TRIAL STATISTICAL ANALYSIS PLAN

BI Trial No.:	1199.272
Title:	An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib as per approved Indian Label for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.
Investigational Product(s):	Nintedanib
Responsible trial statistician(s):	[redacted] Email: [redacted]
Date of statistical analysis plan:	01-Dec-2020
Version:	Final 1.0

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1 LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
EDC	Electronic Data Capture
ICH	International Conference On Harmonisation
MedDRA	Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
PT	Preferred Term
PD	Protocol Deviation
Q1	Lower Quartile
Q3	Upper Quartile
SA	Statistical Analysis
SD	Standard Deviation
SOC	System Organ Class
ToC	Table of contents
TSAP	Trial Statistical Analysis Plan

2 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 3.0 dated 19 July 2018 and Case Report Form (CRF) version final 3.0, dated 20 Nov 2020. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 10.7 "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."

SAS® Version 9.4 will be used for all analyses.

This is an active surveillance study and the aim of this study is to monitor the real world safety in Indian patients prescribed nintedanib as per approved Indian Label for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumor histology after first-line chemotherapy. The scientific objective of this active surveillance is to obtain an estimate of the Incidence of all Adverse Drug Reactions (ADRs), and Serious Adverse Events (SAEs) in NSCLC patients with adenocarcinoma histology who had been prescribed nintedanib per the approved label within two years from the date of the commercial availability of the drug in India (23rd January 2017) in the real world setting. In addition, this study will also calculate the percentage of patients who require dose reductions and discontinuation due to adverse events. This would help in assessing the safety of nintedanib in NSCLC patients with adenocarcinoma histology in Indian real world setting.

3 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No changes made in the planned analysis of the study mentioned in the protocol version 3.0 dated 19 July 2018 .

4 OUTCOMES

4.1 PRIMARY OUTCOMES

- Incidence of all ADRs in nintedanib & docetaxel treated patients.
- Incidence of all SAEs in nintedanib & docetaxel treated patients.

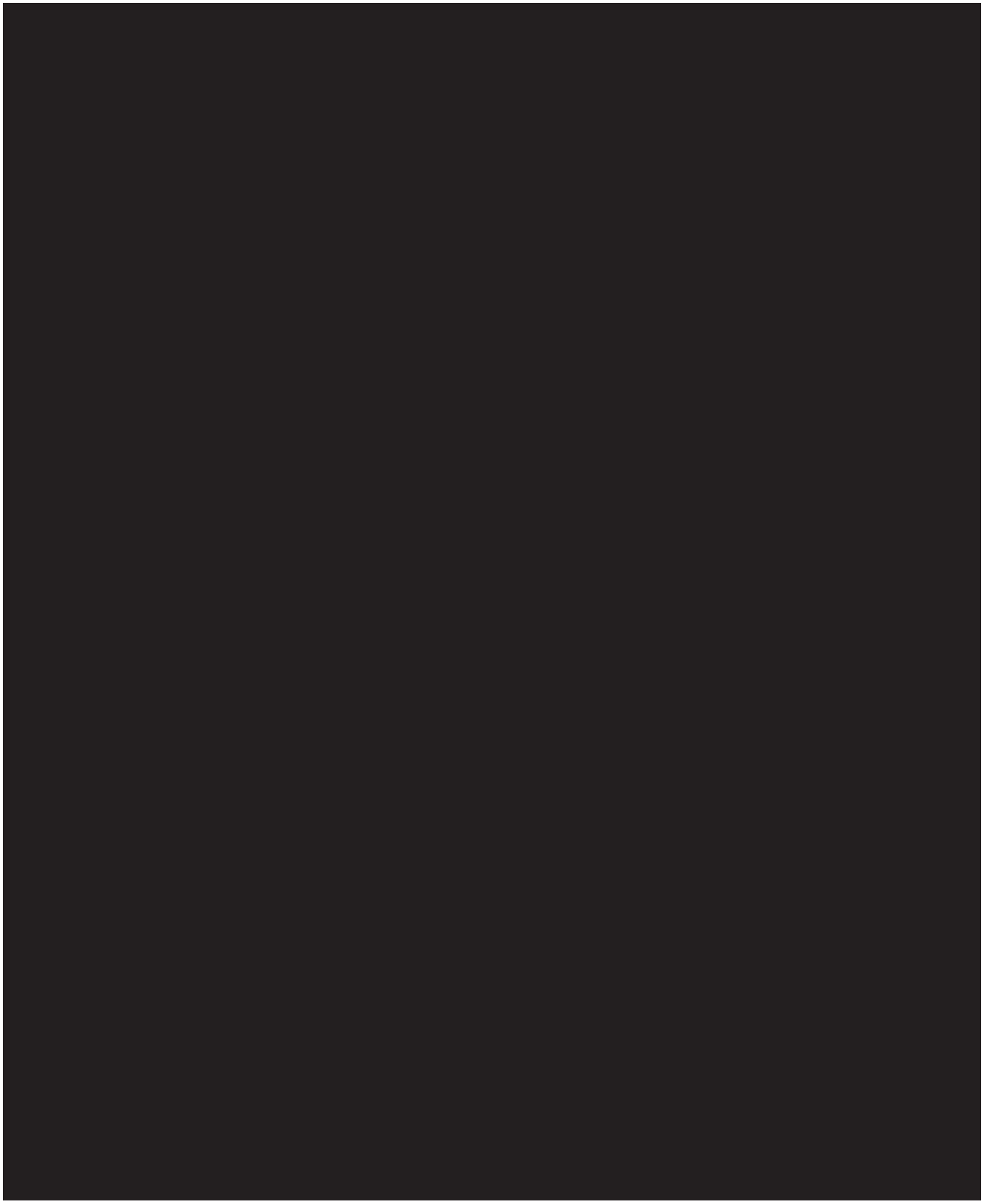
4.2 SECONDARY OUTCOMES

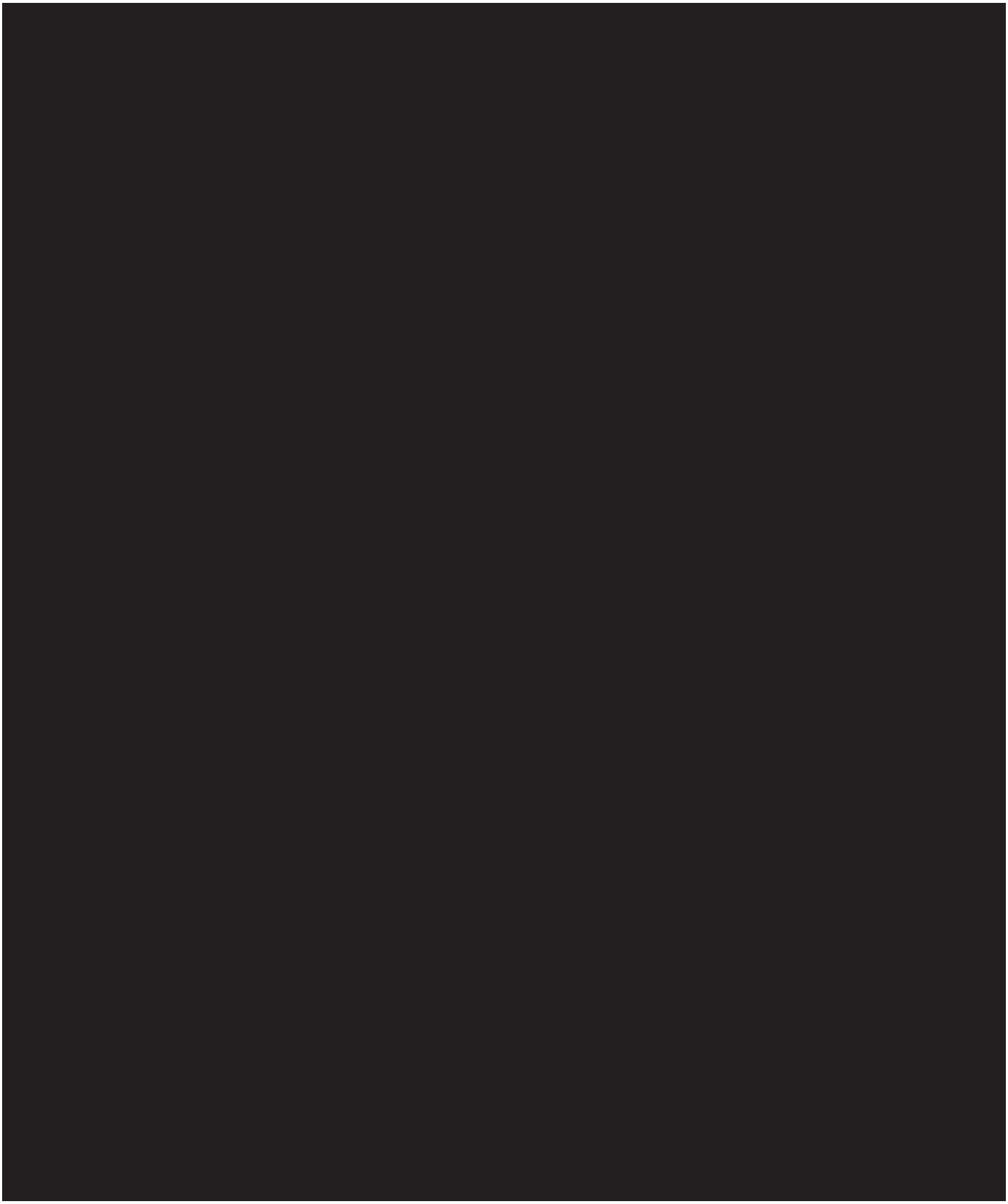
4.2.1 Secondary outcome

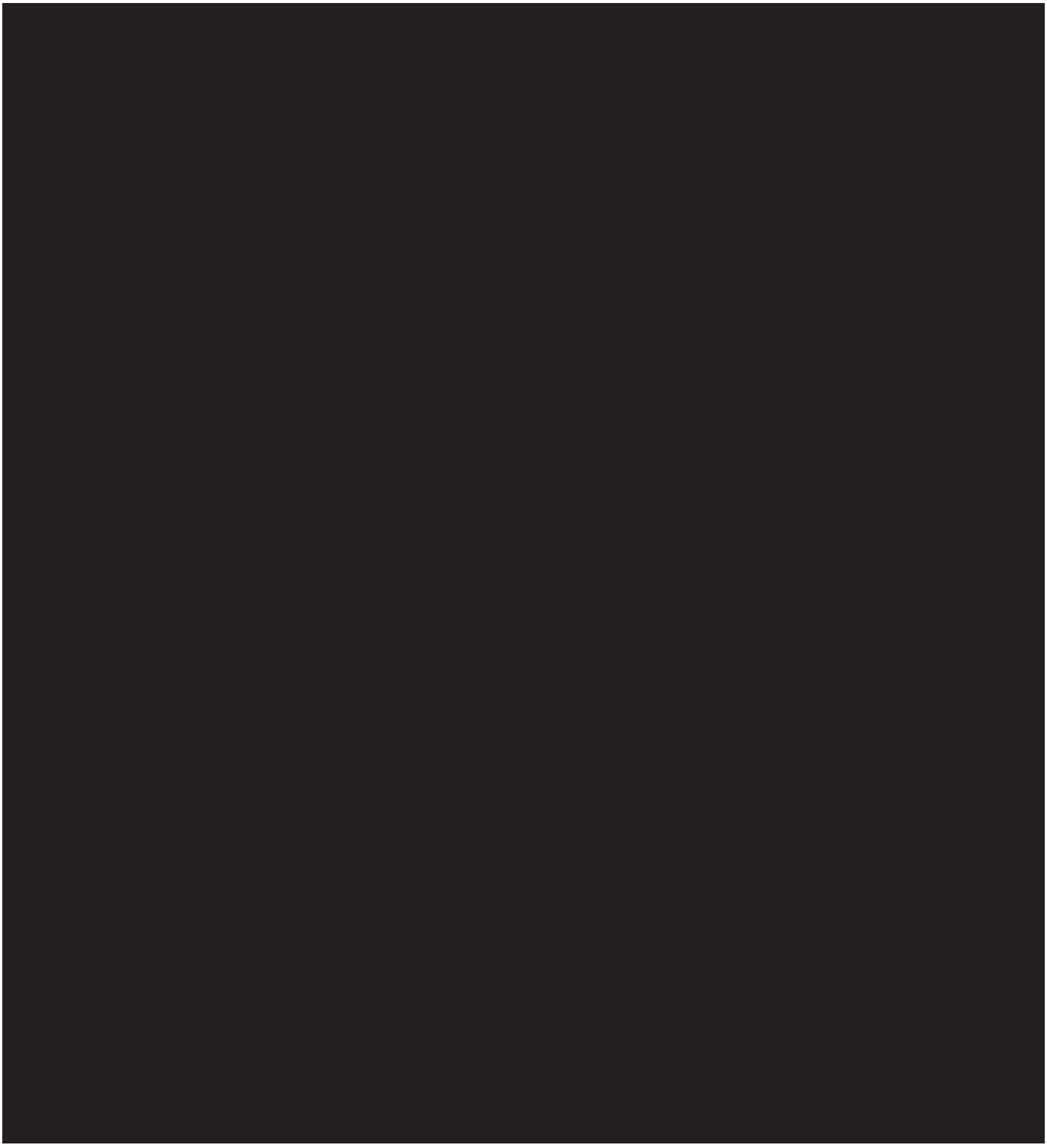
- Percentage of patients who require nintedanib dose reductions and discontinuations due to adverse events

4.2.2 Key secondary outcome

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







5 GENERAL ANALYSIS DEFINITIONS

5.1 TREATMENT

The visit 1 will be considered as baseline visit and at this visit the baseline characteristics will be recorded for all patients. Informed consent of the patients should be obtained prior to the collection of baseline assessments. Informed consent obtained after visit 1 date will be considered as too late. Informed consent may not be possible due to death/non traceability of the patient in Group A & Group I and hence date of informed consent will be entered as NA. This active surveillance includes 100 NSCLC patients treated with nintedanib per the approved Indian label will be enrolled in this active surveillance. They are classified into following groups:

Group A	Patients who started treatment with nintedanib & docetaxel after 23 rd January, 2017 and have discontinued the drug at the time of participation in the active surveillance.
Group B	Patients who started treatment with nintedanib & docetaxel 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 & docetaxel at the time of participation in the active surveillance.

In addition 100 locally advanced, metastatic or recurrent nonsmall cell lung cancer (NSCLC) of adenocarcinoma tumour histology treated with single agent docetaxel after the first line chemotherapy will also be enrolled. They are classified into following groups:

Group I	Patients who started treatment with docetaxel after 23rd January, 2017 and have discontinued the drug at the time of participation in the active surveillance.
Group II	Patients who started treatment with docetaxel after 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 docetaxel at the time of participation in the active surveillance.

The medical records at the slected sites will be screened to enroll Group A and B patients in a retrospective manner. Group C patients will be enrolled prospectively.
The safety data for nintedanib treated patients will be collected till the discontinuation of the drug and an additional follow up visit up to 28 days after the last intake of the drug. Patients who have taken at least one dose of nintedanib will be included in the safety analysis.
Patients who are planned to be treated with single agent docetaxel will not be followed.

5.2 IMPORTANT PROTOCOL DEVIATIONS

This surveillance is mainly focused on occurrence of SAE and ADR on real world setting and no efficacy end point to be evaluated. So in this surveillance per protocol (PP) analysis will not be considered. Hence, the iPD table will be included for completeness and also to demonstrate a level of quality (or adherence to the protocol).
The following table defines the different categories of important PDs but not limited to:

Table 6.2: 1 Important Protocol Deviation

Category/ code		Description	Comment/Example	Detected by	Excluded From
A		**Entrance Criteria Not Met**			
	A1	**Pregnancy Status**			
	A1.1	Inclusion of pregnant patients	Automated PD	Programmatically	None
	A2	**Inclusion criteria not met for patients treated with nintedanib + docetaxel**			
	A2.1	• Patients <18 years of age. • Patients who don't poses the medical condition of locally advanced and/or metastatic NSCLC of	Age criteria will be detected as Automated PD and medical condition will be reviewed manually.	Programmatically and Manually	None

Category/ code		Description	Comment/Example	Detected by	Excluded From
		stage IIIB or IV, or recurrent NSCLC and adenocarcinoma histology after relapse or failure of first line of chemotherapy who are newly prescribed nintedanib according to the package insert.			
	A2.2	• Patients in whom it is not possible to obtain voluntary informed consent from either the patient or patient's legally authorized representative (applicable for Group B and C patients).			
	A2.3	Patients in whom data collection is not possible from the medical records (applicable for Group A and B patients).	Inclusion criteria 3 for patients treated with nintedanib + docetaxel.	Manually	Treated Set
	A2.4	Patients in whom information mentioned in the section 10.3.3 of the Protocol is not available.	Inclusion criteria 4 for patients treated with nintedanib + docetaxel .	Manually	None
	A3	**Exclusion criteria met for patients treated with nintedanib + docetaxel**			
	A3.1	Patient has taken Nintedanib before the participation in this study.	Exclusion criteria 1 for patients treated with nintedanib + docetaxel	Manually	None
	A3.2	Patients who are positive for EGFR mutations or ALK rearrangements	Exclusion criteria 2 for patients treated with nintedanib + docetaxel	Manually	None
	A3.3	Patients who are participating in a clinical trial	Exclusion criteria 4 for patients treated with nintedanib + docetaxel	Manually	None
	A4	**Inclusion criteria not met for patients treated with single agent docetaxel**			

Category/ code		Description	Comment/Example	Detected by	Excluded From
	A4.1	Patients < 18 years of age without locally advanced and/or metastatic NSCLC of stage IIIB or IV, or recurrent NSCLC and adenocarcinoma histology after first line chemotherapy who have initiated or will initiate single agent docetaxel after the commercial availability of nintedanib in India (23rd January 2017).	Age criteria will be detected as Automated PD and medical condition will be reviewed manually.	Programmatically and Manually	None
	A4.2	Patients in whom it is not possible to obtain voluntary informed consent from either from the patient or patient's legally authorized representative (applicable for Group II and III patients).	Inclusion criteria 2 for patients prescribed single agent docetaxel	Manually	None
	A4.3	Patients in whom data collection is not possible from the medical records and/or from the further visit records (applicable for Group I and II patients).			
	A4.4	[redacted]			
	A5	**Exclusion criteria met for patients treated with docetaxel**			
	A5.1	Patients who were previously treated with docetaxel	Exclusion criteria 1 for patients prescribed single agent docetaxel	Manually	None
	A5.2	Patients who are positive for EGFR mutations or ALK rearrangements	Exclusion criteria 2 for patients prescribed single agent docetaxel	Manually	None
	A5.3	Patients who are participating in a clinical trial	Exclusion criteria 3 for patients prescribed single agent docetaxel	Manually	None
B		**Informed consent**			
	B1	Informed consent given too late	In MQRM listing, will mention the Date of	Programmatically	None

Category/ code		Description	Comment/Example	Detected by	Excluded From
			Informed Consent as captured on CRF and based on the Inclusion criteria mentioned in A2.1 and A4.2. Medical reviewer will provide their suggestions on the same regarding severity of PD.		

KEY: IPD- Important Protocol Deviation

Note: Automated PDs are those detected via an automated programming process using SAS. Manual PDs are those identified during the MQRM or review through patients' listings and/or Manual PD log.

Important protocol deviations 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.

When the PD cannot be programmed, the individual patient listings with PD category/code will be generated based on data review and should not be included in the TSAP.

5.3 PATIENT SET ANALYSED

- **Screened Set:**
  Screened set includes all patients who signed the ICF.(ICF details are available for Group B /Group C & Group II/Group III patients and 'NA' for Group A/ Group I patients.)
- **Entered Set:**
  Entered set includes patients in screened set who met the eligibility criteria.
- **Treated Set:**
  Patients in entered set who have taken at least one dose of trial medication (nintedanib & docetaxel and single agent docetaxel).

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

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

Table 6.3: 1 Patient sets analysed

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

Note: No other secondary and further endpoints mentioned in CTP.

[redacted]

5.5 POOLING OF CENTRES

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

5.6 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.

Missing or incomplete AE onset dates will be imputed according to BI standards [(2)] (i.e. "Handling of missing and incomplete AE dates").

5.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Values observed at Visit 1 will be considered as Baseline assessment.

Patients who will be prescribed nintedanib are suggested to have further visits at every 3 weeks for the first 3 visits and every 4 weeks till the discontinuation of the treatment and an additional follow up visit 28 days after the last dose of nintedanib. In case the patient is lost to follow up, an attempt will be made to gather the safety information telephonically for further and follow-up visit and the information will be recorded in the eCRF. For the nintedanib cohort certain information (e.g performance status) will also be collected at further visits, as the status may change over time.

Patients who are planned to be treated with single agent docetaxel will not be followed.

6 PLANNED ANALYSIS

The general principles listed below will be applied throughout the study:

- 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.
- If the non-formatted data that are received (e.g., from the clinical database) are inconsistently presented, a decision on how to present the final data will be made on a case-by-case basis.
- When rounding is required, numbers 4 or below will be rounded down and number 5 or above will be rounded up.
- Numeric presentations:
  - 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 actual data. Standard deviation will be rounded to 2 decimals place more than the actual data. Minimum and maximum will be displayed with the same decimal precision as the original data.Q1 and Q3 will be presented with 1 decimal.
  - For categorical data, frequency and percentage will be presented. Percentages will be rounded to 1 decimal place. Percentages equal to 100 will be output as '100%'.
- All the data analysis will be done using SAS® version 9.4 or higher.
- 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.

- Missing data will not be imputed but will be analyzed as missing. Missing values will be represented with blank spaces. In cases where a value is missing due to non-evaluable nature of the value then it will be represented with a hyphen "-".

- If data summary is planned during the conduct of the trial and no data are generated satisfying the criteria then no data table will be generated with just a comment.

- The baseline characteristics of 100 NSCLC patients treated with single agent docetaxel after the first line chemotherapy will be used to compare the patients profile with the nintedanib & docetaxel users and will assist to put the safety data of nintedanib into perspective.

6.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Patient demographic data at baseline visit(age, gender, weight, height, pregnancy status, smoking status) and baseline characteristics (Time since diagnosis, condition of the disease, stage of NSCLC, brain metastases, EGFR and ALK status, renal impairment, hepatic impairment) will be summarized using descriptive statistics, frequency count and percentage for patients belongs to 'All Patients' set.

All the continuous data (age, weight, height, time since diagnosis) will be summarized using descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum, maximum, Q1 and Q3). Whereas all the categorical data (sex, pregnancy status, smoking status, condition of the disease, stage of NSCLC, brain metastases, EGFR and ALK status, renal impairment, hepatic impairment)will be summarized using frequency counts and percentages.

In addition to the summary tables, listings will be provided by treatment prescribed by Group and patients for all demographics and baseline characteristics data.

6.2 CONCOMITANT DISEASES AND MEDICATION

Relevant past or present medical history at Visit 1 (baseline visit) will be listed individually by treatment prescribed and by patient.

For patients with nintedanib treatment, medications used before the first dose will be considered as prior medications while for patients with single agent docetaxel treatment, medication used before the therapy prescribed will be considered as prior medications. For patients with nintedanib treatment, medications started after the first dose in the study or medication used during the study will be recorded as concomitant medications, while for patients with single agent docetaxel treatment, who has used any medication other than study drug will be considered as concomitant medications.

Concomitant medications will be coded using the MedDRA (version 23.0) and World Health Organization Drug Dictionary (WHO DD), Mar 2020 or later, and will be summarized using frequency counts and percentages as per ATC level 3 text.

6.3 TREATMENT COMPLIANCE

No analysis planned for compliance of treatment.

6.4 PRIMARY OUTCOME(S)

- Incidence of all ADRs in nintedanib & docetaxel treated patients.

  The frequency, percentages and incidence rate of all ADRs) will be tabulated by system organ class and preferred term.

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

- Incidence of all SAEs in nintedanib & docetaxel treated patients

  The frequency, 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 patients per year along with 95% confidence interval.

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

Subjects with specific AE:

Time at risk (AE) in days = (Start date of first specific AE - Treatment start date) +1

Subjects 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 subjects / 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 incase 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* in SAS or other appropriate program.

example:

```
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)

6.5 SECONDARY OUTCOME(S)

6.5.1 Secondary outcome(s)

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

6.5.2 (Other) Secondary outcome(s)

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

[redacted]

6.7 EXTENT OF EXPOSURE

Exposure to nintedanib will be estimated as time from the day drug is initiated until 28 days after the drug is last administrated to the patient (or the final contact with the patient for the last regular observation/end of the study).Days on Treatment = Last Study Visit Date – First Dose Date + 1.

Days on treatment will be summarized using n, mean, SD, minimum, median, maximum, Q1 and Q3. Frequency and percentage will be presented for exposure per visit..

6.8 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 be based on BI standards and will focus on all ADRs and SAEs.

Additionally, physical examinations, vital signs, clinical laboratory test (including hematology, clinical biochemistry, liver function test (LFT), urinalysis, coagulation test) etc. evaluations will be listed.

6.8.1 Adverse events

Analysis of 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 A and B will be evaluated to see if any ADRs or SAEs have occurred in the nintedanib & docetaxel arm during the duration of the treatment and up to 28 days after the last intake of the drug. This data will be entered into eCRF. 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. Adverse event summaries will summarize only treatment-emergent adverse events (TEAEs). All AEs occurring between first intake of nintedanib + docetaxel prescribed at baseline/ visit 1 and up to 28 days (inclusive) after the last intake of nintedanib will be considered 'treatment emergent'.

If a partially missing date or time of onset allows the possibility that an AE may be a TEAE it will be assumed that it is a TEAE.

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

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

An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as 'related'.

AEs will be coded using the version 23.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA).

The grading of ADRs and SAEs will be done by using Common Terminology Criteria for Adverse Events version 04 (CTCAE v04).Adverse events will be categorized by TEAE, serious adverse event (SAE), non serious adverse event, death or withdrawal. These categories will be further summarized by the causal relationship to study drug. An overall summary of the number and percentage of patients in each category will be presented in each category.

The following TEAE summary tables will be prepared:

- Overall Summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of TEAEs by maximum severity (Intensity), SOC, and PT
- Summary of TEAEs related to treatment nintedanib by SOC and PT
- Summary of Serious TEAE by SOC and PT
- Summary of deaths by SOC and PT
- Summary of Serious TEAEs related to treatment nintedanib by SOC and PT
- Summary of non-serious TEAEs related to treatment nintedanib by SOC and PT
- Summary of TEAEs causing discontinuation from study drug by SOC and PT
- Summary of TEAEs causing dose reduction of study drug by SOC and PT

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 occurrences of same AEs are collapsed into one AE event according to BI standard[(6)] if all AE attributes are identical (patient number, LLT, outcome, therapy, intensity, action taken, seriousness, reason for seriousness, causal relationship).

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.

After the collapsing the events to remove duplication and clarify any inconsistencies, the resulting data will form the basis for all reporting of AE data in the listing, table and figures.

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.

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

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 AEs will be derived and presented in all listings. It is calculated as AE stop date minus AE start date. Both start and stop dates need to be present to calculate a duration.

The frequency of patients with adverse events will be summarized by primary system organ class and preferred term. The system organ classes will be sorted in alphabetical order and preferred terms will be sorted by frequency (within system organ class) in descending order.

6.8.2 Laboratory data

Listings of laboratory results (e.g. hematology (CBC), clinical biochemistry, liver function test(LFT), urinalysis, coagulation test) at visit 1 and laboratory test status (i.e. performed, not performed)for further visits will be presented by treatment prescribed for each patient. Values outside of the laboratory's reference range (i.e., those with high or low values) will be flagged in the laboratory listings by Clinical Significance status (Clinically Significant/Non Clinically Significant).

Laboratory tests with continuous results and their changes from baseline for each suggested visits will be summarized descriptively by therapy assigned at visit 1. Categorical data will be summarized using frequency and proportion.

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

6.8.3 Vital signs and Physical Examinations

Vital sign and physical examination results (including heart rate (beats per minute) , systolic and diastolic blood pressure, height, weight and pregnancy status, body temperature and ECOG) will be listed by therapy prescribed and by patient. Also, continuous results of vital sign and physical examinations and their changes from baseline for each schedule visit will be summarized descriptively (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment prescribed.

6.8.4 ECG

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

6.8.5 Others

This section is not applicable as no other analysis is needed.

7 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.	XAE User Manual : Document No. 4058.321.06 Version 3.0

9 HISTORY TABLE

Version	Date (DD-MMM-YY)	Author	Sections Changed	Brief description of change
1.0	01-Dec-2020	[redacted]	None	NA