TITLE PAGE

TRIAL STATISTICAL ANALYSIS PLAN

c11675456 - 02

BI Trial No.:	BI 1199.252
Title:	Investigating the Idiopathic Pulmonary Fibrosis (INDULGEIPF)
Investigational Product(s):	Not Applicable
Responsible trial statistician(s):	[redacted] Tel.: [redacted], Fax: [redacted]
Date of statistical analysis plan:	13 May [redacted] 2020
Version:	2.0
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
ALT	Alanine Aminotransferase
Anti-VEGF	Anti–vascular endothelial growth factor
AST	Aspartate Transaminase
BNP	B-type natriuretic peptide
BRPM	Blinded Report Planning Meeting
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CPET	Cardiopulmonary Exercise Test
CRF	Case Report Form
DMG	Dictionary Maintenance Group
ECG	Electrocardiogram
FAS	Full Analysis Set
GERD	Gastroesophageal Reflux Disease
HRCT	High-resolution computed tomography
ICH	International Conference On Harmonisation
ILD	Interstitial lung disease
IPF	Idiopathic Pulmonary Fibrosis.
MedDRA	Medical Dictionary For Regulatory Activities
NOAC	Novel Oral Anticoagulant
NSAID	Nonsteroidal anti-inflammatory drugs
NTproBNP	N-terminal pro b-type natriuretic peptide
PT	Preferred Term
PV	Protocol Violation
SEAP	Statistical and Epidemiological Analysis Plan
SD	Standard Deviation
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

"As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data in order to support future publications based on IPF patients.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 9.8 "Data Analysis". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization".

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

As described in the study protocol only descriptive analysis will be applied for the purpose of the present study. Further to the summary tables of frequencies and measures of central tendency, Kaplan Meier curves will be produce to illustrate the survival distribution of patients in the study.

Analysis of the baseline characteristics was decided to be performed when all subjects had entered the trial.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The main objective of this IPF registry is to gain further knowledge on the characteristics, management, progression and outcomes of patients with IPF as treated under real-world, clinical practice conditions in Greece.

More specifically, this registry is going to:

• Provide a comprehensive clinical picture for IPF

• Track access to health care and cost of caring for IPF patients over time

• Examine the implementation of treatment guidelines, used on patients diagnosed with IPF, according to the existing diagnosis guidelines

• Characterize patients on different treatments.

Endpoints are targeting the description of the following:

- Demographic data including age, gender and race, employment status and insurance status.
- Change from baseline in vital signs as measured at 3,6,12,18 and 24 months following to the baseline visit.
- Vital Status.
- Cardiopulmonary exercise testing (6-minute walk distance and CPET, if performed)
- Change from baseline in 6-minute walk distance VO2max (CPET) as measured at 3,6,12,18 and 24 months following to the baseline visit.
- IPF risk factors as measured at baseline visit: (cigarette smoking including pack years, alcohol and substance abuse, environmental and occupational exposure, exposure to drugs associated with IPF, exposure to viral infection possibly related to IPF, gastro - oesophageal reflux, genetic factors - family history).
- Description of the comorbidities throughout the trial.
- Risk of bleeding and thrombosis as stated in the CRF.
- Description of the newly diagnosed patients of acute respiratory worsening, exacerbations, and hospitalization due to any cause and due to IPF.
- Description of the intensity of treatment, frequencies and resource utilization for pharmaco-economic analyses.
- Description of methods and procedures used in the diagnosis of IPF and time since diagnosis.
- Description of IPF symptoms (dyspnea, cough, weight loss, fatigue, dizziness, chest pain, anxiety, clubbing, bibasilar crackles)

- Description of autoimmune biomarker.
- Description of lung function and/or exercise capacity.
- Description of IPF treatment modalities.
- Description of Physician's clinical rating of the probable course of IPF (stable, slow or rapid progression).
- Description of Clinical events and hospitalizations especially due to: (acute) respiratory worsening, including pneumonia, exacerbations of IPF, occurrence of pulmonary or cardiovascular complications, pulmonary rehabilitation, pulmonary embolism, pneumothorax, or cardiac failure.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

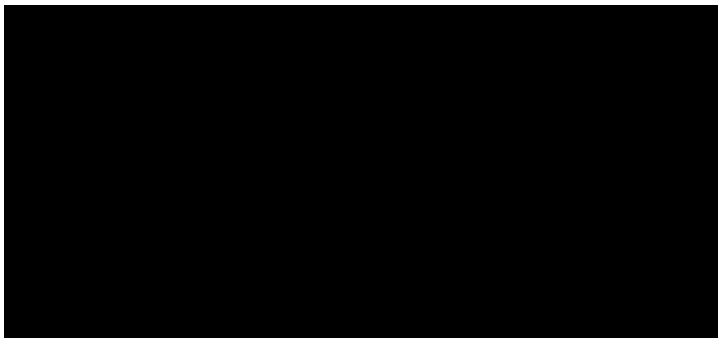
Not applicable. No key secondary endpoints have been specified in the protocol.

5.2.2 Secondary endpoint(s)

As secondary objective is to document in details the concomitant medication of specific drugs. Therefore, as secondary endpoints the drug name, dosage, duration of administration of each of the following drugs and their combinations will be summarized.

- Steroids
- Immunomodulators (azathioprine, cyclophosphamide, cyclosporine A, mycophenolate mofetil etc)
- N-Acetylcysteine
- Pirfenidone
- Nintedanib
- Anticoagulants
- Vit-K antagonist
- Heparin
- Antiplatelet therapy (if yes it will be specified if high dose antiplatelet therapy)
- Aspirin (if yes it will be specified if used as antiplatelet)
- GERD medication
- PDE-5 inhibitor (sildenafil, tadalafil)
- Endothelin receptor antagonist (bosentan, ambrisentan, macitentan)
- Long term oxygen therapy
- Listed for lung transplantation
- NSAIDs, other than aspirin
- Hormone replacement therapy
- Hormonal contraceptives
- Anti-VEGF drugs

- NOAC
- Other (specify).



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

This is a non-international study and no treatment arms are considered for this trial. The subjects can receive treatment according to the standard practice for the IPF management.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Important PVs are those that can potentially influence the primary outcome measure for the respective subjects in a way that is neither negligible nor in accordance with the study objectives. All study inclusion/exclusion criteria are of equal importance.

Inclusion Criteria

- Newly diagnosed (less than 6 months) or patients previously diagnosed with IPF (more than 6 months prior to baseline visit),based upon the consensus statement jointly issued by ATS/ERS/JRS/ALAT in 2011 (see Annexes 6 and 7 on HRCT and histological criteria in Annex 6).
- Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)
- Evaluation of IPF with HRCT or combinations of HRCT and surgical lung biopsy, if available
- Age ≥40 years old at the time of inclusion
- Written informed consent for participation in the registry
- Patients that can be further followed up by the investigator, during the scheduled study period

Exclusion Criteria

- Expected lung transplantation within the following 6 months
- Participation in clinical trials

6.3 SUBJECT SETS ANALYSED

The statistical analysis of the study will be based on the Full Analysis Set (FAS).
FAS is comprised of all subjects enrolled in the study with at least one measurement of the primary endpoint during the trial. This population will be used to run any statistics of the study. As there is no BI medication or product given for this study, there is not going to be any Treated Set. Therefore, any safety analysis will be performed also in the FAS.

[redacted]

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because no statistical modelling will be employed.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No imputation technique to fill in any missing values will be performed. Accordingly the Last Observation Carried Forward technique will not be applied.
Missing values will be differentiated from negative answers.
Summary statistics will be performed only on subjects with available information (unknown data will not account in the total population for each specific variable).
For missing or incomplete AE dates or drug administration dates, or other significant dates, the BI internal procedures and guidelines will be employed.

Missing dates related to AE events will not be imputed since no analysis based on duration of AEs or time to event will be employed:

Missing dates related to deaths will be handled according to BI standards and therefore, no subjects with incomplete date of death will be included in the time to event analysis.

Regarding outliers, the distributional properties should be examined by PP and/or QQ plots in conjunction with the summary statistics of mean/median/SD. Should the distributional properties of a variable indicate the existence of outliers, then the values will not be neglected from the analysis, but the variance will be reduced following the logarithmic transformation.
Any implausible data will be treated separately and it will be judged based on case by case basis.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

No visit windows will be used. The CRF nominal visits will be applied for the analysis. Unscheduled visits are not expected and if any they will not be counted for primary and secondary endpoints. However, they will be considered for the safety analysis regarding Adverse Events (if any).

The baseline value will be the first measurement made after the enrolment to the study.

Baseline information will be presented appropriately in the “by visit” summaries.

7. PLANNED ANALYSIS

Continuous variables will be listed as mean value with standard deviation (SD) and median, along with minimum and maximum values (depending on the underlying distribution). The minimum and maximum values will have the precision of the data reported; mean, median values will have one additional decimal, whereas SD will have two additional decimals.
Categorical values will be listed as absolute and relative frequencies. Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers.

[redacted]

As soon as all patients are recruited and have the baseline visit recorded, then this visit will be analyzed. The information to be reported is shown at the corresponding revised display plan of the study, dated 24 April 2020.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned to be performed.

7.2 CONCOMITANT DISEASES AND MEDICATION

As concomitant medication is considered any treatment received after the enrollment to the study. Concomitant medication will be presented according to the CRF order.

Any comorbidity reported which started prior to the study enrollment will be summarized as medical history. Separate table will summarize all comorbidities started following to the participation to the study.

Only descriptive statistics are planned to be performed.

7.3 TREATMENT COMPLIANCE

Not applicable.

7.4 PRIMARY ENDPOINT(S)

Only descriptive statistics are planned to be performed in the overall sample as well in the stratified by time of diagnosis subgroups.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoint(s)

Only descriptive statistics are planned to be performed.

[redacted]

7.7 EXTENT OF EXPOSURE

This section is not applicable as this is an observational trial with no study treatment administration.

7.8 SAFETY ANALYSIS

7.8.1 Adverse events

Safety analysis will be performed in the FAS population. No stratified analysis for safety will be considered. All adverse events will be coded according to MedDRA dictionary.

The analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

The frequency of subjects with adverse events following the ICF signature will be summarized according to primary system organ class and preferred term (MedDRA version to be displayed in the tables). System organ classes will be sorted alphabetically, preferred terms will be sorted by frequency (within system organ class).

Summary statistics will be provided for the following categories: all AEs, all SAEs and AEs with causal relationship to BI medication. AE listings will also be provided.

7.8.2 Laboratory data

Summary of laboratory data (haemoglobin, AST, ALT, Total Bilirubin, BNP and NT pro-BNP) will be based on all lab data performed during the trial.

Descriptive statistics for the absolute value of all continuous evaluations and the change from baseline to study visits will be presented for each visit.

Change from baseline = post baseline value – baseline value.

The components of the *Differential Cell Count* (Lymphocytes, Macrophages, Granulocytes, Eosinophils) will be expressed as percentages (%) of the absolute cell count (e.g. lymphocytes [x/ml] / absolute cell count [y/ml])

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. Descriptive statistics for the absolute value of vital signs and the change from baseline to study visits will be presented for each visit.

Change from baseline = post baseline value – baseline value.

7.8.4 ECG

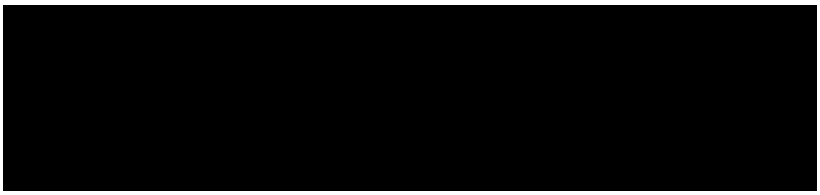
Not Applicable

7.8.5 Others

Not Applicable

8. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
[redacted]	
3	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports,current version



10. HISTORY TABLE

Only changes and reason for changes between the final signed version and the revised signed version(s) will be briefly explained using the "History table" (if applicable).
Changes between non-signed versions should not be recorded in this table.

Table 10: 1 History table

Version	Date	Author	Sections changed	Brief description of change
Initial	**21-FEB-2017**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Version 2.0	**13-MAY-2020**		4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY 7. PLANNED ANALYSIS 7.8.2 Laboratory data	This is the final revised to V2.0 TSAP

10. REVIEWERS AND APPROVAL SIGNATURES

Study Title: Investigating the Idiopathic Pulmonary Fibrosis (INDULGEIPF)

Study No: BI 1199.252

Protocol Version: 2.0

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

Position: TSTAT	[redacted] / Date: 13 May 2020	Signature: [redacted]
Position: TSTAT	[redacted] / Date:	Signature:
Position: NIS [redacted]	[redacted] / Date:	Signature: