Non-Interventional Study (NIS) Protocol

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BI Investigational Product(s):	Not applicable
Title:	Characteristics and Management of Patients with CTD Related ILD National - Multicentric Database (2023-2024)
Brief lay title:	IMETA CTD-ILD Chart Review
Protocol version identifier:	V2
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Medicinal product:	Not applicable
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	Boehringer Ingelheim MENA
Joint PASS:	No
Research question and objectives:	Describe CTD-ILD patient, demographics, and clinical characteristics
Country(-ies) of study:	Turkey, UAE, Kuwait, Egypt, Saudi Arabia
Author:	Bulent Bagci MD, PhD, bulent.bagci@boehringer-ingelheim.com, Mostafa Ibrahim mostafa.ibrahim@boehringer-ingelheim

Marketing authorisation holder(s):	Boehringer Ingelheim MENA
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:	17.MAY.2023
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2. LIST OF ABBREVIATIONS

AS	Ankylosing Spondylitis
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CT	Computed Tomography
CTD	Connective Tissue Disease
DLCO	Diffusing Capacity for Carbon Monoxide
DM	Dermatomyositis
EC	Ethics Committee
EDC	Electronic Data Capture
HRCT	High-resolution Computed Tomography
FVC	Forced Vital Capacity
ILA	Interstitial Lung Abnormalities
ILD	Interstitial Lung Disease
IIP	Idiopathic Interstitial Pneumonia
MCTD	Mixed Connective Tissue Disease
PM	Polymyositis
PSS	Progressive Systemic Sclerosis
SLE	Systemic Lupus Erythematosus
SS	Sjogren's Syndrome
RA	Rheumatoid Arthritis

3. RESPONSIBLE PARTIES

BI NIS lead: Mostafa Ibrahim

4. ABSTRACT

Interstitial lung disease (ILD) encompasses a heterogeneous group of diseases including idiopathic interstitial pneumonia (IIP) and lung diseases associated with environmental/occupational exposures or systemic diseases[1,2]. Connective tissue disease (CTD) is one of the common systemic diseases associated with ILD. CTD is defined as systemic disorders characterized by autoimmune-mediated organ damages and circulating autoantibodies[3].

The connective tissue diseases (CTDs) constitute a group of auto-immune disease and their common denominator is damage to components of connective tissue at a variety of sites in the body. The CTDs depicting features of ILD include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), progressive systemic sclerosis (PSS), dermatomyositis (DM) and polymyositis (PM), ankylosing spondylitis (AS), Sjogren's syndrome (SS), and mixed connective tissue disease (MCTD).

Previous studies have clearly shown that the presence of CTD in ILD has great impact on the prognosis[4,5]. Furthermore, the treatment options are dependent upon the underlying CTD.

Hence, the guidelines emphasize the classification of ILD based on etiologies and uniformly recommended search for evidence of CTD in newly diagnosed ILDs[1,6,7]. However, due to complexities in diagnosis and treatment of CTD itself and lack of evidence, current guidelines do not clearly provide strategies for evaluation and management of CTD-ILD despite its significance.

This study aims to describe CTD-ILD patient, demographics, and clinical characteristics and also describe the management of CTD-ILD disease from symptoms to treatment considering comorbidities, complications, and concomitant medications.

Name of company: Boehringer Ingelheim MENA			
Name of finished medicinal product: Not applicable			
Name of active ingredient: Not applicable			
Protocol date: *24.JAN.2023*	**Study number:** 1199-0525	**Version/Revision:** 2.0	**Version/Revision date:** 17.MAY.2023
Title of study:	Characteristics and Management of Patients with CTD Related ILD National - Multicentric Database (2023-2024)		
Rationale and background:	There is little to no local information on patients with CTD-ILD in IMETA. The study aims to fill this knowledge gap by describing CTD-ILD patient, demographics, and clinical characteristics and also describing the management of CTD-ILD disease from symptoms to treatment considering comorbidities, complications, and concomitant medications.		
Research question and objectives:	This study aims to describe CTD-ILD patient, demographics, and clinical characteristics and also describe the management of CTD-ILD disease from symptoms to treatment considering comorbidities, complications, and concomitant medications.		
Study design:	Non-interventional study using existing data		
Population:	Inclusion Criteria: • 18 years and older. • All patients who were diagnosed as CTD-ILD between January 2018 and December 2019. Exclusion Criteria: • Patients under 18 years.		
Variables:	• Demographics: Age, sex, job, smoking status, comorbidities, concomitant medication • Clinical Information: CTD type and diagnosis date, ILD diagnosis date, symptoms, HRCT, 6 min walking test, FVC, DLCO, lung biopsy • Laboratory Information: Antinuclear antibody, rheumatoid factor, creatinine kinase, CRP, erythrocyte sedimentation rate, anti-ro, anti-la, anti-Scl70, anti-Smith antibody • Prescribed treatment for CTD, CTD-ILDs and accompanying symptoms		

Data sources:	Approximately 20 participating centers will be chosen from rheumatology and pulmonology departments. Data will be collected by primary investigator or authorized representative. All data will be taken from patient's medical records and patients do not need to have a visit for study. The data will be collected depending on the availability.
Study size:	The study is anticipated to include approximately 400 patients from 20 sites. This study is a retrospective study. Even though no hypothesis will be formally tested, patient journey will be assessed. Accordingly, no formal sample size calculation has been performed.

Data analysis:	Because of the nature and design of the study, since the secondary data will be used, it is expected that missing data will be encountered. For each variable number and percentage of missing data will be given. Also due to retrospective nature, no follow-up will be conducted during the study. Data will be appropriately summarized and analysed using tabulation and graphs with respect to demographic/baseline characteristics and treatment groups (immunosuppressive therapies, immunomodulators and monoclonal antibodies, etc) . Standard descriptive summary statistics (i.e., n, arithmetic mean, and standard deviation, median, minimum /maximum value - quartiles, if appropriate) will be calculated for continuous variables. Categorical data will be presented in frequency tables using counts and percentages. Summary tables will be displayed for each treatment group and for the total of the sample. Change in parameters compared to will be performed with t-test, Mann Whitney U test and Chi-square test, or whenever applicable with Fisher's exact test. Primary Outcome Analysis: Demographics: age, sex, job, smoking status, comorbidities, concomitant medication. Clinical characteristics: CTD type and diagnosis year, ILD diagnosis year, symptoms, HRCT, 6 min walking test, FVC, DLCO, lung biopsy Laboratory parameters: antinuclear antibody, rheumatoid factor, creatinine kinase, CRP, erythrocyte sedimentation rate, anti-ro, anti-la, anti Scl70, anti-Smith antibody will be described as min-max, median, standard deviation and frequencies where applicable. Secondary Outcomes Analysis: • Time from symptoms to diagnosis will be calculated as days and expressed as min max and median. • Time from diagnosis to treatment initiation will be calculated as days and expressed as min max and median.

Milestones:		
	Milestone	**Planned Date**
	IRB/IEC approval	*FEB 2023*
	Start of data collection	*MAR 2023*
	End of data collection	*MAR 2024*
	Final report of study results:	*JUN 2024*

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	*FEB 2023*
Start of data collection	*MAR 2023*
End of data collection	*MAR 2024*
<Study progress report 1>	*APR 2023*
<Study progress report 2>	*SEP 2023*
<Study progress report 3>	*JAN 2024*
<Interim report 1>	*SEP2023*
<Registration in the EU PAS register>	*N/A*
Final report of study results:	*JUN 2024*

7. RATIONALE AND BACKGROUND

Interstitial lung disease (ILD) encompasses a heterogeneous group of diseases including idiopathic interstitial pneumonia (IIP) and lung diseases associated with environmental/occupational exposures or systemic diseases[1,2]. Connective tissue disease (CTD) is one of the common systemic diseases associated with ILD. CTD is defined as systemic disorders characterized by autoimmune-mediated organ damages and circulating autoantibodies[3].

The connective tissue diseases (CTDs) constitute a group of auto-immune disease and their common denominator is damage to components of connective tissue at a variety of sites in the body. The CTDs depicting features of ILD include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), progressive systemic sclerosis (PSS), dermatomyositis (DM) and polymyositis (PM), ankylosing spondylitis (AS), Sjogren's syndrome (SS), and mixed connective tissue disease (MCTD).

Previous studies have clearly shown that the presence of CTD in ILD has great impact on the prognosis[4,5]. Furthermore, the treatment options are dependent upon the underlying CTD. Hence, the guidelines emphasize the classification of ILD based on etiologies and uniformly recommended search for evidence of CTD in newly diagnosed ILDs[1,6,7]. However, due to complexities in diagnosis and treatment of CTD itself and lack of evidence, current guidelines do not clearly provide strategies for evaluation and management of CTD-ILD despite its significance.

There is little to no local information on patients with CTD-ILD in IMETA. The study aims to fill this knowledge gap by describing CTD-ILD patient, demographics, and clinical characteristics and also describing the management of CTD-ILD disease from symptoms to treatment considering comorbidities, complications, and concomitant medications.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective is:

- To describe CTD-ILD patient, demographics, and clinical characteristics

Secondary objectives:

- To describe the management of CTD-ILD disease from symptoms to treatment considering comorbidities, complications, and concomitant medications

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, multicenter study using existing data, chart review that incorporates data generated during assessments and visits conducted as per local standard medical practice, local label, and reimbursement guidelines.

An eligible patient data will be entered into the chart review after the investigator determines that the patient records meet all eligibility criteria. No identifying data for the patient will be collected.

Because of the nature and design of the study, since the secondary data will be used, it is expected that missing data will be encountered.

As all data will be taken from patient's medical records, patients do not need to have a visit for the study. And the parameters that will be collected are routine procedures, these data will be available at the hospital records.

Primary objective is:

- To describe CTD-ILD patient, demographics, and clinical characteristics

9.1.1 Primary outcomes

- Demographics, patient / clinical characteristics will be given as a tabulation. Demographics like age, sex, job, smoking status, comorbidities, concomitant medication, clinical characteristics like CTD type and diagnosis year, ILD diagnosis year, symptoms, HRCT, 6 min walking test, FVC, DLCO, lung biopsy and laboratory parameters like antinuclear antibody, rheumatoid factor, creatinine kinase, CRP, erythrocyte sedimentation rate, anti-ro, anti-la, anti-Scl70, anti-Smith antibody will be described

9.1.2 Secondary objectives

- To describe the management of CTD-ILD disease from symptoms to treatment considering comorbidities, complications, and concomitant medications

9.1.3 Secondary outcomes

- Time from first ILD symptoms to diagnosis of CTD-ILD (i.e. lung involvement on HRCT) will be calculated as days and expressed as min max and median.
- Time from diagnosis to treatment initiation will be calculated as days and expressed as min max and median.

9.2 SETTING

The study population will consist of approximately 400 male and female patients with medically confirmed diagnosis of CTD-ILD (i.e. lung involvement on HRCT) between January 2018 and December 2019.
Secondary data (medical records) will be used.

9.2.1 Study sites

Due to nature of the disease require mostly multidisciplinary care, 20 participating centers will be chosen from rheumatology and pulmonology departments. For the site selection sites will be evaluated according to the data sources availability and potential for the target population.

9.2.2 Study population

All patient's data will be collected from participating sites according to the below criterias;

Inclusion Criteria

18 years and older.
All patients who were diagnosed as CTD-ILD between January 2018 and December 2019.

Exclusion Criteria

Patients under 18 years.

9.2.3 Study visits

This study designed as a non-interventional study using existing data, there is not predefined treatment and visit schedule.

9.2.4 Study discontinuation

Not applicable since it is NIS with existing data.

9.3 VARIABLES

- Demographics: Age, sex, job, smoking status, comorbidities, concomitant medication
- Clinical Information: CTD type and diagnosis date, ILD diagnosis date, symptoms, HRCT, 6 min walking test, FVC, DLCO, lung biopsy
- Laboratory Information: Antinuclear antibody, rheumatoid factor, creatinine kinase, CRP, erythrocyte sedimentation rate, anti-ro, anti-la, anti-Scl70, anti-Smith antibody
- Prescribed treatment for CTD, CTD-ILDs and accompanying symptoms

9.3.1 Exposures

This is a non-interventional study using existing data. All the data that will be collected consist of hospital medical records. Due to nature of this type study design there is not any predefined treatment and visit schedule.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

As all data will be taken from patient's medical records, patients do not need to have a visit for the study. And the parameters that will be collected are routine procedures, these data will be available at the hospital records.

Primary objective is:

- To describe CTD-ILD patient, demographics, and clinical characteristics

Primary outcome:

- Expression of demographics, patient / clinical characteristics. This will be given as a tabulation. Demographics like age, sex, job, smoking status, comorbidities, concomitant medication, clinical characteristics like CTD type and diagnosis year, ILD diagnosis year, symptoms, HRCT, 6 min walking test, FVC, DLCO, lung biopsy and laboratory parameters like antinuclear antibody, rheumatoid factor, creatinine kinase, CRP, erythrocyte sedimentation rate, anti-ro, anti-la, anti-Scl70, anti-Smith antibody will be described
- Time Frame: Initiation of the data collection to the end of the data collection

- Safety Issue: No

9.3.2.2 Secondary outcomes

Secondary objectives:

- To describe the management of CTD-ILD disease from symptoms to treatment considering comorbidities, complications, and concomitant medications

Secondary outcomes:

- Time from first ILD symptoms to diagnosis of CTD-ILD (i.e. lung involvement on HRCT) will be calculated as days and expressed as min max and median.
- Time from diagnosis to treatment initiation will be calculated as days and expressed as min max and median.
- Safety Issue: No

9.3.2.3 Further outcomes

Not applicable

9.3.3 Covariates

The covariates listed below will be collected during medical record abstraction to describe patient and clinical characteristics. These covariates will also be considered for use as stratifying variables.

- Patient age (in years)
- Patient sex (male/female)
- CTD-ILD disease characteristics and treatment:
    - Year of CTD initial diagnosis
    - Year of ILD initial diagnosis
    - HRCT
    - 6 min walking test
    - FVC
    - DLCO

9.4 DATA SOURCES

20 participating centers will be chosen from rheumatology and pulmonology departments. Data will be collected by primary investigator or authorized representative.

All data will be taken from patient's medical records and patients do not need to have a visit for study. The baseline and following visit data will be collected depending on the

availability. The baseline is defined as time of first ILD symptoms and/or first HRCT scan showing lung involvement.

Some of the centers use only electronic records and some of them use both electronic and paper-based records. Data will be entered to electronic case report forms specially designed for the study from the hospital records.

Patients' clinical data will be extracted from both structured and unstructured documents (e.g. physician notes and scanned lab reports) within patients' electronic and paper based health records.

Eligibility will be checked in accordance with the inclusion criteria, all patient's data have to be in concordant with the inclusion criteria.

Since there has been pandemic by the beginning of 2020, covid would have changed the treatment patterns, patient registration and referrals to hospitals and patient follow ups. In general, pandemic may have an impact on patient journey and management, so in order to avoid any bias and see the real picture, we rather take the period before 2020. The period that will be covered is from 2018 to 2019.

9.5 STUDY SIZE

The study population will consist of approximately 400 male and female patients with medically confirmed diagnosis of CTD-ILD (i.e. lung involvement on HRCT) between January 2018 and December 2019.
Secondary data (medical records) will be used.
The study is anticipated to include approximately 400 patients from 20 sites.
This study is a retrospective study. Eventhough, no hypothesis will be formally tested, patient journey will be assessed. Accordingly, no formal sample size calculation has been performed.

9.6 DATA MANAGEMENT

The data management plan is summarized below.
A contract research organization (CRO), will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC). In the event of discrepant data, CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

9.7 DATA ANALYSIS

Because of the nature and design of the study, since the secondary data will be used, it is expected to that missing data will be encountered. For each variable number and percentage of missing data will be given. Also due to NIS using existing data, no follow-up will be conducted during the study.

Data will be appropriately summarized and analysed using tabulation and graphs with respect to demographic/baseline characteristics and treatment groups (immunosuppressive therapies, immunomodulators and monoclonal antibodies, etc) . Standard descriptive summary statistics (i.e., n, arithmetic mean, and standard deviation, median, minimum /maximum value - quartiles, if appropriate) will be calculated for continuous variables. Categorical data will be presented in frequency tables using counts and percentages. Summary tables will be displayed for each treatment group and for the total of the sample. Change in parameters compared to will be performed with t-test, Mann Whitney U test and Chi-square test, or whenever applicable with Fisher's exact test.

9.7.1 Main analysis

Primary Outcome Analysis:

Demographics: age, sex, job, smoking status, comorbidities, concomitant medication.
Clinical characteristics: CTD type and diagnosis year, ILD diagnosis year, symptoms, HRCT, 6 min walking test, FVC, DLCO, lung biopsy
Laboratory parameters: antinuclear antibody, rheumatoid factor, creatinine kinase, CRP, erythrocyte sedimentation rate, anti-ro, anti-la, anti Scl70, anti-Smith antibody will be described as min-max, median, standard deviation and frequencies where applicable.

Secondary Outcomes Analysis:

- Time from symptoms to diagnosis will be calculated as days and expressed as min max and median.
- Time from diagnosis to treatment initiation will be calculated as days and expressed as min max and median.

9.7.2 Further analysis

Not applicable

9.7.3 Safety Analysis

Not applicable for this NIS since the safety and efficacy data will not be collected.

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below.

The sponsor and its representative must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments and documentation of EC.

The sponsor shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

All eCRFs should be completed by designated trained site staff. ECRFs should be reviewed and electronically signed and dated by the physician or a designee. E-CRF data entry could also be done by trained and authorized CRO staff.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in the clinical study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Because of the nature and design of the study, since the secondary data will be used, it is expected that missing data will be encountered. For each variable number and percentage of missing data will be given.

Since this is not a prospective study, this study will use data from hospital records, there are a number of limitations. After diagnosis, each patient's follow-up period could differ due to lost to follow-up. Follow-up time will be given as median, min and max months. Although queries will be created during the study for inconsistencies within the data management activities, due to retrospective design, data entry errors could occur.

Centers will be chosen according to the required parameters that can supply and give commitment to adequate data. Nevertheless, it is possible that some information may be missing. Generally, the data to be collected is available in various sources, including electronic and paper based. There is a slight possibility of encountering missing information in patients whose laboratory data are followed on another platform. Missing data will also be listed as unknown to the database; valid number of "n" will be given. In order to avoid bias, all sites will include each eligible patient according to the protocol even if the patient has some missing data.

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 or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence of this study.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture, if applicable.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
Data reported *entered in the* eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

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

9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents.
CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). BI study staff and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

10. PROTECTION OF HUMAN SUBJECTS

No safety data will be collected as per the approval of ethics committee.

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional study using existing data based on secondary data sources, therefore prospective follow-up of individual adverse events is not applicable. Treatment active ingredients and their efficacy / safety data will not be collected, so the collection of data and reporting of adverse event will not be applicable.

11.1 DEFINITIONS OF ADVERSE EVENTS

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

Adverse drug reaction
An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

The following are considered as AESIs:

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

Not applicable for this study since safety and efficacy data will not be collected.

11.3 REPORTING TO HEALTH AUTHORITIES

Not applicable for this study since safety and efficacy parameters will not be collected.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

13. REFERENCES

13.1 PUBLISHED REFERENCES

1. American Thoracic Society, European Respiratory Society, American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias, This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001, Am. J. Respir. Crit. Care Med. 165 (2002) 277–304. R09-05338

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6. G. Raghu, M. Remy-Jardin, J. et al. E.R.S.J.R.S. American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, Latin American Thoracic Society Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med; 2018; 198(5); e44-e68. R18-2794

7. Wells AU, Hirani N, British Thoracic Society Interstitial Lung Disease Guideline Group. A. Thoracic Society of, S. New Zealand Thoracic, S. Irish Thoracic, Interstitial lung disease guideline: the British thoracic society in collaboration with the thoracic society of Australia and New Zealand and the Irish Thoracic Society, Thorax 63 (Suppl. 5) (2008) v1–58. P08-12186

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

None

ANNEX 4. 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:

Study Number:

Protocol Version:

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

Position: ___ Name/Date: _____ Signature**:** _____

Position: Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

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Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

APPROVAL / SIGNATURE PAGE

Document Number: c41097080 **Technical Version Number:2.0**

Document Name: non-interventional-study-protocol-v1

Title: Characteristics and Management of Patients with CTD Related ILD National - Multicentric Database (2023-2024)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author	Ibrahim,Dr.,Mostafa	30 Oct 2023 11:57 CET
Approval-Head Medical Affairs	Karakurum,Dr.,Caglar	30 Oct 2023 12:04 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed