TRIAL STATISTICAL ANALYSIS PLAN

BI Trial No.:	1199.280
Title:	An active surveillance to monitor the real world safety in Indian patients prescribed Nintedanib for the treatment of Idiopathic Pulmonary Fibrosis.
Investigational Product(s):	Nintedanib
Responsible trial statistician(s):	[redacted] Phone: [redacted] Email : [redacted]
Date of statistical analysis plan:	15-Mar-2019
Version:	Final 2.0

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2 LIST OF ABBREVIATIONS

Term	Definition / description
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Anti-Nuclear Antibody
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
BNP	Brain Natriuretic Peptide
CDISC	Clinical Data Interchange Standards Consortium
CK	Creatinine Kinase
Cr	Creatinine
CRF	Case Report Form
CRP	C-reactive Protein
CTP	Clinical Trial Protocol
DCGI	Drug Controller General of India
DLCO	Diffusing capacity or transfer factor of the lung for carbon monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GERD	Gastroesophageal Reflux Disease
GGT	Gamma-glutamyltransferase
HRCT	High-Resolution Computed Tomography

Term	Definition / description
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
IPF	Idiopathic Pulmonary Fibrosis
IPV	Important Protocol Violation
LDH	Lactate Dehydrogenase
LLT	Lowest Level Term
MedDRA	Medical Dictionary For Regulatory Activities
mMRC	modified Medical Research Council
NOAC	New Oral Anticoagulants
NSAIDs	Non-steroidal Anti-inflammatory Drugs
$PaCO_2$	Arterial CO_2 Pressure
PaO_2	Arterial O_2 Pressure
PASS	Post-authorization Safety Study
PDE	Phosphodiesterase
PT	Preferred Term
PT-INR	Prothrombin Time- International Normalized Ratio
Q1	Lower Quartile
Q3	Upper Quartile
RF	Rheumatoid factor
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
TEAE/TESS	Treatment Emergent Adverse Event
TSAP	Trial Statistical Analysis Plan
UIP	Usual interstitial pneumonia

Term	Definition / description
VEGF	Vascular Endothelial Growth Factor
WHO DD	World Health Organization Drug Dictionary

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.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP) version 5.0, dated [redacted] and Case Report Form (CRF) version final 3.0, dated [redacted]. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 10.7 'Data Analysis'. Also the 6 subjects (Subject ID: [redacted]) enrolled in the study based on inclusion\exclusion criteria of protocol version 2.0, dated [redacted] and remaining subjects are on protocol version 5.0. 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."

This TSAP is to contain the analysis specification for a status report of the active surveillance to be submitted to DCGI annually and for the final analysis

SAS® version 9.4 will be used for all analyses.

This is an active surveillance study and aim of this study to monitor the real world safety in Indian patients prescribed nintedanib for the treatment of Idiopathic Pulmonary Fibrosis (IPF). The scientific objective of this active surveillance is to obtain an estimate of the occurrence of all ADRs and SAEs in IPF patients prescribed nintedanib per the approved label in the real world setting. In addition, this study will also calculate the percentage of patients who require dose reductions, interruptions and discontinuation due to adverse events. This would help in assessing the safety of nintedanib in IPF patients in Indian real world setting.

4 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No changes made in the planned analysis of the study mentioned in the protocol version 5.0, dated 01 August 2018.

5 OUTCOMES

5.1 PRIMARY OUTCOMES

- Incidence of all ADRs in nintedanib treated patients
- Incidence of all SAEs in nintedanib treated patients

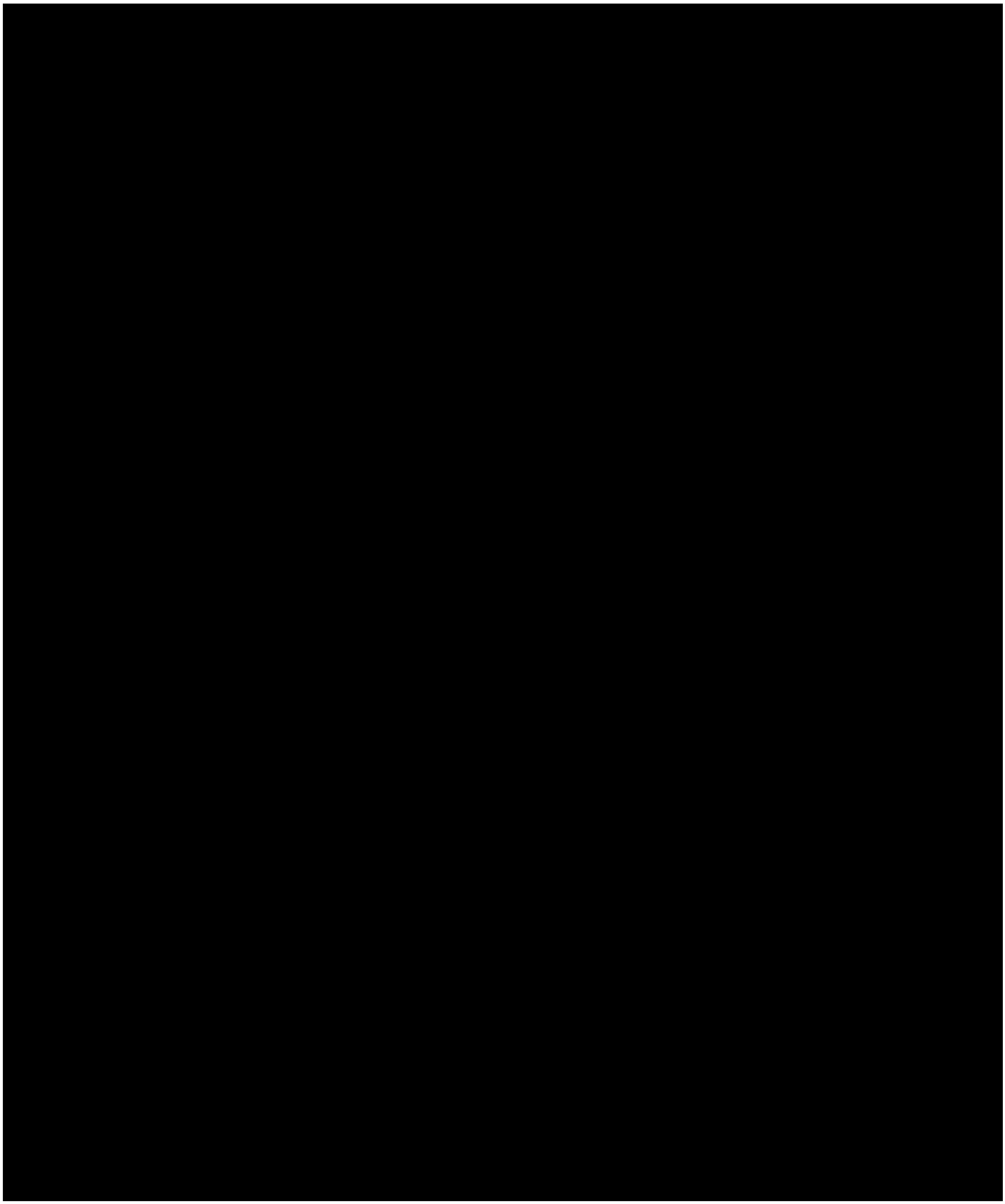
5.2 SECONDARY OUTCOMES

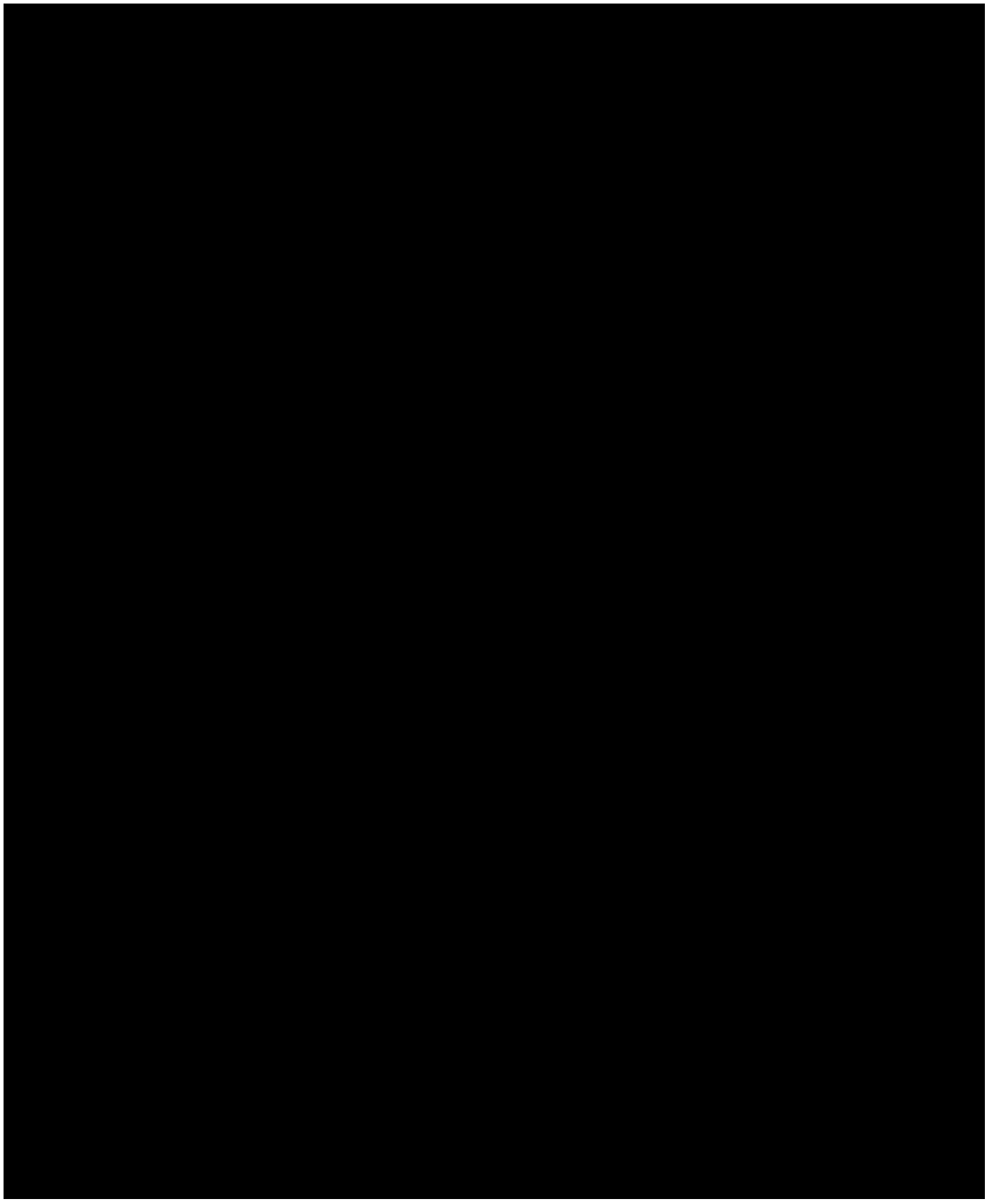
5.2.1 Key secondary outcome

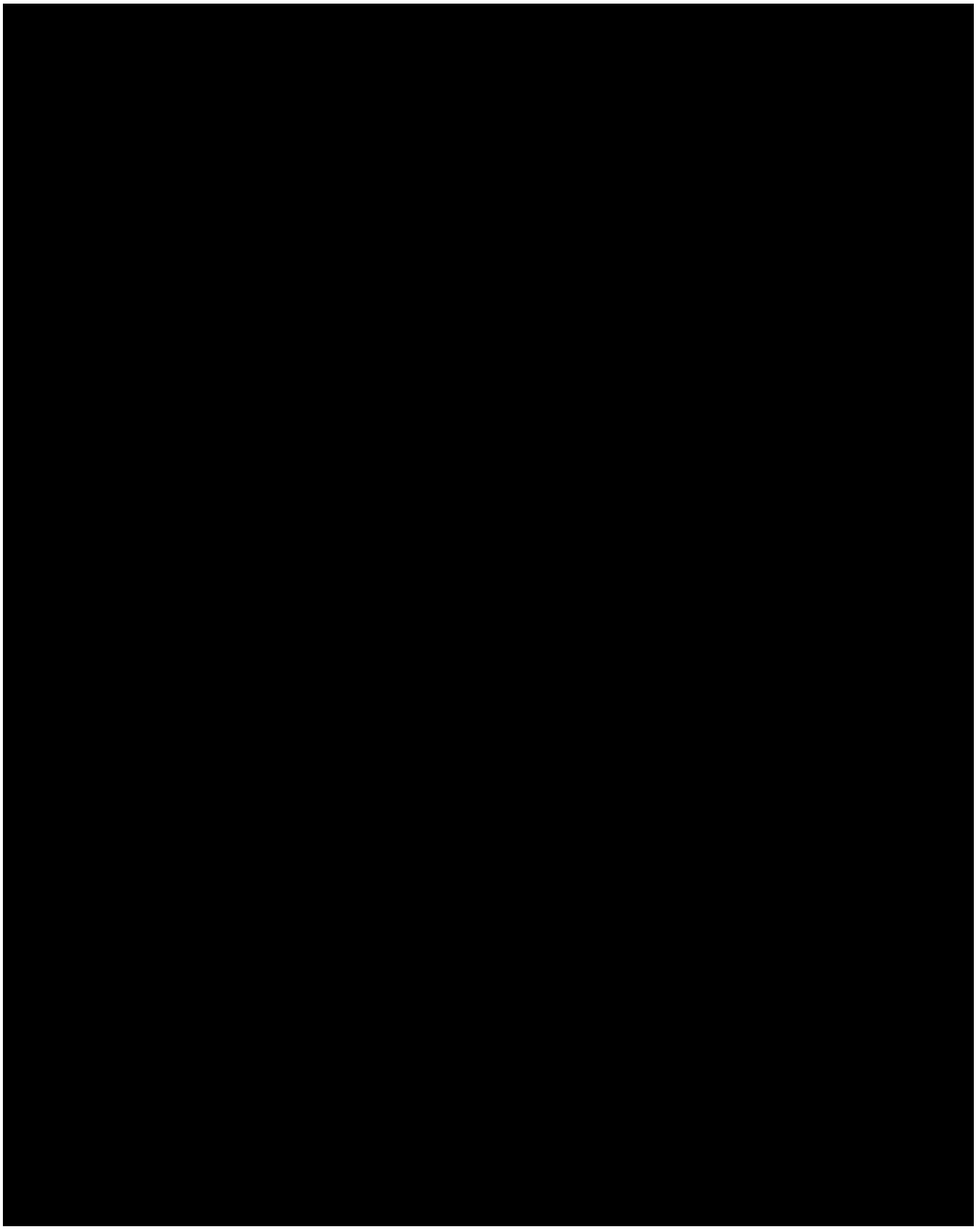
This section is not applicable as no key secondary outcome has specified in the protocol.

5.2.2 Secondary outcome

- Percentage of patients who require dose reductions, interruptions and discontinuation due to adverse events.







6 GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

This active surveillance will include 200 IPF patients treated with nintedanib per the Indian label. They are classified into following groups:

Group B:	Patients who started treatment with nintedanib after 23rd January, 2017 and are continuing the drug at the time of participation in the active surveillance.
Group C:	Patients who have been newly prescribed nintedanib at the time of participation in the active surveillance.

In addition 200 IPF patients treated with pirfenidone will also be enrolled. They are classified into following groups:

Group II:	Patients who started treatment with pirfenidone after the 23rd January, 2017 and are continuing the drug at the time of participation in the active surveillance.
Group III:	Patients who have been newly prescribed pirfenidone at the time of participation in the active surveillance.

The medical records at the selected sites will be screened to enroll Group B patients in a retrospective manner till the date of start of their participation in this active surveillance program and prospectively thereafter. Group C patients will be enrolled prospectively. The first patient enrolled at a given site should be in the nintedanib group. Once a patient is enrolled into the nintedanib group, the site team is suggested to enroll the next eligible patient, who has initiated or will be initiating pirfenidone at the same site in the pirfenidone group.

As this is an active surveillance of patients prescribed nintedanib in the real world, no specific treatment is mandated or withheld from the patients. The choice of maintenance treatment for IPF must be according to regular medical practice and at the discretion of the physician. As for any active surveillance study, the assignment of the patient to nintedanib

or any other treatment falls within current practice and prior to the decision to talk to the patient about the study, so that the decision to prescribe nintedanib is clearly separated from the decision to include the patient in this active surveillance. The decision of treatment, including the intended duration of treatment, is at the discretion of the physician providing care for the patient.

Patients who have taken at least one dose of nintedanib will be included in the safety analysis.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table 6.2 defines the different categories of important protocol violations based on protocol versions 5.0. The final column (i.e. Excluded From) in both the tables describes which PVs will be used to exclude patients from the different patients analysis sets.

In this example, patients are either excluded from "All" analysis sets, "Treated Set" or "None" of the analysis sets. The PVs that will not exclude the patient from any analysis set are included for completeness and also to demonstrate a level of quality (or adherence to the protocol). of important PVs but not limited to:

Table 6.2: Important protocol violations

The following table defines the different categories

Category/ code		**Description**	**Requirements**	**Detected by**	**Excluded From**
A		**Entrance criteria not met**			
	A1	**Inclusion criteria not met for patients treated with nintedanib**			
	A1.1	Patients with documented diagnosis of IPF which is either not based upon ATS/ERS/JRS/ALAT 2011 guidelines (nintedanib naïve or pirfenidone pre-treated) or who have	Patients (nintedanib naïve or pirfenidone pre-treated) whose diagnosis of IPF is not as per the guideline	Manually	None

Category/ code		Description	Requirements	Detected by	Excluded From
		initiated or will initiate nintedanib not according to the package insert after the commercial availability of nintedanib in India (23rd January 2017).	ATS/ERS/JRS/ALAT 2011 and/or who have initiated or will initiate nintedanib not according to the package insert after the commercial availability of nintedanib in India (23rd January 2017).		
	A1.2	Patients in whom it is not possible to obtain voluntary informed consent either from the patient or patient's legally authorised representative	Not provided ICF or ICF is provided too late or Missing ICF date.	Automated iPV-Programmatically	All
	A1.3	Patients in whom data collection is not possible from the medical records applicable for Group B patients.	No data is collected from medical records or medical records are not available for the Group B patients	Manually	None
	A1.4	Patients in whom information on baseline characteristics (which are required for registration procedure) mentioned in the protocol section 10.3.3 is not available.	Baseline characteristics data which is mandatory for the registration process (Section 10.3.3 from Protocol) in not available.	Manually	None
	A2	**Exclusion criteria met for patients treated with nintedanib**			
	A2.1	Patients who were previously treated with	Patients who have taken nintedanib	Manually	None

Category/ code		Description	Requirements	Detected by	Excluded From
		nintedanib.	before the commercial availability of drug in India (23rd January 2017).		
	A2.2	Patients who have initiated or are planned to be concomitantly treated with pirfenidone	Patients who have initiated or are planned to be concomitantly treated with pirfenidone	Manually	None
	A2.3	Patients who are participating in a clinical trial	Patients who are participating in a clinical trial	Manually	None
	A3	**Inclusion criteria not met for patients treated with pirfenidone**			
	A3.1	Patients with documented diagnosis of IPF which is either not based upon ATS/ERS/JRS/ALAT 2011 guidelines (antifibrotic naïve) or who have initiated or will initiate pirfenidone not according to the package insert after the commercial availability of nintedanib in India (23rd January 2017).	Patients (antifibrotic naïve) whose diagnosis of IPF is not as per the guideline ATS/ERS/JRS/ALAT 2011 and/or who have initiated or will initiate pirfenidone not according to the package insert after the commercial availability of nintedanib in India (23rd January 2017).	Manually	None
	A3.2	Patients in whom it is not possible to obtain voluntary informed consent either from the patient or patient's	Not provided ICF or ICF is provided too late or Missing ICF date.	Automated iPV-Programmatically	All

Category/ code		Description	Requirements	Detected by	Excluded From
		legally authorised representative.			
	A3.3	Patients in whom data collection is not possible from the medical records applicable for Group II patients.	No data is collected from medical records or medical records are not available for Group II patients.	Manually	None
	A3.4	Patients in whom information on baseline characteristics (which are required for registration procedure) mentioned in the protocol section 10.3.3 is not available.	Baseline characteristics data which is mandatory for the registration process (section 10.3.3 from Protocol) in not available.	Manually	None
	A4	**Exclusion criteria met for patients treated with pirfenidone**			
	A4.1	Patients who were previously treated with nintedanib or pirfenidone.	Patients who have treated with nintedanib or pirfenidone before the commercial availability of drug in India (23rd January 2017).	Manually	None
	A4.2	Patients who have initiated or will initiate pirfenidone concomitantly with nintedanib.	Patients who have initiated or will initiate pirfenidone concomitantly with nintedanib.	Manually	None
	A4.3	Patients who are participating in a clinical trial.	Patients who are participating in a clinical trial.	Manually	None

KEY: IPV- Important Protocol Violation

Note: Automated PVs are those detected via an automated programming process. Manual PVs are those that cannot be detected through the data stored in the trial database and is picked up through other processes such as site monitoring or IPV that is too complex to program which identified by the trial team.

Important protocol violations will be defined and documented prior to clinical database lock. A strategy for dealing with data affected by protocol deviations will be agreed upon by the coordinator, sponsor and biostatistician before clinical database lock.

6.3 PATIENT SET ANALYSED

- **Screened Set:**

  Screened Set includes all patients who sign the ICF by either voluntarily or patient's legally authorized representative.

- **Entered Set:**

  Entered Set includes patients in screened set who met the eligibility criteria.

- **Treated Set:**

  Treated Set includes patients in entered set who have taken at least one dose of nintedanib.

Analysis for all primary and secondary outcomes will be done on treated set.

The following table defines the patient set is to be used for planned analysis.

Table 6.3: 1 Patient sets analyzed

Class of endpoints/outcomes	Patient set		
	Screened Set	Entered Set	Treated Set
Primary and key secondary outcomes (Safety)	-	-	X
(Other) Secondary and further outcomes	-	-	X
Demographic/baseline outcomes	-	X	-

Note: No key secondary and further outcomes mentioned in CTP.

6.5 POOLING OF CENTRES

This section is not applicable because this is the safety surveillance PASS study and no statistical model is involved in the analysis.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

No missing data analysis is planned for this study. Missing values will be considered as missing, no imputation will be done for the analysis purpose.

No imputation is planned for missing AE data except for missing or incomplete AE onset dates which will be imputed according to BI standards [(2)] (i.e. "Handling of missing and incomplete AE dates") as below.

Step 1: For each missing / incomplete AE onset date, an interval (INT_START, INT_END) is defined. The true unknown analysis start date of AE is assumed to be within the interval.

Scenario of AE onset date	INT_START	INT_END
Completely missing AE onset date	Min (AE end date, Date of informed consent)	Min (AE end date, Date of last visit)

Scenario of AE onset date	INT_START	INT_END
Only year of AE onset date is non-missing	Min (AE end date, 01 JAN of the reported year)	Min (AE end date, 31 DEC of the reported year)
Only year and month of AE onset date is non-missing	Min (AE end date, 01 of the reported month)	Min (AE end date, Last date of the reported month)

Note: Completely missing AE end date will not be considered in this derivation step. Partially missing AE end date will be temporarily assigned the largest possible date in the observed year or month in the derivation step.

Step 2: Derive an imputed AE onset date based on the interval from step 1.

Scenarios	TESS/ Non-TESS	Imputed AE onset date
1. Date of first drug administration is within the interval [INT_START, INT_END]	TESS	Date of first drug administration
2. Date of first drug administration is before INT_START*	TESS	INT_START from step 1
3. Date of first drug administration is after INT_END or missing	Non-TESS	INT_END from step 1

TESS- Treatment emergent AE
*Note: If INT_START is after the date of the last drug administration plus residual effect period, then the AE is non-TESS.

Step 3: The AE onset date imputation flag(s) are set according to the level of imputation performed and the standard CDISC rules for imputation or the legacy data imputation rules.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Values observed at visit 1 will be considered as baseline assessment.

The medical records of patients belonging to Group B will be evaluated in the nintedanib treated arm till the date of start of their participation in this active surveillance program. Group B and Group C patients will be followed up according to clinical practice for at least 52 weeks or up to the discontinuation (whichever is earlier) from the start of the treatment at regular intervals (i.e. approximately every 4 weeks for the first 3 visits and approximately every 12 weeks thereafter till week 52).

There may be unscheduled visit(s) between the scheduled visits. In case the patient is lost to follow up (patient not contactable for further visits), the site should attempt to contact the patient telephonically to gather the information on the vital status and record it in the eCRF. Patients who are prescribed pirfenidone will not be followed.

7 PLANNED ANALYSIS

- All study data will be included in individual patient study data listings. In general, all data will be listed by therapy prescribed and by visit (if applicable). The basic data like demographic and baseline characteristics, patient disposition and patient analysis set will be listed and also summarized by therapy prescribed, by Group. All summary tables will represent descriptive statistics for the parameters being analyzed, wherever applicable.
- Numeric presentations:
  - Non-integer numerical data should be presented with decimal point.
  - If the non-formatted data (e.g. which is received from the clinical database) is inconsistently presented, a decision on how to present the final data will be made on a case-by-case basis.
  - When rounding is required, number 4 or below will be rounded down and number 5 or above will be rounded up.
  - When deriving new variable(s) based on raw data, no rounding will be performed at intermediate calculation. Rounding will only be performed when displaying data.
  - Descriptive analysis for continuous data will include number of non-missing observations (n), mean, standard deviation (SD), median, minimum, maximum, Q1, and Q3. Means, medians, Q1 and Q3 will be rounded to 1 decimal place more than the original data. Standard deviation will be rounded to 2 decimals place more than the original data. Minimum and maximum will be displayed with the same decimal precision as the original data.
  - For categorical data, frequency and percentage with corresponding 95% confidence interval will be presented wherever applicable. Confidence interval and percentages will be rounded to 1 decimal place. Percentages equal to 100 will be output as '100'. The counts and percentages equal to 0 will be represented as ‘0’ only.
- Missing data will not be imputed but will be analyzed as missing.

- Baseline assessments are the assessments taken at the Visit 1 for all patients. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used.
- The change from baseline is defined as the post-baseline value minus the baseline value.
- Text column should be left justified.
- All the data analysis will be done using SAS® version 9.4.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

At visit 1, the baseline characteristics (e.g. demographics, pulmonary function tests, HRCT evaluation etc.,) will be recorded for all patients (either treated with nintedanib or pirfenidone) from the same centre during the same time period.

Demographic characteristics at visit 1 will be listed individually by therapy prescribed by Group by sites and patients. Age and time since IPF diagnosis calculated till the first exposure of study drug will be summarized using descriptive statistics. Gender (male and female), smoking status (Never Smoked, Ex-smoker, Current smoker, Unknown), alcohol consumption (Never, Former, Current, Unknown), cocaine (Never, Former, Current, Unknown), any other Drug Abuse (Yes/No), result of chest HRCT evaluation (UIP Pattern, Possible UIP Pattern, inconsistent UIP Pattern, Emphysema, Not available) and result of surgical lung biopsy (UIP Pattern, Probable UIP Pattern, Possible UIP Pattern, Inconsistent with UIP Pattern, Not available) will be summarized using frequency counts and percentages.

Symptoms of IPF (mMRC score) will be listed separately by therapy prescribed and by patients and summarized using frequency counts and percentages. The details about mMRC score are as follows:

Table 7.1: 1 The classification of mMRC dyspnea scale

Grade 0:	I only get breathless with strenuous exercise.
Grade 1:	I get short of breath when hurrying on the level or walking up a slight.
Grade 2:	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
Grade 3:	I stop for breath after walking about 100 meters or after a few minutes on the level.
Grade 4:	I am too breathless to leave the house or I am breathless when dressing or undressing.

7.2 CONCOMITANT DISEASES AND MEDICATION

Relevant past or present medical history at visit 1 will be listed individually by therapy prescribed and by site and patient. Medical history data will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD), version June 2017 or later. It will be summarized using frequency counts and percentages as per ATC level 3 text and separate listing presented by therapy prescribed and by site and patient.

Prior IPF treatments (Pirfenidone or Other) for patients prescribed Nintedanib will be listed separately by site and patients.

7.3 TREATMENT COMPLIANCE

No analysis planned for compliance of treatment.

7.4 PRIMARY OUTCOME(S)

- Incidence of all ADRs in nintedanib treated patients:

The frequency with percentages and incidence rate of all ADRs in nintedanib treated patients will be tabulated by system organ class and preferred term.

The incidence rate will be presented as rate per 100 patient years along with 95% confidence interval.

- Incidence of all SAEs in nintedanib treated patients:

The frequency with percentages and incidence rate of SAEs will be tabulated by system organ class and preferred term.

The incidence rate will be presented as rate per 100 patient years along with 95% confidence interval.

All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs.

Incidence Rate of AE

Incidence rate is the number of new cases of an AE occurring in a specified time period divided by the cumulative time at risk.

Derivation of Time at Risk in Patients-years for a specific AE

- Patients with specific AE:

  Time at risk (AE) in days = (Start date of first specific AE - Treatment start date) +1
- Patients without specific AE:

  Time at risk (AE) in days = Overall time at risk = (End date of time at risk - Treatment start date) +1

Total AE-specific time at risk is derived as below:

Time at risk (AE) [years] = Sum of time at risk [days] across all patients / 365.25

Derivation of Incidence Rate of AE

Incidence rate [1/100 patient-years (pt-yrs)] = 100* number of patients with AE/ Time at risk (AE) [years]

The Incidence rate is based only on the first onset of an event in case of when patient may have multiple events during the trial.

The confidence interval for incidence rate can be estimated under assumption that the number of events occurring in a fixed interval of time follows a poisson distribution.

Incidence rate and its relevant confidence interval can be estimated using *Proc genmod* or exact method in SAS or other appropriate program.

Example:

1. *Proc Genmod:*

```
proc genmod data=<data-set>;
 model c = / offset=ln dist=poisson lrci;
Estimate 'Mean' intercept 1 ;
run;
```

(Note: c=number of new cases, ln=log transformed person-year)

OR

2. Exact method for 95% CI:

LCL= (quantile('chisq', 0.025, (Number of new cases*2))/(person-years*2))*100

UCL= (quantile('chisq', 0.975, ((Number of new cases+1)*2))/(person-years*2))*100

7.5 SECONDARY OUTCOME(S)

7.5.1 Key secondary outcome(s)

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

7.5.2 (Other) Secondary outcome(s)

Frequency and percentage of patients who require dose reductions, interruptions and discontinuation due to adverse events will be presented separately by system organ class and preferred term.

[redacted]

7.7 EXTENT OF EXPOSURE

Exposure to nintedanib will be estimated as time from the day nintedanib is initiated until 52 weeks or discontinuation of the drug (or the final contact with the patient for the last regular observation/end of the study)..

Days on treatment will be summarized using N, mean, SD, minimum, median, maximum, Q1 and Q3. Frequency and percentage will be presented for extent of exposure in weeks till Week 52.

7.8 SAFETY ANALYSIS

Patients who have taken at least one dose of nintedanib will be included in the safety analysis.

In general, safety analyses will be descriptive in nature and will focus on any suspected ADRs (adverse drug reactions) associated with nintedanib and SAEs (serious adverse events) in patients exposed to nintedanib.

Additionally, physical examinations, vital signs, pulmonary function test, clinical laboratory test (including clinical biochemistry, liver function test (LFT), urinalysis, coagulation test, immunological test and arterial blood gas) etc. evaluations will be listed.

7.8.1 Adverse events

Adverse events will be collected at the time points or visits specified in flowchart presented in the CTP. The medical records of patients belonging to Group B will be evaluated to see if any ADRs and SAEs have occurred in the nintedanib treated arm during the duration of the treatment before participation in the active surveillance. Group B and Group C patients will be followed up according to clinical practice as per the suggested visit. At each visit, all ADRs associated with nintedanib and SAEs will be recorded and reported.

No adverse events of special interest (AESI) have been defined for this active surveillance.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher and will be based on the concept of treatment emergent AEs. All AEs occurring between first intake of nintedanib prescribed and up to 52 weeks or discontinuation of the drug (or the final contact with the patient for the last regular observation/end of the study) will be considered ‘treatment emergent’. Adverse event summaries will summarize only treatment emergent adverse events (TEAEs), which are defined as AEs not present prior to the nintedanib prescribed.

An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship (at least a reasonable possibility of a causal relationship) between event and drug checked as 'Yes'.

TEAEs will be categorized into one or more of the following categories depending on the type of events reported:

- All TEAEs
- All TEAEs by severity
- All SAEs
- Non- Serious TEAEs
- TEAEs leading to death
- All treatment related TEAEs
- All treatment related SAEs
- All treatment related Non-Serious TEAEs
- All treatment related TEAEs leading to death
- TEAEs leading to Treatment discontinuation
- TEAEs leading to dose reduction
- TEAEs leading to dose interruption

The frequency and incidence rate of AEs/SAEs and ADRs will be tabulated by system organ class and preferred term.

Multiple overlapping or adjacent AE occurrence of same AE are collapsed into one AE event according to BI standard [(7)].

Two AE are considered to be time-overlapping if the start date of the second, later occurrence is earlier or equal to the end date of the first occurrence.

Two AE are considered to be time-adjacent if the start date of the second, later occurrence is one day later than the end date of first occurrence.

Patients reporting more than one AE for a given MedDRA Preferred Term will be counted only once for that term using the most severe incident. Patients reporting more than one type

of event within a SOC will be counted only once for that SOC. Any deaths, other SAEs, and other significant adverse events, including those leading to premature discontinuation, will be separately identified.

All AEs will be listed individually for each patient by system organ class (SOC), preferred term (PT) and lowest level term (LLT) assigned to the AEs.

AE onset date should not have any missing value in year/month/day. If any missing dates issues, communicate it to data management first.

No imputation is planned for missing AE data except AE onset date. Missing AE onset dates will be handled according to BI standard [(2)].

All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs.

An overall summary of adverse events will be presented.

The frequency of patients with adverse events (serious and non-serious adverse events), adverse drug reaction (serious and non-serious ADRs), adverse events leading to death, adverse drug reaction leading to death and other significant adverse events (according to ICH E3) will be summarized by primary system organ class and preferred term along with the incidence rate and its 95% confidence interval.

Adverse event leading to treatment discontinuation, treatment interruption and dose reduction will be separately summarized by primary system organ class and preferred term along with the incidence rate and its 95% confidence interval.

The system organ classes will be sorted by default alphabetically and preferred terms will be sorted by frequency in descending order within system organ class. Death due to adverse event will be listed separately.

According to ICH, other significant AE includes non-serious AE with action taken is either "dose reduced" or "drug withdrawn" or Trial Clinical Monitors classify non-serious AE as 'other significant' (e.g. marked hematological abnormality).

Duration of AE will be calculated as AE stop date - AE start date +1. Both start and stop dates need to be present to calculate a duration.

7.8.2 Laboratory data

Laboratory data will be presented as per the time point or visits specified in CTP. Listing of laboratory test status (Performed/ Not performed/ Unknown/ Performed but missing value) at visit 1 and (Performed/ Not performed/ Unknown) for further visits will be presented by therapy prescribed. Listings of laboratory results, units, lower and upper limits, range (Normal/Out of range/Unknown), if out of range then Clinical Significance status (Clinically Significant/Non Clinically Significant) for lab tests like clinical biochemistry, liver function test (LFT), urinalysis, coagulation test, immunological test and arterial blood gas etc. will be presented by therapy prescribed for each patient for each suggested visits. In addition to this after visit 1, if the out of range lab test results are clinically significant then Relationship with Nintedanib (Related to Nintedanib/ Not Related to Nintedanib) will also be presented. Values outside of the laboratory's reference limits (i.e., those with high or low values) will be flagged in the laboratory listings.

Laboratory tests with continuous results and their changes from baseline for each suggested visits will be summarized descriptively by therapy assigned. For categorical data will be summarized using frequency and proportion.

Frequency count with percentage for possibly clinically significance abnormalities will be presented separately by visits.

7.8.3 Vital signs and Physical Examinations

Vital signs and Physical examinations assessments will be performed at the time points or visits specified in CTP. Vital sign and physical examination results (including heart rate, systolic and diastolic blood pressure, height, weight and pregnancy status) will be listed by therapy prescribed and by site and patient. Also, continuous results of vital sign and physical examinations and their changes from baseline for each suggested visits will be summarized descriptively (n, mean, SD, median, minimum, and maximum) by therapy prescribed.

7.8.4 ECG

This section is not applicable as no ECG data are collected.

7.8.5 Others

Pulmonary function test result will be performed as per suggested visits specified in CTP. Pulmonary function test results will be listed by therapy prescribed and by site and patient. Descriptive statistics for results of pulmonary function test and its change from baseline for each suggested visits will be presented by therapy prescribed.

8 REFERENCES

1.	001-MCS-40-415_RD-02: "Trial Statistical Analysis Plan (TSAP) Template (annotated, PDF copy)",version: 1.0
2.	001-MCG-156_RD-01: "Handling of Missing and Incomplete AE Dates", version: 3.0
3.	001-MCS-90-140: "Post-Authorization Safety Studies", version: 3.0
4.	001-MCS-05-504: "Reconciliation of Adverse Events Information in BI studies, version: 7.0
5.	001-MCS-50-408: "Medical and Quality Review in Clinical Trials", version: 5.0
6.	001-MCG-156: “Analysis and Presentation of Adverse Event Data from Clinical Trials”, version 8.0
7.	XAE User Manual : Document No. 4058.321.06 Version 3.0

10 HISTORY TABLE

Table 11: 1 History table

Version	Date	Author	Sections Changed	Brief description of change
Final 2.0	15-Mar-2019	[redacted]	3.0 and 6.2	Important Violation table 6.2:1 (CTP version 2.0) removed and Table 6.2:2 renamed as 6.2. Also, Introduction section 3 updated accordingly.
Final 2.0	26-Feb-2019	[redacted]	3.0 and 6.2	This section is updated according to CTP version 2.0 and CTP version 5.0 as 6 subjects enrolled in the study based on CTP version 2.0 and remaining on CTP version 5.0.
Final 2.0	10-Jan-2019	[redacted]	2.0	Updated list of abbreviations as applicable
			3.0	Updated for protocol and CRF versions and interim analysis is replaced by annual status report submission to DCGI. Replaced suspected ADRs (serious and non-serious), serious and fatal AEs by "all ADRs and SAEs" and added 'interruptions' term as per updated protocol text.
			4.0	Protocol version updated
			5.1	Occurrence of ADRs (serious and non-serious) is replaced by Incidence of all ADRs in nintedanib treated patients. Occurrence of AEs (serious and fatal) is replaced by Incidence of all SAEs in nintedanib treated patients as per updated protocol.
			5.2.2	Interruptions term is added.
			[redacted]	[redacted]
			6.1	Updated for the group wise definitions according to protocol version 5.0.

			6.2	IPV for Enrolled pregnant patients is removed and updated all the IPVs as per version 5.0 of protocol.
Version	**Date**	**Author**	**Sections Changed**	**Brief description of change**
			6.3	Definitions of Screened and Treated set are updated according to Groups.
			6.6	Note is added for completely and partially missing AE end date.
			6.7	Updated for visit information as per Groups.
			7.0	Removed Significant digit related rules as significant digit concept is not used for this study. The text "Baseline characteristics of consecutive 100 IPF patients not treated with nintedanib will be used to compare the patients profile with the patient treated with nintedanib and will allow to put the safety date of nintedanib into perspective." has been removed.
			7.1	Added text "At visit 1,the baseline characteristics (e.g. demographics, pulmonary function tests, HRCT evaluation etc.,) will be recorded for all patients (either treated with nintedanib or pirfenidone) from the same centre during the same time period." Added Table 7.1 The classification of mMRC dyspnea scale.
			7.2	Updated section and removed the text "Previous medication used for IPF prior to baseline/visit 1 assessment and co-medications for IPF at visit 1 and further visits (i.e. during surveillance) will be listed separately." Added text as "Prior IPF treatments (Pirfenidone or Other) for patients prescribed Nintedanib will be listed separately by site and patients."
			7.4	Updated primary and secondary outcomes as per version 5.0 protocol. Added text "All analyses of AEs will be based on the number of patients with

				AEs and not on the number of AEs." Added EXACT method for 95 % CI with formulae.
			7.5.2	Added "interruptions" word.
Version	**Date**	**Author**	**Sections Changed**	**Brief description of change**
			7.7	Updated text as "Exposure to nintedanib will be estimated as time from the day nintedanib is initiated until 52 weeks or discontinuation of the drug (or the final contact with the patient for the last regular observation/end of the study)."
			7.8	Updated as per ADRs and SAEs terminology and added "pulmonary function test" in the listed evaluations.
			7.8.1	Updated this section as for AEs as per protocol version 5.0.
			7.8.2	Updated laboratory test related information collected after Visit 1. Also additional information is updated as per CRF at visit 1.
			7.8.3	Modified text from "by patients" to "by site and patients".
			7.8.5	Modified text from "by patients" to "by site and patients". Deleted Section 8 for Interim analysis.
			[redacted]	[redacted]
Final 1.0	24-May-2018	[redacted]	None	This is the final version 1.0 of TSAP with necessary information for trial conduct