I3Y-IN-JPEC Statistical Analysis Plan (Version 1)

A Single-Arm, Phase 4 Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, in Combination With Endocrine Therapy (Anastrozole/Letrozole or Fulvestrant) in Participants With Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative Locally Advanced and/or Metastatic Breast Cancer in India

NCT04707196

Approval Date: 08-Feb-2021

STATISTICAL ANALYSIS PLAN

Protocol title: A Single-Arm, Phase 4 Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, in combination with Endocrine Therapy (Anastrozole/Letrozole or Fulvestrant) in Participants with Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative Locally Advanced and/or Metastatic Breast Cancer in India	
Protocol number: I3Y-IN-JPEC	**Applicable Protocol Version:** V1.0
Author: PPD	**Internal reviewer(s):** PPD **Sponsor representative(s):** PPD
Revision history: NA	**Date:** NA

The layout of this document is based on the Guideline on the International Conference on Harmonization (ICH E9).

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Glossary of abbreviations

ABBREVIATION	DESCRIPTION
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CDK	Cyclin-Dependent Kinase
CDK 4&6	Cyclin-Dependent Kinases 4 & 6
CI	Confidence interval
CV	Coefficient of variation
DBL	Database lock
eCRF	Electronic case report form
HER2-	Human Epidermal Growth Factor Receptor 2 negative
HR+	Hormone Receptor Positive
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational product
MedDRA	Medical dictionary for regulatory activities
N	Sample size
ODS	Output delivery system
Participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PT	Preferred term
RTF	Rich text format
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
TEAEs	Treatment-emergent adverse events
TLFs	Tables, data listings and figures
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

1. Overview

1.1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of data from clinical trial I3Y-IN-JPEC titled “A Single-Arm, Phase 4 Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, in combination with Endocrine Therapy (Anastrozole/Letrozole or Fulvestrant) in Participants with Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative Locally Advanced and/or Metastatic Breast Cancer in India”

This statistical analysis plan (SAP), is based on protocol I3Y-IN-JPEC, V1.0, dated 20-Jan-21.

2. Trial objectives

The following objectives are those stated in the protocol.

2.1 Primary objectives

- To characterize the safety of abemaciclib in combination with ET (anastrozole/letrozole or fulvestrant)

2.2 Secondary objectives

- To evaluate incidence of treatment discontinuation of abemaciclib

3. Endpoints

The following endpoints are those stated in the protocol.

3.1 Primary endpoints

- TEAEs (including SAE and AESI) by per CTCAE criteria version 5.0

3.2 Secondary endpoints

- Discontinuation of abemaciclib only, due to an AE

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4. Trial design

4.1 Design overview

This is a Phase 4, single-arm, cohort study of abemaciclib in combination with either a NSAI (anastrozole or letrozole) or fulvestrant, in patients with HR+, HER2- locally advanced and/or MBC. This study is designed to characterize the safety of abemaciclib plus ET in Indian patients.

Participants receiving initial endocrine-based therapy for advanced/MBC will be assigned to cohort A to receive abemaciclib in combination with anastrozole/letrozole. Participants who have received prior ET in the advanced/metastatic setting or relapsed while on/or within 1 year after ET in the adjuvant setting, will be assigned to cohort B to receive abemaciclib in combination with fulvestrant. To evaluate the safety of abemaciclib in combination with anastrozole/letrozole or fulvestrant, AEs will be assessed throughout the study and the clinical safety laboratory will be assessed on day 1 and 14 in the first 2 cycles and then day 1 every 28 days in the 4 subsequent cycles. Participants will continue treatment for a total duration of 6 cycles or less in case of radiographic or clinical progression as per investigator's judgment or another discontinuation criterion has been met. Participants who complete the study after 6 cycles of treatment may continue to receive abemaciclib (for example, through a patient support program) as per investigators discretion.

4.2 Schedule of events

Please refer to section 1.3 of the study protocol.

5. Changes/deviations from the planned analysis

Not applicable.

6. Analysis populations

6.1 Entered Population

This analysis population will include all participants who sign the informed consent form.

6.2 Safety Population

This analysis population will include all participants assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analysed according to the intervention they actually received.

7. General considerations

7.1 Visit and date conventions

No visit windowing (i.e., remapping of visits based on visit windows) will be performed for this trial. In the situation where the assessment/event date is partial or missing in any cycle, and any corresponding durations will appear missing in the data listings. Unscheduled measurements will not be included in cohort wise summaries. Data listings will include scheduled, unscheduled, retest and early discontinuation data. Trial visit will be assigned as delineated in Table 7.1:

Table 7.1: Trial visit assignment schedule

Study phases	Screening		On treatment cycle duration = 28 days					End of Visit	Post-Treatment follow up
	Baseline		Cycle 1		Cycle 2		Cycle 3 to 6	Cycle 6	Short-Term Follow-Up b
Relative Day within Dosing Cycle & Visit Window (±n days)	≤28	≤14	D1 (±3)	D15 (±3)	D1 (±3)	D15 (±3)	D1 (±3)	D28 (±3)	V801 (30 days +7)

7.2 Baseline

Baseline is defined as the last non-missing observation made prior to the first administration of study intervention.

7.3 Stratifications

For analysis purposes, trial participants may be sub-classified into the following stratification levels, where applicable:

- Cohort
  - Cohort A: abemaciclib 150 mg twice daily (BD) plus either anastrozole or letrozole
  - Cohort B: abemaciclib 150 mg BD plus fulvestrant

7.4 Statistical tests

The default significance level for this trial is set at 5%. All 95% confidence intervals (CIs) and statistical tests will be two-sided.

7.5 Common calculations

For quantitative measurements, change from baseline will be calculated as: (Test value at Visit Day X – Baseline value), where the baseline value is defined as the last non-missing observation taken prior to first exposure to study intervention.

7.6 Software

All analyses will be conducted using SAS® Version 9.4.

8. Statistical considerations

8.1 Multicentre studies

Not applicable.

8.2 Missing data

Missing data is assumed to be missing and no imputation will be performed. Partial date imputation will be performed for the adverse events data.

9. Output presentations

Summary tables will be stratified by cohorts.

The templates provided in the separate output templates document describe the format and content for presentation of tables, listings and figures (TLFs).

All percentages (%) for a summary are calculated using the total number of participants in the safety population as the denominator.

Data listings will be based on safety population.

Descriptive statistics for quantitative measurements will include the number of participants (n), mean, standard deviation (SD), minimum, median and maximum.

10. Participant disposition and withdrawal

10.1 Variables and derivations

End of trial classifications are defined as follows:

- Screening failure:

  Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study.

- Study completer:

  The study completer is defined as the participant completed 6 cycles of study intervention.

- Lost to follow-up:

  A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site

- The following parameters will be summarised for the patient disposition table.
- No. of participants in entered population
- No. of participants in safety population
- No. of participants who completed the study
- No. of subjects who discontinued from the study

The following parameters will be summarised for the patient discontinuation table as per eCRF Patient's primary reason for discontinuation (reasons mentioned in eCRF treatment discontinuation form) which are as follows:

- Progressive disease
- Adverse event
- Death
- Withdrawn by subject
- Physician decision
- Non-compliance with study drug
- Protocol deviation
- Study terminated by IRB or ERB
- Study terminated by sponsor
- Lost to follow-up
- Pregnancy

10.2 Analysis

Participant disposition and withdrawals (obtained from the 143 page of eCRF) will be summarized and presented in data listings for the entered population.

In participants' disposition table, the entered participants and treated patients will be summarised (frequency) by total. Rest of the categories (e.g., completed patients, discontinued patients etc.) will be summarised (frequency and percentage) by stratification factor. The listing will be provided for the participant disposition status.

11. Participant demographics and other baseline characteristics

11.1 Variables and derivations

The following demographic and other baseline characteristics will be summarized by cohort:

- Age (Years) (Calculated relative to date of informed consent)
- Sex
- Race
- Weight
- Height
- BMI
- ECOG status
- Disease duration in months
- Initial Pathological Diagnosis
- Disease Stage

Age (Years) and BMI (kg/m^2) will be calculated as follows:

- $Age\ (Years) = [\frac{Date\ of\ informed\ consent - Date\ of\ birth}{365.25}]$
- $BMI\ (kg/m^2) = \frac{weight\ (kg)}{[height\ (m)]^2}$

Age Categories:

- Age <65 years
- Age ≥ 65 years

11.2 Analysis

Demographics and other baseline characteristics variables will be summarized by stratification factor. Overall summaries will include descriptive statistics for continuous measures (n, missing frequency, mean, standard deviation, median, minimum, and maximum…etc.) and for categorical measures (frequency, missing frequency and percent). Listing will be provided for safety population.

12. Exposure to Study Intervention

12.1 Variables and derivations

The date of first study intervention administration will be derived as the first date of dosing from the study intervention administration eCRF page. The date of last study intervention administration will be derived as the date of last dose of study intervention from the subject disposition eCRF page. If this date is not available, then the date of last study intervention administration will be derived as the last date of dosing from the study intervention administration eCRF page.

Interruptions, compliance, and dose changes will not be considered for calculating the duration of exposure, which will be derived as follows:

Duration of exposure (weeks) for oral study drug = (Date of last study intervention administration- Date of first intervention administration +1)/7

Duration of exposure (weeks) for Fulvestrant study drug = (Date of last study intervention administration + planned cycle length - Date of first intervention administration +1)/7

12.2 Analysis

Exposure to study intervention will be summarized and listed for the safety population.

13. Study Intervention compliance

13.1 Variables and derivations

The actual total number of tablets/capsules administered for each IMP will be obtained from the drug accountability eCRF page.

The expected number of tablets/capsules administered for each study intervention is described in Section 9.4.2.4 of the protocol. The expected number of tablets/capsules administered for each study intervention only applies for days the participant was dosed (as per study intervention exposure eCRF page). the compliance will be done for oral drug only.

The estimate of percent compliance for oral drug will be given by:

Percent Compliance = (Actual cumulative dose taken / Expected cumulative dose to be taken) X 100

The actual cumulative dose taken will be determined based on counting the number of capsules/tablets returned at each visit and subtracting that number from the number of capsules/tablets dispensed. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or omissions.

13.2 Analysis

Overall treatment compliance to study intervention will be summarized and listed for the safety population by each cohort.

14. Extent of Exposure

For abemaciclib/letrozole or anastrozole, extent of exposure will be measured by pill counts and summarized by cumulatively. The summary will include total dosage taken, number of cycles taken and dose intensity. Dose intensity will be calculated as the ratio of total dose taken to the assigned cumulative dose. For example, the assigned cumulative dose for each patient during each cycle is 150 mg per dose × 2 doses per day × 28 days = 8400 mg. The assigned cumulative dose while on study is 150 mg per dose × 2 doses per day × number of days on treatment.

For letrozole or anastrozole the cumulative dose will be calculated same way as per prescribing information.

For fulvestrant, extent of exposure will be measured using the fulvestrant administration eCRF and summarized by cycle and cumulatively. The summary will include total dosage administered and dose intensity. Dose intensity will be calculated as the ratio of total dose administered to the assigned cumulative dose. The cumulative dose will be calculated same way as per prescribing information.

Dose adjustments and omissions, along with the reason for adjustment or omission, will be summarized for abemaciclib/ letrozole or anastrozole and fulvestrant.

15. Medical and treatment history

15.1 Variables and derivations

Medical history will be coded using the CTCAE grade, Version 5.0.

The following grade categories will be summarised for the patient's Medical history as mentioned in eCRF:

- Grade 1; Mild
- Grade 2; Moderate
- Grade 3; Severe
- Grade 4; Life threatening

15.2 Analysis

Medical history will be summarized (frequency and percentage) for each cohort, by CTCAE grade for the safety population. Medical history will be presented as data listings for the safety population.

16. Prior, concomitant and other medications

16.1 Variables and derivations

Prior medications are defined as medication taken prior to first administration of the study intervention.

Concomitant medications are defined as any medication taken after or on the first administration of the study medication till the end of the trial or any medication taken prior to the first treatment administration and having “ONGOING” status at the first administration of the study medication.

16.2 Analysis

Prior, concomitant medication will be summarized and listed for safety population.

17. Adverse events

17.1 Variables and derivations

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 25.0x or higher.

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

An adverse event (AEs) is any undesirable sign, symptom or medical condition occurring after the patient signs the Informed Consent Form, even if the event is not considered to be treatment related. Each adverse event is to be recorded on the appropriate Adverse Event eCRF page. Adverse events will be graded. The severity grade will be estimated using a scale of mild (grade 1), moderate (grade 2), severe (grade 3), Life-threatening (grade 4) and Death related to AE (grade 5).

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

Treatment-emergent adverse events (TEAEs) are defined as AEs that started at the time of, or after the, first study medication administration as well as those events that started prior to the first study drug administration, but which worsened after the first study medication administration.

Adverse Events will be assessed by Investigator for causal relationship to the study mediation. The relationship between an AE and the study medication will be determined by the Investigator on the basis or his/her medical/ pharmacological knowledge and clinical judgment and using the categories yes or no.

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Life threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent disability/incapacity
5. Is a congenital anomaly/birth defect
6. Other

Imputations will only be performed where at least the year is provided. The imputations derived for partial dates will be as follows:

- Missing days will default to the first of the month for start dates and the last day of the month for stop dates.
- Missing months will default to the first month (January) for start dates and to the last month (December) for stop dates.
- There will be no default for a missing year field.

In Appendix 2 the algorithm is given for calculation of partial date imputation for adverse events (AEs) and it will be used for partially missing adverse event start and end date imputation.

The following parameters will be summarised for the patients overall adverse events as mentioned in eCRF

- Patients with at least one TEAEs
- Patients with at least one drug related TEAE
- Patients with at least one serious AEs
- Patients with at least one drug related serious AEs
- TEAEs/ related to study medication TEAEs by maximum CTCAE severity grade
- TEAEs by Causal Relationship to study medication
- TEAEs leading to death
- TEAEs /related to study medication TEAEs
- SAEs
- Drug-related TEAEs leading to death
- TEAEs leading to patient discontinuation from study
- Deaths on study
- Deaths within 30 days of treatment discontinuation or within 30 days of last dose.

The following AEs are considered to be AESIs for abemaciclib:

- neutropenia
- infections
- diarrhoea

- hepatic events, including increases in AST and ALT
- venous thromboembolic events (VTEs), and
- ILD/pneumonitis

Note: All above parameters will be summarised as well for the patients overall adverse events of special interest.

17.2 Analysis

- All the Adverse events tables will be summarised as number of patients with an event as well as percentage (%) patients with an event. The overall TEAEs tables will be presented by cohort for safety population. Separate listing for AEs and SAEs will be provided with TEAEs flag variable by cohort and participant. A data listing with all TEAEs (including coding details [SOC and PT only]) will be presented. The TEAE listing may include details but not limited to AE outcome, start date, stop date, seriousness criteria for SAEs.

18. Safety laboratory tests

All required variables for listing will be captured from the central lab (Clinical Laboratory Assessments (Haematology, Clinical chemistry, Pregnancy test, Postmenopausal Confirmation Testing)).

18.1 Variables and derivations

For safety laboratory data, baseline will be defined as the last observation made prior to the first administration of study intervention.

The following laboratory tests will be captured via central labs and to be included in the analysis:

- Haematology
- Clinical chemistry
- FSH and Estradiol (As applicable i.e. only required for women <55 years of age)

Quantitative laboratory measurements reported as "< X", i.e., below limit of quantitation, or "> X", i.e., above the upper limit of quantification, will be converted to X for quantitative summaries, but will be presented as recorded, i.e., as "< X" or "> X" in the data listings.

18.2 Analysis

The safety population alone will be used to analyse safety laboratory data.

- Grading for Safety laboratory results will be performed according to table 1.3 of the protocol. Summaries of haematology, clinical chemistry and FSH and Estradiol testing for each cohort, by cycles, will include descriptive statistics of the following:
- Actual and change from baseline (for quantitative measurements)
- Frequencies and percentages (n and %) (for qualitative measurements)

Listings will be provided for laboratory parameters by each cohort. Listing of abnormal lab values with upper and lower limit will be produced.

19. Vital signs

All summaries for vital signs will be based on the safety population. Data listings for the vitals will be based on the safety population.

19.1 Variables and derivations

For vital signs, baseline is defined as the last observation made prior to the first administration of study intervention.

The following vital signs will be reported for this study:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate

19.2 Analysis

The following summaries will be provided for vital signs data for each cohort, by days (cycles):

- Actual and change from baseline by cycles.

20. Primary safety assessments

The primary endpoint parameter is mention below.

20.1 Variables and derivations

The following variables will be reported for this study:

- TEAEs, including severity in CTCAE grade and possible relationship to study intervention
- SAEs, including possible relationship to study intervention
- Discontinuations from study treatment due to TEAEs

20.2 Analyses

20.2.1 Primary analysis

Note: TEAEs including SAEs and AESIs related endpoint covered in Section 16 (Adverse event).

20.2.2 Sensitivity analyses

Not applicable

21. Secondary safety assessments

To evaluate incidence of treatment discontinuation of abemaciclib

21.1 Variables and derivations

The following variables will be reported for this study:

- Discontinuation of abemaciclib only due to an TEAE

$$Incidence\ Rate = \frac{No.of\ subjects\ \ with\ treatment\ discontinuation\ only\ due\ to\ TEAE}{No.of\ subject\ in\ safety\ population}$$

21.2 Analyses

21.2.1 Secondary analysis

Descriptive summary (frequency & percentage) will be provided by each cohort for discontinuation cases. Data listings for these cases will be based on the safety population.

22. Other assessments

The following assessments will only be presented in data listings for the safety population:

- Physical examination data
- Biopsy Assessment
- Hepatic Monitoring Procedures
- Hepatic Risk Factor Assessment
- Hospitalization Events
- Initial Pathological Diagnosis
- Liver Related Signs and Symptoms
- New Tumour Assessment
- Response Assessment
- Systemic and Loco regional Therapies

23. Revision history

Version	Date	Change

24. Appendix 1: Programming Conventions for Tables, Data Listings and Figures (TLFs)

24.1 Paper Size, Orientation and Margins

The margin, page size and line size specifications as stipulated in Table 23.1 will be used for the presentation of all TLFs.

Table 23.1: Output margin, page size and line size specifications

	Landscape	Portrait
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® specifications:		
PAGESIZE	46	67
LINE SIZE	134	93

24.2 Fonts

The font type “Courier New” should be used as default for tables and data listings, with a font size of 8. The font color should be black. No bolding, underlining and italics are permitted.

Figures should have a default font of “Times Roman”, “Helvetica” or “Courier New”.

24.3 Header Information

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- The sponsor name should appear in row 1, left-aligned.
- The word “CONFIDENTIAL” should appear in row 1, right-aligned.
- The protocol number should appear in row 2, left-aligned.

- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right-aligned.
- The TLF identification number should appear in row 3, centered.
- The TLF title should start in row 4, centered.
- The TLF population should appear in row 5, centered. The population should be spelled out in full, e.g. *Safety analysis population* in preference to *Safety analysis population*.
- Row 6 should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- Row 7 should be a blank line.
- Mixed case should be used for titles.
- Titles should not contain quotation marks or footnote references.
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings containing numbers should be centered.
- Column headings should be in mixed case.
- In general, the analysis population count should appear in the column header in the form "(N=XX)".

24.4 Table and Data Listing Table, Listing and Figure (TLF) Conventions

24.4.1 General

- The first row in the body of the table or data listing should be blank.
- The left-hand column should start in Column 1. No indenting or centering of the TLF should occur.
- Rounding should be done with the SAS® function ROUND.
- Numerical values in tables should be rounded, not truncated.
- Numerical values should be decimal point aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug should appear first in tables with treatment group as columns.
- All variables contained on the eCRF (which have data present) should appear in the data listings, along with all derived data appearing in the corresponding tables.

- The width of the TLF should match the line size.

24.4.2 Univariate statistics

- Statistics should be presented in the same order across tables (i.e., n, mean, SD, minimum, median and maximum).
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - Minimum, maximum and CV (%): N.= 2
  - Mean and median: N + =2.
  - SD: N + 2.

24.4.3 Frequencies and percentages [n, (m) and %]

- Mentions should be reported inside parentheses, with one space between the count and the left parenthesis of the mentions. An example is given below:
  - 124 (645)

- Percent values should be reported inside parentheses, with one space between the right parenthesis of the mention and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  - 77 (156) (100.0)
  - 50 (56) (64.9)
  - 0 (0) (0.0)

- Percentages will be reported to one decimal place, except percentages <100.0 but >99.9 will be presented as '>99.9' (e.g., 99.99 is presented as >99.9); and percentages <0.1 will be presented as '<0.1' (e.g., 0.08 is presented as <0.1). Rounding will be applied after the <0.1 and >99.9 rule.
  - (<0.1)
  - (6.8)
  - (>99.9)

- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).

- Where counts are zero, mentions of 0 and percentages of 0.0 should appear in the table.

24.4.4 Confidence intervals (CIs)

- CIs should be presented with one additional decimal place as that of the raw data, and SDs and standard errors (SEs) with two additional decimal places as that of the raw data.
- CIs should be justified so that parentheses displayed on consecutive lines of a table “line up”.

24.4.5 Spacing

- There should be a minimum of 1 blank space between columns (preferably 2).

24.4.6 Missing values

- A “0” should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in data listings.

24.5 Figure output conventions

Figures should be provided in RTF files using the SAS® Output Delivery System (ODS).

24.6 Dates and times

Depending on data available, dates and times will take the form ddMMMyyyy and hh: mm.

24.7 Spelling format

The spelling format to be used is English US.

24.8 Presentation of cohorts

- Abemaciclib+ anastrozole or letrozole

- Abemaciclib+ fulvestrant

24.9 Presentation of visits

- Baseline
- Cycle 1- Day 1
- Cycle 1- Day 15
- Cycle 2- Day 1
- Cycle 2- Day 15
- Cycle 3 to 6- Day 1
- Cycle 6- Day 28
- Short-Term Follow-Up

25. Appendix 2: Partial date conventions and TEAE derivation guidelines

No date imputations will be done for this study. Conventions pertaining to partial dates are presented in Table 24.1.

Table 24.1: Algorithm for Treatment-emergent Adverse Events (TEAEs)

START DATE	STOP DATE	ACTION
Known	Known, partial or missing	If start date < Study drug start date, then not TEAE. If start date > Study drug start date, then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "no", then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "yes", then not TEAE.
Partial, but known components show that it cannot be on or after study drug start date	Known, partial or missing	Not TEAE.
Partial, could be on or after study drug start date	Known	If stop date < Study drug start date, then not TEAE. If stop date > Study drug start date, then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "no", then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "yes", then not TEAE.
	Partial	Assume stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < Study drug start date, then not TEAE. If stop date > Study drug start date, then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "no", then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "yes", then not TEAE.
	Missing	Assumed TEAE.
Missing	Known	If stop date < Study drug start date, then not TEAE.

		If stop date > Study drug start date, then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "no", then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "yes", then not TEAE.
	Partial	Assume stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < Study drug start date, then not TEAE. If stop date > Study drug start date, then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "no", then TEAE. If start date = Study drug start date and the variable "prior to first dose of study intervention" is equal to "yes", then not TEAE.
	Missing	Assumed TEAE.