Protocol version identifier:	1.4
Date of last version of protocol:	29 Nov. 2023
PASS:	Not applicable
EU PAS register number:	Not applicable
Active substance:	Not applicable
Medicinal product:	Not applicable
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	Not applicable
Research question and objectives:	PRIMARY OBJECTIVE To investigate the incidence probability of progression to PF-ILDs in patients with fibrosing ILD other than IPF in real-world setting in Japan SECONDARY OBJECTIVE To investigate the characteristics of procedures for management and treatment in patients with fibrosing ILD other than IPF in real-world setting in Japan
Country(-ies) of study:	Japan
Author:	[redacted]
Co-Author:	

Marketing authorisation holder(s):	[redacted]
In case of PASS, add: **MAH contact person:**	Not applicable
In case of PASS, add:	Not applicable
In case of PASS, add:	Not applicable
Date:	29 Nov. 2023

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
CTD-ILD	Connective Tissue Disease-Interstitial Lung Disease
DPC	Diagnosis Procedure Combination
HP	Hypersensitivity Pneumonitis
HRCT/CT	High-Resolution Computed Tomography/Computed Tomography
ILD	Interstitial Lung Disease
IHD	Instant Health Data
IIPs	Idiopathic Interstitial Pneumonias
iNSIP	Idiopathic Nonspecific Interstitial Pneumonia
IPF	Idiopathic Pulmonary Fibrosis
KL-6	Krebs von den Lungen-6
MCTD	Mixed Connective Tissue disease
MDV	Medical Data Vision
PF-ILD	Progressive Fibrosing Interstitial Lung Disease
PM/DM-ILD	Polymyositis/Dermatomyositis-Interstitial Lung Disease
RA-ILD	Rheumatoid Arthritis-Interstitial Lung Disease
SAS	Statistical Analysis System
SLE-ILD	Systemic Lupus Erythematosus-Interstitial Lung Disease
SP-D	Surfactant Protein D
SSc-ILD	Systemic Sclerosis-Interstitial Lung Disease

3. RESPONSIBLE PARTIES

NIS [redacted]

[redacted]

Co-NIS [redacted]

[redacted]

Data Management and Statistical Analysis

[redacted]

Medical Advisor

[redacted]

Data source

[redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim Co., Ltd.			
Name of finished medicinal product: Not applicable			
Name of active ingredient:			
Protocol date: *DD Month YYYY*	**Study number:**	**Version/Revision:** 1.4	**Version/Revision date:** 29 Nov. 2023

Title of study:	Incidence probability of progression to progressive fibrosing interstitial lung diseases and status of management and treatments in patients with fibrosing interstitial lung diseases other than idiopathic pulmonary fibrosis in Japan
Rationale and background:	While idiopathic pulmonary fibrosis (IPF) is the best-known progressive fibrosing interstitial lung disease (PF-ILD), there is a group of patients with different underlying clinical interstitial lung disease (ILD) diagnoses other than IPF who develop a progressive fibrosing phenotype during the course of their disease. There is minimal literature available to estimate the proportion of patients who develop PF-ILDs in patients with fibrosing ILD other than IPF and, the current management and treatment for these diseases are not well-known in Japan. These information are keys to gaining a better understanding of the size of this population with high unmet need and for physicians, patients and other stakeholders to optimize allocation of resources, diagnostic assessment and management of this patient population.
Research question and objectives:	PRIMARY OBJECTIVE To investigate the incidence probability of progression to PF-ILDs in patients with fibrosing ILD other than IPF in real-world setting in Japan SECONDARY OBJECTIVE To investigate the characteristics of procedures for management and treatment in patients with fibrosing ILD other than IPF in real-world setting in Japan
Study design:	This is a retrospective cohort study using the database from Medical Data Vision (MDV). Data from 01-Jan-2012 to 28-May-2020 will be used. It will be considered that each patient is observable from his/her first encounter to his/her last encounter in the database. The patients with fibrosing ILD will be identified in the period from 01-Jan-2013 to 6 months before 28-May-2020. Each patient who meets all the inclusion criteria and none of the exclusion criteria will be followed up from the day after the index date until the end of study period (i.e., 28-May-2020), the last encounter in the MDV database, in-hospital death, whichever occurs first.

Population:	Patients who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be included in the study population. **Inclusion Criteria:** 1) Patients diagnosed with at least two fibrosing ILD codes on different dates in the patient identification period from 01-Jan-2013 to 6 months before 28-May-2020 2) Patients aged 18 years and older on the index date 3) Patients for whom data for the 12 months prior to the index date can be extracted as baseline data **Exclusion Criteria:** 1) Patients grouped into the underlying disease of IPF 2) Patients who have met PF-ILD progression criteria during the baseline period Note: only diagnosis records without 'suspect flag' are to be considered for evaluating diagnosis related in/excl criteria"
Variables:	The following information will be extracted from MDV database in this study; sex, age, comorbidity and medical history of interest, Underlying disease (pre-specified ILD), clinical examination, treatment and management of interest
Data sources:	The MDV database consists of anonymized administrative claims and Diagnosis Procedure Combination (DPC) data for inpatient and outpatient settings from acute hospitals (mainly considered as advanced treatment hospitals). The database includes >35 million patients from >400 hospitals. Patients in Japan have free access to health care facilities and data from the other hospitals not included in the database are unavailable.
Study size:	The planned sample size is not based on the formal statistical hypothesis testing and statistical precision. Because the MDV database consists of >35 million patients, it is expected that the sufficient number of non-IPF fibrosing ILD patients will be included in the study.
Data analysis:	**Primary outcome** Incidence probability of progression to PF-ILDs at 6, 12, 18, and 24 months after the index date. Cumulative incidence probability will be estimated by using Kaplan-Meier method. **Secondary outcomes** Management and treatment during follow-up period Frequency of patients with management and treatment of interest during follow-up period will be analyzed descriptively.
Milestones:	- Final protocol: 28 Mar 2023 - IRB approval: Prior to study start - Start of data analysis: After the IRB approval - Final results: Q2 2023 - Final study report: Q3 2023 - Publications: Q3, 2023

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	*28 March 2023*	*9.2.2.1 Exclusion Criteria*	*2)Patients who have met PF-ILD progression criteria during the baseline period and 3) delete*	*To further clarify and simplify the exclusion criteria*
2	*21 Sep. 2023*	*ANNEX 2 and 3*	*Add Generic names and correct ATC codes*	*To correct the drug codes*
3	*21 Sep. 2023*	*ANNEX 2 and 3*	**transdermal patch, sublingual agent, Transmucosal agent, suppository are excluded*	*To reflect the updated definition of opioid use*
4	*10 Nov. 2023*	*ANNEX 2 and 3*	*K514-4* *K514-6*	*To correct codes for lung transplant*
5	*29 Nov. 2023*	*ANNEX 2 and 3*	*N02A0*	*To correct the drug code for opioid*

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Prior to study start
Start of Data Analysis	After the IRB approval
Interim Report	NA
Final report of study results:	Q3 2023

7. RATIONALE AND BACKGROUND

The term interstitial lung disease (ILD) encompasses a large group of over 200 pulmonary disorders. While idiopathic pulmonary fibrosis (IPF) is the best-known progressive fibrosing ILD (PF-ILD), there is a group of patients with different underlying clinical ILD diagnoses other than IPF who develop a progressive fibrosing phenotype during the course of their disease (e.g., idiopathic interstitial pneumonias [IIPs] such as idiopathic nonspecific interstitial pneumonia [iNSIP] and unclassifiable IIP; hypersensitivity pneumonitis [HP]; autoimmune interstitial lung disease [connective tissue disease-ILDs (CTD-ILD) such as rheumatoid arthritis-ILD (RA-ILD), systemic sclerosis-ILD (SSc-ILD) and anti-synthetase syndrome]; Sarcoidosis; Pneumoconiosis/exposure related ILD) [P17-10582, P18-04729, P19-01738, R19-0854]. These patients demonstrate a number of similarities to patients with IPF, with their disease being defined by the presence of progressive pulmonary fibrosis, worsening respiratory symptoms, declining lung function despite immunomodulatory therapies and, ultimately, early mortality.

Although there had been no indicated therapies for patients with chronic fibrosing ILDs with a progressive phenotype (other than IPF), Nintedanib has just been approved for SSc-ILD in the end of Dec. 2019 based on the results of the SENSCIS trial (NCT02597933) [P19-04387] and for PF-ILDs in the end of May 2020 in Japan based on the results of the INBUILD trial (NCT02999178) [P19-08802, P20-02333].

There is minimal literature available to estimate the proportion of patients who develop PF-ILDs in patients with fibrosing ILD other than IPF in Japan. In addition, the current management and treatment for these diseases are not well-known. These information are keys to gaining a better understanding of the size of this population with high unmet need and for physicians, patients and other stakeholders to optimize allocation of resources, diagnostic assessment and management of this patient population.

Therefore, this study will use the database from Medical Data Vision (MDV) to investigate the incidence probability of progression to PF-ILDs according to each co-existing underlying diseases and the characteristics of procedures for management and treatment in patients with fibrosing ILD other than IPF.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

To investigate the incidence probability of progression to PF-ILDs in patients with fibrosing ILD other than IPF in real-world setting in Japan

8.2 SECONDARY OBJECTIVE

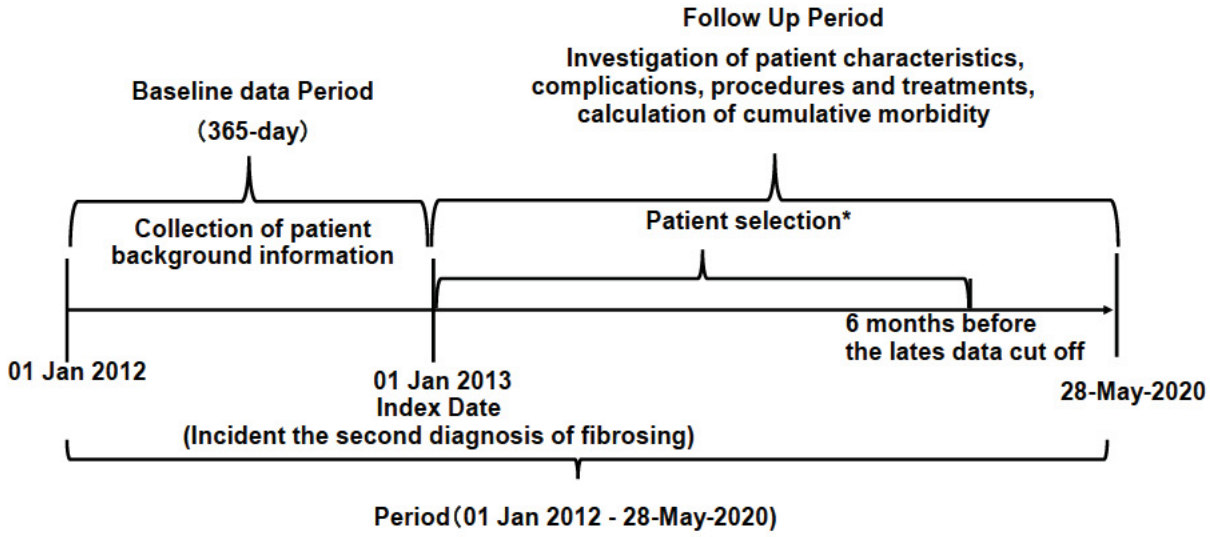
To investigate the characteristics of procedures for management and treatment in patients with fibrosing ILD other than IPF in real-world setting in Japan

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a retrospective cohort study using the database from MDV.
Data from 01-Jan-2012 to 28-May-2020 will be used. It will be considered that each patient is observable from his/her first encounter to his/her last encounter in the database. The patients with fibrosing ILD will be identified in the period from 01-Jan-2013 to 6 months before 28-May-2020. Each patient who meets all the inclusion criteria and none of the exclusion criteria will be followed up from the day after the index date※ until the end of study period (i.e. 28-May-2020), the last encounter in the MDV database, in-hospital death, whichever occurs first.

※The index date will be the date of the second diagnosis of fibrosing ILD. Please refer to the Section 9.2.2.1 for the detailed codes of fibrosing ILD.



**The index date will depend on the time the patient fulfils the eligibility criteria*

Figure 1 . Schematic of the Study Design

9.2 SETTING

9.2.1 Study sites

There are no study sites for this study because it is a database study.

9.2.2 Study population

9.2.2.1 Eligibility criteria

Patients who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be included in the study population.

Inclusion Criteria:

1) Patients diagnosed with at least two fibrosing ILD codes[*1] on different dates in the patient identification period from 01-Jan-2013 to 6 months before 28-May-2020
2) Patients aged 18 years and older on the index date
3) Patients for whom data for the 12 months prior to the index date can be extracted as baseline data

*1 International Statistical Classification of Diseases and Related Health Problems (ICD-10) code or disease code: J84.1, J84.9, 8844510, 8848382, 8844341, 8848278, 8836513, 8848267, 8848302, 8839362, 8848283, 8837013, 8834158, 8848245, 8840951, 8847737

Exclusion Criteria:

1) Patients grouped into the underlying disease of IPF[*1]
2) Patients who have met PF-ILD progression criteria during the baseline period

*1 Please refer to the ANNEX 5 for algorithm to define underlying diseases

Note: only diagnosis records without ‘suspect flag’ are to be considered for evaluating diagnosis related in/excl criteria”

9.3 VARIABLES

9.3.1 Outcomes

9.3.1.1 Primary outcome

Incidence probability of progression to PF-ILDs at 6, 12, 18, and 24 months after the index date※

Progression to PF-ILD as event in this study is defined in Table 1 as well as Annex 2. Event date will be the date when the one of criteria of the progression to PF-ILD is met.

※The index date will be the date of the second diagnosis of fibrosing ILD. Please refer to the Section 9.2.2.1 for the detailed codes of fibrosing ILD.

Table 1. Interstitial lung disease progression proxies

Proxy
- ≥ 3 pulmonary function tests on different dates of service within 365 days - The date of the 3rd pulmonary function test will be the date of progression
- ≥ 3 HRCT/CT on different dates of service within 365 days - The date of the 3rd HRCT/CT will be the date of progression
≥ 1 claim for oxygen therapy (HOT) during follow-up period
≥ 1 respiratory hospitalization during follow-up period
≥ 1 claim for palliative care during follow-up period
≥ 1 lung transplant during follow-up period
≥ 1 new* claim for immunosuppressive drugs during follow-up period with at least two out of the three test codes** within 3 months before new claims for immunosuppressive drugs Rituximab Tacrolimus Mycophenolate Cyclosporine Cyclophosphamide Azathioprine Tocilizumab *: Not received in the 12 months prior to the index date **: ① Pulmonary function tests, ② HRCT/CT, ③ KL-6 or SP-D
≥ 1 new* claim for oral corticosteroid with a prednisone-equivalent dose of >20 mg during follow-up period and with at least two out of the three test codes* within 3 months before new claims for oral corticosteroid *: Not received in the 12 months prior to the index date **: ① Pulmonary function tests, ② HRCT/CT, ③ KL-6 or SP-D
≥ 1 claim for Nintedanib* during follow-up period *: Patients meeting this criterion will be counted only if patients with fibrosing ILDs meet this criterion on or after 29-May-2020, because nintedanib was approved for PF-ILD on 29-May-2020. Even if patients with fibrosing ILDs meet this criterion on or before 28-May-2020, they will not be counted.

HRCT; high-resolution computed tomography, CT; computed tomography, KL-6; krebs von den lungen-6, SP-D; surfactant protein D

9.3.1.2 Secondary outcome

Management and treatment during follow-up period
The management and treatment of interest are shown in **Table 2**.

9.3.2 Covariates

The following information will be extracted from MDV in this study.

Table 2. Definition of variables

Variable	Data extraction period	Details
Sex	Index date	Male/Female
Age	Index date	Age at Index date
Comorbidity and medical history	12 months before the index date (included)	- Coronary heart disease - Gastro-esophageal reflux disease - Obstructive sleep apnoea syndrome - Chronic obstructive pulmonary disease (COPD) - Lung cancer - Pulmonary hypertension See Annex 4 for code to define each comorbidity and medical history
Underlying disease (Pre-specified ILD)	12 months before the index date (included)	- Underlying Autoimmune Disease (Autoimmune ILD, Non-autoimmune ILD, Multiple, Unknown) - ILD Category (Hypersensitive pneumonitis, Exposure-related ILD, idiopathic nonspecific interstitial pneumonia (iNSIP), Unclassifiable idiopathic interstitial pneumonias (IIP), Sarcoidosis, RA-ILD, SSc-ILD, mixed connective tissue disease-ILD (MCTD-ILD), Other autoimmune ILD, Other ILD, Multiple, Unknown) - Pre-Specified ILD Clinical Diagnosis (Hypersensitive pneumonitis, Exposure-related ILD, iNSIP, Unclassifiable IIP, Sarcoidosis, RA-ILD, SSc-ILD, MCTD-ILD, Systemic Lupus Erythematosus-ILD (SLE-ILD), Polymyositis/Dermatomyositis-ILD (PM/DM-ILD), Sjogren ILD, Other autoimmune ILD, Other ILD, Multiple, Unknown) See Annex 5 for algorithm to define underlying diseases
Treatment	6 months before the index date (included) Follow-up period	- Rituximab - Tacrolimus - Mycophenolate - Cyclosporine - Cyclophosphamide - Azathioprine - Oral Corticosteroid - Tocilizumab - Nintedanib See Annex 3 for code to define each treatment As for corticosteroid and immunosuppressive drugs during follow-up period, the same condition used for criteria of progression to PF-ILD will be applied.
Management	Follow-up period	- Oxygen therapy (HOT) - Lung transplant - Palliative care (oxygen inhalation, opioid use) See Annex 3 for code to define each management
Clinical examination	6 months before the index date (included)	- Pulmonary function test - HRCT/CT - KL-6 - SP-D See Annex 3 for code to define each clinical examination

9.4 DATA SOURCES

The MDV database consists of anonymized administrative claims and DPC data for inpatient and outpatient settings from acute hospitals (mainly considered as advanced treatment hospitals). At present, the database includes >35 million patients from >400 hospitals.
Patients in Japan have free access to health care facilities and data from the other hospitals not included in the database are unavailable.

9.5 STUDY SIZE

The planned sample size is not based on the formal statistical hypothesis testing and statistical precision. Because the MDV database consists of >35 million patients, it is expected that the sufficient number of non-IPF fibrosing ILD patients will be included in the study.

9.6 DATA MANAGEMENT

The anonymised data received from hospitals has been checked by data managers in MDV to update the database. The database Boehringer Ingelheim (BI) received from MDV will be used.
The analyses will be performed using Instant Health Data (IHD) platform, SAS statistical software (version 9.3 or higher) and/or R.

9.7 DATA ANALYSIS

9.7.1 Common handling for statistical analysis

Unless otherwise specified, descriptive analysis is planned.
The summary statistics for continuous variables are N, mean, standard deviation, minimum, 25th percentile (Q1), median, 75th percentile (Q3), and maximum.
Tabulations of frequencies for categorical variables will include all possible categories and will display the number of observations in a category as well as percentage (%) relative to the population analysed. The precision for percentage will be one decimal point.

9.7.2 Statistical analysis

9.7.2.1 Patient background characteristics and treatment

- Patient demographics (sex, age at the index date)
- Comorbidity and medical history during 12 months prior to the index date (included)
- Clinical examination, management, and treatment during 6 months prior to the index date (included)
- Duration of follow-up period, which is defined as “end of follow-up period” – “start of follow-up period” + 1 day
- Underlying diseases

These will also be analysed in patients with progression to PF-ILD and those without progression to PF-ILD respectively.

9.7.2.2 Primary outcome

- Incidence probability of progression to PF-ILDs at 6, 12, 18, and 24 months after the index date

Cumulative incidence probability of progression to PF-ILD at 6, 12, 18 and 24 months after the index date will be estimated by using Kaplan-Meier method. Greenwood's variance estimate will be used for calculating 95% confidence interval. Kaplan-Meier curve will also be displayed.

Of the patients with progression to PF-ILD, frequency of patients meeting each criteria of progression to PF-ILD will be analysed descriptively.

9.7.2.3 Secondary outcomes

- Management and treatment during follow-up period

Frequency of patients with management and treatment during follow-up period will be analyzed.

9.7.3 Subgroup analysis

The three subgroup analyses by underlying diseases defined by disease codes on the index date and 12-months lookback period as described in Annex 5 will be performed for patient background characteristics and treatment, primary outcome, and secondary outcomes.

<Subgroup Patterns>
Underlying Autoimmune Disease (Subgroup1): Autoimmune ILD, Non-autoimmune ILD, Multiple, Unknown

ILD Category (Subgroup 2): Hypersensitive pneumonitis, Exposure-related ILD, iNSIP, Unclassifiable IIP, Sarcoidosis, RA-ILD, SSc-ILD, MCTD-ILD, Other autoimmune ILD, Other ILD, Multiple, Unknown

Pre-Specified ILD Clinical Diagnosis (Subgroup 3): Hypersensitive pneumonitis, Exposure-related ILD, iNSIP, Unclassifiable IIP, Sarcoidosis, RA-ILD, SSc-ILD, MCTD-ILD, SLE-ILD, PM/DM-ILD, Sjogren ILD, Other autoimmune ILD, Other ILD, Multiple, Unknown

9.7.4 Sensitivity analysis

1) The end of data extraction period will be changed from 28-May-2020 to the latest data cut off. OFEV was approved for PF-ILD on 29-May-2020, and the characteristics of claims data before and after the above approval for new indications might not be different. To increase the sample size, all the analyses will be repeated with this data extraction period.
2) The index date will be changed from the date of the second code of fibrosing ILD to the date of the first code of fibrosing ILD because there might be patients who are asked to visit hospitals annually after the first diagnosis. All the analyses will be repeated with this index date.

In addition, all the analyses will be repeated with both data extraction period and index date changed.

After exploring the proxy patterns among patients meeting the criteria of progression to PF-ILD as described in Section 9.7.2.2, a sensitivity analysis with modified progression criteria might be performed.

9.8 QUALITY CONTROL

The analysis program and the data codes used in the analysis will be checked by someone different from the creator.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The MDV database does not have pulmonary function test results and there have been no evidence on the validated algorithm to define fibrosing ILD patients other than IPF and progression to PF-ILD as events by using claims data. Therefore, the estimated incidence in this study might be biased and the sensitivity analysis by using different algorithm is planned to assess the robustness of the results.
Due to the characteristics of health care system in Japan as described in Section 9.4, data generated in the clinics/hospitals other than hospitals included in the MDV database are not captured and the incidence probability and frequency might be underestimated.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees. The quality assurance auditor will have access to all study-related files.

9.10.2 Study records

Not applicable. (This study will not use Case Report Forms.)

9.10.3 Completion of study

Not applicable.

9.10.4 Protocol deviations

Deviations from the research protocol that may occur in this study include deviations from the procedures for handling databases and methods of analysis and reporting. Any deviations should be reported to the principal investigator by the co-investigator or contract research organization.

9.10.5 Compensation available to the patient in the event of study related injury

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

The MDV data used in this study is existing information and does not involve the acquisition of new information. In addition, it is anonymized processed information and cannot identify individuals. Therefore, the protection of subjects does not apply to this study.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable based on secondary use of data without any potential that any employee of BI or agent working on behalf of BI will access individually identifiable patient data.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this research will be presented at conferences and published in peer-reviewed journals.

13. REFERENCES

13.1 PUBLISHED REFERENCES

P17-10582 Flaherty KR, Brown KK, Wells AU, et al Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease BMJ Open Respiratory Research 2017;4:e000212. doi: 10.1136/bmjresp-2017-000212

P18-04729 Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal Victor J. What's in a name? That which we call IPF, by any other name would act the same. European Respiratory Journal. 2018;51(5). Prevalence and characteristics of progressive fibrosing interstitial lung disease in a prospective registry

R11-4318 Guidelines for Good Pharmacoepidemiology Practices (GPP) (revision 2: April 2007). http://www.pharmacoepi.org/resources/guidelines_08027.cfm (access date: 13 September 2011) ; Bethesda: International Society for Pharmacoepidemiology (ISPE) (2007)

R15-4859 Guidance for industry and FDA staff: best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data (May 2013, drug safety). http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guida nces/ucm243537.pdf (access date: 28 August 2015) ; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2013)

R15-4870] European Medicines Agency (EMA). The ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies (London, 21 November 2011, EMA/929209/2011). http://www.encepp.eu/code_of_conduct/documents/CodeofConduct_Rev2.pdf (access date: 28 August 2015) ; London: European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (2011)

P19-01738 Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. Eur Resp Rev 2019;28:180100.

R19-0854 Kolb M, Vasakova M. The natural history of progressive fibrosing interstitial lung diseases. Respir Res (Lond) 2019;20(1):57

P19-08802 Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al, INBUILD Trial Investigators. Nintedanib in progressive fibrosing interstitial lung diseases. New England Journal of Medicine, published on September 29, 2019, doi: 10.1056/NEJMoa1908681; 2019. p. 1718-1727.

P20-02333 Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al, INBUILD Trial Investigators. Nintedanib in patients with progressive fibrosing interstitial lung diseases - subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respiratory Medicine, Published Online March 5, 2020, doi: 10.1016/S2213-2600(20)30036-9; 2020. p. 453-460.

13.2 UNPUBLISHED REFERENCES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	Annex 1	20 February 2023	List of stand-alone documents
2	Annex 2	20 February 2023	INTERSTITIAL LUNG DISEASE PROGRESSION PROXIES
3	Annex 3	20 February 2023	CODE FOR TREATMENT, MANAGEMENT & CLNICAL EXAMINATION
4	Annex 4	20 February 2023	CODE FOR COMORBIDITY AND MEDICAL HISTORY
5	Annex 5	20 February 2023	ALGORITHMS FOR DEFINING UDERLYING DISEASES
6	Annex 6	20 February 2023	INFORMATION OF THE CODE TO DEFINE FIBROSING ILD AND UNDERLYING DISEASES
7	Annex 7	20 February 2023	REVIEWERS AND APPROVAL SIGNATURES

ANNEX 2. INTERSTITIAL LUNG DISEASE PROGRESSION PROXIES

Proxy	billing code / generic names / EphMRA ATC code
≥ 3 pulmonary function tests on different dates of service within 365 days The date of the 3rd pulmonary function test will be the date of progression	160062610 160062710 160062810
≥ 3 HRCT/CT on different dates of service within 365 days The date of the 3rd HRCT/CT will be the date of progression	170022290 170011710 170011810 170028610 170033410 170034910 170040210 170040410 170040610 170040810 170041010
≥ 1 claim for oxygen therapy (HOT) during follow-up period	114003710
≥ 1 respiratory hospitalization during follow-up period	A221 A379 A370 B250 B440 J00 J01.x J02.x J03.x J04.x J05.x J06.x J110 J12.x J13 J14 J15.x J160 J18.x J20x J21.x J22 J40 J41.x J42 J43.x J44.x J45.x J84.x J96.x Segment of disease based on DPC is “01: Disease name which input the most medical resources”, “11: Main disease name”, or “21: Disease name behind hospitalization”
≥ 1 claim for palliative care during follow-up period	Oxygen inhalation: 140005610 Opioid use:

	N02A0 [Excluding methadone, buprenorphine, naloxonecombinations (Suboxone)] * *transdermal patch, sublingual agent, Transmucosal agent, suppository are excluded
≥ 1 lung transplant during follow-up period	K514-4 K514-6
≥ 1 new* claim for immunosuppressive drugs during follow-up period with at least two out of the three test codes** within 3 months before new claims for immunosuppressive drugs Rituximab Tacrolimus Mycophenolate Cyclosporine Cyclophosphamide Azathioprine Tocilizumab *: Not received in the 12 months prior to the index date **: ① Pulmonary function tests, ② HRCT/CT, ③ KL-6 or SP-D	Rituximab/ L01G1 Tacrolimus/ L04X0 Mycophenolate/ L04X0 Cyclosporine or (Ciclosporin, Cyclosporin) / L04X0 Cyclophosphamide/ L01A0 Azathioprine/ L04X0 Tocilizumab/ M01C0 & L04C0 (Generic names/ MphMRA ATC codes which each drug is under)
≥ 1 new* claim for oral corticosteroid with a prednisone-equivalent dose of >20 mg during follow-up period and with at least two out of the three test codes* within 3 months before new claims for oral corticosteroid *: Not received in the 12 months prior to the index date **: ① Pulmonary function tests, ② HRCT/CT, ③ KL-6 or SP-D	H02A2 excluding Florinef
≥ 1 claim for Nintedanib* during follow-up period *: Patients meeting this criterion will be counted only if patients with fibrosing ILDs meet this criterion on or after 29-May-2020, because nintedanib was approved for PF-ILD on 29-May-2020. Even if patients with fibrosing ILDs meet this criterion on or before 28-May-2020, they will not be counted.	Nintedanib/ L01H9 & R07D0 (Generic name/ MphMRA ATC codes which nintedanib is under)

ANNEX 3. CODE FOR TREATMENT, MANAGEMENT & CLNICAL EXAMINATION

Drug name / Treatment	Generic names/ Codes
Rituximab	Rituximab/ L01G1
Tacrolimus	Tacrolimus/ L04X0
Mycophenolate	Mycophenolate/ L04X0
Cyclosporine	Cyclosporine or (Ciclosporin, Cyclosporin)/ L04X0
Cyclophosphamide	Cyclophosphamide/ L01A0
Azathioprine	Azathioprine/ L04X0
Oral Corticosteroid	H02A2 excluding Florinef
Tocilizumab	Tocilizumab/ M01C0 & L04C0
Nintedanib	Nintedanib/ L01H9 & R07D0
Oxgen therapy (HOT)	114003710
Lung transplant	K514-4 K514-6
Palliative care	Oxygen inhalation: 140005610 Opioid use: N02A0 [Excluding methadone, buprenorphine, naloxonecombinations (Suboxone)] * *transdermal patch, sublingual agent, Transmucosal agent, suppository are excluded
PFT	160062610 160062710 160062810
HRCT/CT	170022290 170011710 170011810 170028610 170033410 170034910 170040210 170040410 170040610 170040810 170041010
KL-6	160168550
SP-D	160168450

ANNEX 4. CODE FOR COMORBIDITY AND MEDICAL HISTORY

Comorbidity / Medical history	Codes
Coronary heart disease	I20-25
Gastro-esophageal reflux disease	K21
Obstructive sleep apnoea syndrome	G473
COPD	J41-44
Lung cancer	C34
Pulmonary hypertension	I27

ANNEX 5. ALGORITHMS FOR DEFINING UDERLYING DISEASES

The following three subgroups will be defined to assess the distribution of underlying diseases and to perform subgroup analysis by underlying diseases.

Subgroup1: Autoimmune ILD, Non-autoimmune ILD, Multiple, Unknown, IPF[#]
Subgroup2: Hypersensitive pneumonitis, Exposure-related ILD, iNSIP, Unclassifiable IIP, Sarcoidosis, RA-ILD, SSc-ILD, MCTD-ILD, Other autoimmune ILD, Other ILD, Multiple, Unknown, IPF[#]
Subgroup3: Hypersensitive pneumonitis, Exposure-related ILD, iNSIP, Unclassifiable IIP, Sarcoidosis, RA-ILD, SSc-ILD, MCTD-ILD, SLE-ILD, PM/DM-ILD, Sjogren ILD, Other autoimmune ILD, Other ILD, Multiple, Unknown, IPF[#]
#Note: Patients grouped into IPF are excluded from study population according to the exclusion criteria.

The patients will be grouped according to the following three steps.
Step 1: Patients will be grouped based on the fibrosing-ILD code on the index date
If two or more different [(1)] disease codes specified in this step 1 exist on index date
, **then** subgroup1=subgorup2=subgrou3=Multiple
else if disease code on index date=8844510, **then** Subrgoup1=Autoimmune ILD, subgroup2=SSc-ILD, subgroup3=SSc-ILD
else if disease code on index date=8847737, **then** subgroup1=Autoimmune ILD, subgroup2=RA-ILD, subgorup3=RA-ILD
else if disease code on index date=8848382, **then** subrgoup1=Autoimmune ILD, subgroup2=Other autoimmune ILD, subgroup3=Other autoimmune ILD
else if disease code on index date=in(8848278, 8836513, 8844341), **then** subgroup1=Autoimmune ILD, subgroup2=Other autoimmune ILD. Subgroup3=SLE-ILD
else if disease code on index date=in(8848267, 8848302, 8839362, 8848283, 8837013), **then** subgroup1=Autoimmune ILD, subgroup2=Other autoimmune ILD, subgroup3=PM/DM ILD
else if disease code on index date=8834158, **then** subgroup1=Autoimmune ILD, subgroup2=Other autoimmune ILD, subgroup3=Sjogren ILD

(1)Note: The disease codes in the same conditional statement are NOT considered different. For example, disease codes of 8848278 and 8836513 are in the same conditional statement and these are not considered different disease codes. On the other hand, disease codes of 8848278 and 8848267 are in the different conditional statement and these are considered different disease codes.

Step 2: Patients not grouped in the step 1 will be grouped based on the earliest underlying disease code in the lookback period and fibrosing-ILD code on the index date
else if two or more different [(2)] earliest underlying disease codes specified in this step 2 exist AND disease code on index date=in(J84.1, J84.9), **then** subgroup1=subgorup2=subgrou3=Multiple
else if earliest underlying disease code=in(D86.0, D86.1, D86.3, D86.8, D86.9) AND disease code on index date=in(J84.1, J84.9), **then** subgroup1=Non-autoimmune ILD, subgroup2=Sarcoidosis, subgroup3=Sarcoidosis
else if earliest underlying disease code=in(J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9) AND disease code on index date=in(J84.1, J84.9), **then** subgroup1=Non-autoimmune ILD, subgroup2=Hypersensitive pneumonitis, subgroup3=Hypersensitive pneumonitis
else if earliest underlying disease code=J84.0 AND disease code on index date=in(J84.1, J84.9), **then** subgroup1=Non-autoimmune ILD, subgroup2=Other ILD, subgroup3=Other ILD
else if earliest underlying disease code=in(J60, J61, J62.8, J63.0, J63.1, J63.2, J63.3, J63.4, J63.5, J64, J65, J66.0, J66.1, J68.0, J68.4, J70.1, J70.3, J70.4, J70.8) AND disease code on index date=in(J84.1, J84.9), **then** subgroup1=Non-autoimmune ILD, subgroup2=Exposure-related ILD, subgroup3=Exposure-related ILD

Note: Disease codes of 8840951 and 8848245 are added to the coitional statement.
else if earliest underlying disease code=in(M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06.0, M06.2, M06.3, M06.4, M06.8, M06.9) AND disease code on index date=in(J84.1, J84.9, 8840951, 8848245), **then** subgroup1=Autoimmune ILD, subgroup2=RA-ILD, subgroup3=RA-ILD
else if earliest underlying disease code=in(M32.1, M32.9) AND disease code on index date=in(J84.1, J84.9, 8840951, 8848245), **then** subgroup1=Autoimmune ILD, subgroup2=Other autoimmune ILD, subgroup3=SLE-ILD
else if earliest underlying disease code=in(M33.0, M33.1, M33.2, M33.9) AND disease code on index date=in(J84.1, J84.9, 8840951, 8848245), **then** subgroup1=Autoimmune ILD, subgroup2=Other autoimmune ILD, subgroup3= PM/DM ILD
else if earliest underlying disease code=in(M34.0, M34.1, M34.8, M34.9) AND disease code on index date=in(J84.1, J84.9, 8840951, 8848245), **then** subgroup1=Autoimmune ILD, subgroup2=SSc-ILD, subgroup3=SSc-ILD
else if earliest underlying disease code=M35.0 AND disease code on index date=in(J84.1, J84.9, 8840951, 8848245), **then** subgroup1=Autoimmune ILD, subgroup2=Other autoimmune ILD, subgroup3=Sjogren ILD
else if earliest underlying disease code=7109008 AND disease code on index date=in(J84.1, J84.9, 8840951, 8848245), **then** subgroup1=Autoimmune ILD, subgroup2=MCTD-ILD, subgroup3=MCTD-ILD
else if earliest underlying disease code=in(8841317, 8850417, 8848245, M35.2, M35.3, M35.4, M35.5, M35.6, M35.7, M35.8, M35.9, M30.0, M30.1, M30.2, M30.3, M30.8, M31.0, M31.1, M31.2, M31.3, M31.4, M31.6, M31.7, M31.8, M31.9) AND disease code on index date=in(J84.1, J84.9, 8840951, 8848245), **then** subgroup1= Autoimmune ILD, subgroup2=Other autoimmune ILD, subgroup3=Other autoimmune ILD
(2)Note: The earliest underlying disease codes in the same conditional statement are NOT considered different. For example, earliest underlying disease codes of D86.0 and D86.1 are in the same conditional statement and these are not considered different earliest underlying disease codes. On the other hand, earliest underlying disease codes of D86.0 and J67.0 are in the different conditional statement and these are considered different earliest underlying disease codes.

Step 3: Patients not grouped in the step 1 and 2 will be grouped based on the fibrosing-ILD code on the index date
else if disease code on index date=in(5163005, 5150011, 8849927) AND no other fibrosing-ILD code on the index date, **then** subgroup1=subgroup2=subgroup3=IPF. These patients will be excluded from study population.
else if two or more different (3) disease codes including disease code of IPF specified in this step 3 exist on index date, **then** subgroup1=subgorup2=subgrou3=Multiple
else if disease code on index date=in(8850547, 8845727), **then** subgroup1=Non-autoimmune ILD, subgroup2=iNSIP, subgroup3=iNSIP
else if disease code on index date=in(5168008, 5168009, 5150001, 8845731, 8845640，J84.9), **then** subgroup1=Non-autoimmune ILD, subgroup2=Unclassifiable IIP, subgroup3=Unclassifiable IIP
else if disease code on index date=in(1363003, 8845663, 8845714, 8845719, 5168010), **then** subgroup1=Non-autoimmune ILD, subgroup2=Other ILD, subgroup3=Other ILD
else if disease code on index date=in(8840951, 8848245), **then** subgroup1=Autoimmune ILD, subgroup2=Other autoimmune ILD, subgroup3=Other autoimmune ILD
else subgroup1=subgroup2=subgroup3=Unknown
(3)Note: The disease codes in the same conditional statement are NOT considered different. For example, disease codes of 8850547 and 88457271 are in the same conditional statement and these are not considered different disease codes. On the other hand, disease codes of 8850547 and 5168008 are in the different conditional statement and these are considered different disease codes.
END

ANNEX 6. INFORMATION OF THE CODE TO DEFINE FIBROSING ILD AND UNDERLYING DISEASES

Disease	ICD-10 Code	billing code	Underlying Autoimmune Disease	ILD Category	Pre-Specified ILD Clinical Diagnosis
respiratory disorder in dermatosclerosis	M348	8844510	autoimmune	SSc-ILD	SSc-ILD
rheumatoid arthritis interstitial pneumonia	M0510	8847737	autoimmune	RA-ILD	RA-ILD
respiratory disorder complicated by granulomatosis with polyangiitis	M313	8848382	autoimmune	Other autoimmune ILDs	Other autoimmune ILDs
systemic lupus erythematosus interstitial pneumonia	M321	8848278	autoimmune	SLE-ILD	other autoimmune ILDs
respiratory disorder in systemic lupus erythematosus	M321	8836513	autoimmune	SLE-ILD	other autoimmune ILDs
interstitial pneumonia in juvenile dermatomyositis	M330	8848267	autoimmune	PM/DM ILD	other autoimmune ILDs
interstitial pneumonia in dermatomyositis	M331	8848302	autoimmune	PM/DM ILD	other autoimmune ILDs
respiratory disorder in dermatomyositis	M331	8839362	autoimmune	PM/DM ILD	other autoimmune ILDs
interstitial pneumonia in polymyositis	M332	8848283	autoimmune	PM/DM ILD	other autoimmune ILDs
respiratory disorder in polymyositis	M332	8837013	autoimmune	PM/DM ILD	other autoimmune ILDs
respiratory disorder in Sjogren's syndrome	M350	8834158	autoimmune	Sjogren ILD	other autoimmune ILDs

Disease	ICD-10 Code	billing code	Underlying Autoimmune Disease	ILD Category	Pre-Specified ILD Clinical Diagnosis
postinflammatory pulmonary fibrosis	J841	8845640	Non-autoimmune	Unclassifiable	Unclassifiable
usual interstitial pneumonia	J841	5168008	Non-autoimmune	Unclassifiable	Unclassifiable
idiopathic interstitial pneumonia	J841	5168009	Non-autoimmune	Unclassifiable	Unclassifiable
diffuse interstitial pneumonia	J841	5150001	Non-autoimmune	Unclassifiable	Unclassifiable
diffuse alveolar damage	J841	8845731	Non-autoimmune	Unclassifiable	Unclassifiable
idiopathic pulmonary fibrosis	J841	5163005	IPF	IPF	IPF
pulmonary fibrosis	J841	5150011	IPF	IPF	IPF
combined pulmonary fibrosis and emphysema	J841	8849927	IPF	IPF	IPF
Idiopathic nonspecific interstitial pneumonia	J841	8850547	Non-autoimmune	iNSIP	iNSIP

nonspecific interstitial pneumonia	J841	8845727	Non-autoimmune	iNSIP	iNSIP
acute interstitial pneumonia	J84.1	1363003	Non-autoimmune	Other IIPs	Other IIPs
respiratory bronchiolitis-associated interstitial lung disease	J841	8845663	Non-autoimmune	Other IIPs	Other IIPs
cryptogenic organizing pneumonia	J841	8845714	Non-autoimmune	Other IIPs	Other IIPs
desquamative interstitial pneumonia	J841	8845719	Non-autoimmune	Other IIPs	Other IIPs
lymphocytic interstitial pneumonia	J841	5168010	Non-autoimmune	Other IIPs	Other IIPs
-	-	-	Non-autoimmune	Unclassifiable	Unclassifiable
interstitial pneumonia	J849	4860015	Non-autoimmune	Unclassifiable	Unclassifiable
interstitial lung disease	J849	5168003	Non-autoimmune	Unclassifiable	Unclassifiable
respiratory disorder in dermatosclerosis	M348	8844510		SSc-ILD	SSc-ILD
respiratory disorder complicated by granulomatosis with polyangiitis	M313	8848382		other CTD-ILD	other CTD-ILD
lupus pneumonia	M321	8844341		SLE-ILD	SLE-ILD

systemic lupus erythematosus interstitial pneumonia	M321	8848278		SLE-ILD	SLE-ILD
respiratory disorder in systemic lupus erythematosus	M321	8836513		SLE-ILD	SLE-ILD
interstitial pneumonia in juvenile dermatomyositis	M330	8848267		PM/DM-ILD	PM/DM-ILD
interstitial pneumonia in dermatomyositis	M331	8848302		PM/DM-ILD	PM/DM-ILD
respiratory disorder in dermatomyositis	M331	8839362		PM/DM-ILD	PM/DM-ILD
interstitial pneumonia in polymyositis	M332	8848283		PM/DM-ILD	PM/DM-ILD
respiratory disorder in polymyositis	M332	8837013		PM/DM-ILD	PM/DM-ILD
respiratory disorder in Sjogren's syndrome	M350	8834158		Sjogren-ILD	Sjogren-ILD
interstitial pneumonia due to collagen disease	M351	8848245		other CTD-ILD	other CTD-ILD
rheumatoid lung disease	M0510	8840951		other CTD-ILD	
rheumatoid arthritis interstitial pneumonia	M0510	8847737		RA-ILD	RA-ILD

N-Total number of study patients in each ILD underlying autoimmune disease category, IPF – Idiopathic Pulmonary Fibrosis, iNSIP – Idiopathic Nonspecific Interstitial Pneumonia, IIP – Idiopathic Interstitial Pneumonia, SSc-ILD – Systemic Sclerosis- Associated ILD, RA-ILD – Rheumatoid-Associated ILD, SLE-ILD – Systemic Lupus Erythematosus ILD, PM/DM ILD – Polymyositis/Dermatomyositis ILD

Disease	ICD-10 Code	billing code	Linkage Fibrotic code	Underlying Autoimmune Disease	ILD Category	Pre-Specified ILD Clinical Diagnosis
Sjogren's syndrome	M350	7102001	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Sjogren ILD
Sjogren's syndrome myopathy	M350	8841440	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Sjogren ILD
respiratory disorder in Sjogren's syndrome	M350	8834158	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Sjogren ILD
primary Sjogren's syndrome	M350	8848230	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Sjogren ILD
secondary Sjogren's syndrome	M350	8848298	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Sjogren ILD

overlap syndrome	M351	8841317	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
anti-ARS antibody syndrome	M351	8850417	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
mixed connective tissue disease	M351	7109008	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	MCTD-ILD	MCTD-ILD
interstitial pneumonia due to collagen disease	M351	8848245	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
Behcet's disease	M352	1361002	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
vulval Behcet's disease	M352	1361011	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD

ocular Behcet's disease	M352	8845881	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
vasculo-Behcet's disease	M352	1361009	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
oral Behcet's disease	M352	1361010	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
neuro-Behcet disease	M352	1361005	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
entero-Behcet disease	M352	8842203	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
incomplete Behcet disease	M352	8846052	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
polymyalgia rheumatica	M353	7250004	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD

diffuse eosinophilic fasciitis	M354	8839540	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
eosinophilic fasciitis	M354	7294009	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
acrosclerosis	M355	7108005	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
multifocal fibrosclerosis	M355	8836987	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
Weber-Christian disease	M356	8830767	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
hyperkinetic syndrome	M357	7285007	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD

familial ligament relaxation	M357	8831279	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
eosinophilia-myalgia syndrome	M358	7101038	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
IgG4-related disease	M359	8848113	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
systemic autoimmune disease	M359	8836526	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
collagen disease	M359	7109004	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
anemia associated with collagen disease	M359	8833428	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
pericarditis of collagen disease	M359	4239017	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmune/CTD ILD	Other-autoimmune/CTD ILD
polyarteritis nodosa	M300	8833125	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD

eosinophilic granulomatosis with polyangiitis	M301	8848338	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
juvenile multiple arteritis	M302	8835258	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
acute febrile mucocutaneous lymph node syndrome	M303	4461009	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
Kawasaki's disease	M303	4461003	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
ischemic heart disease due to Kawasaki's disease	M303	8831474	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
Kawasaki disease-related coronary artery aneurysm	M303	4461004	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
incomplete Kawasaki disease	M303	8846336	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
polyangiitis overlap syndrome	M308	8837016	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD

skin polyarteritis nodosa	M308	8846209	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
cutaneous arteritis	M308	8849445	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
Goodpasture's syndrome	M310	4462001	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
hypersensitivity vasculitis	M310	4462002	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
cutaneous leukocytoclastic vasculitis	M310	8851019	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
drug-induced hypersensitivity vasculitis	M310	8844108	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
thrombotic thrombocytopenic purpura	M311	4466002	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
thrombotic microangiopathy	M311	8833136	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
acquired thrombotic thrombocytopenic purpura	M311	8849965	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
congenital thrombotic thrombocytopenic purpura	M311	8847881	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
gangrenous rhinitis	M312	4609006	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD

localized granulomatosis with polyangiitis	M313	8848336	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
generalized granulomatosis with polyangiitis	M313	8848371	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
granulomatosis with polyangiitis	M313	8848381	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
respiratory disorder complicated by granulomatosis with polyangiitis	M313	8848382	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
Takayasu's arteritis	M314	8848380	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
aortitis syndrome	M314	4467003	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
-	-	-	-	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
giant cell arteritis	M316	4465001	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD

microscopic polyangiitis	M317	8842086	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
ANCA-associated vasculitis	M318	8845513	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
hypocomplementemic urticarial vasculitis	M318	8849413	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
necrotizing angitis	M319	4460015	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD
polyangiitis	M319	4460017	J84.1, J84.8, J84.9, J99.0, J99.1	Autoimmune	Other-autoimmue/CTD ILD	Other-autoimmue/CTD ILD

N-Total number of study patients in each ILD underlying autoimmune disease category,
SSc-ILD – Systemic Sclerosis- Associated ILD, RA-ILD – Rheumatoid-Associated ILD, SLE-ILD – Systemic Lupus Erythematosus ILD, PM/DM ILD – Polymyositis/Dermatomyositis ILD

CTD-ILD – connective tissue disease- associated ILD, MCTD-ILD – Mixed Connective Tissue Disease-ILD

ANNEX 7. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol 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
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

** After review by Global TM for function*

Study Title:
Iincidence probability of progression to progressive fibrosing interstitial lung diseases (PF-ILDs) in non-IPF fibrosing ILD patients and their current management and treatments in Japan
Study Number:

Protocol Version:
Version 1.2

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

Position: PI Name/Date: **N/A** Signature: _____

Position: NIS [redacted] Name/Date: [redacted] Signature: _____

Position: Japan Med [redacted] Name/Date: Signature: _____

Position: Global TM Epi Name/Date: Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____