NOVARTIS

Clinical Development

BYL719/Alpelisib

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ALpelisib INdia Safety STudy (ALPINIST): A Phase IV, prospective, multicenter, open-label, non-comparative, interventional study to assess the safety of alpelisib plus fulvestrant, in men and post-menopausal women with HR- positive, HER2-negative, advanced or metastatic Breast Cancer (ABC or MBC) with a PIK3CA mutation, whose disease has progressed on or after endocrine based treatment.

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    - *Author removed from SAP cover page*
    - *CREDI changed to DMS*
    - *Use "subject" or "participant" (not "Subject") to align with OneCTP*
    - *SAP posted to Registries so no personal information on trial participant should be included.*
    - *SAP can be included as is in CSR Appendix 16.1.9*
    - *Reference to SMART SAP LEANing principles*
    - *TP and MW added as Approvers for SAP*
    - *Post DBL data-drive analyses must be included in a SAP and/or TFL Shells Addendum if the analyses are to be included in the CSR*
    - *"Investigational" treatment term used instead of study/trial treatment*
    - *Only subgroup analyses addressing the key study objectives (and included in the CSR) should to be described in the SAP*
    - *Do separate analyses for pediatrics and adults if both populations are included in the study*
    - *Guidance on language that allows the flexibility to conduct primary analysis when a target sample size based on overall study population has been attained*
    - *State which population is considered primary based on the primary endpoint estimand definition.*
    - [redacted]
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    - *Analysis sets definition should be aligned with the population attributes of the chosen estimands. Per-protocol set should be used with caution under estimand framework, as E9(R1) highlights the difficulties with a naïve analysis of the per-protocol set. In section 5.5, Table 1 'Protocol deviations that cause subjects to*

be excluded' was removed; in Table 2, column of 'PD ID that cause subjects to be excluded' and row of PPS were removed.

- *Supportive analysis is split into sensitivity analysis and supplementary analysis. Subgroup analysis in section 2.2.1 belongs to supplementary analysis.*
- *Created a subsection for analysis of demographics and other baseline characteristics.*
- *Treatment attribute of the estimands (treatment of interest) may be different from investigational treatment. Analysis of treatment of interest may be necessary to interpret efficacy/safety analyses.*
- *Structures for section 2.5 and 2.6 were updated according to OneCTP to align with estimand framework.*
- *Used 'analysis supporting primary/secondary objectives' (not 'analysis of the primary objective')*
- *Removed section of analysis of the key secondary objective to align with OneCTP*

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List of abbreviations

ABC	Advanced Breast Cancer
ADR	Adverse Drug Reaction
AE	Adverse Event
AKT	Protein Kinase B
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/GPT
ARA	Acid Reducing Agents
aPTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/GOT
ATC	Anatomical Therapeutic Chemical Classification System
BAL	Broncho-alveolar Lavage
BAP	Bone-specific Alkaline Phosphatase
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CK	Creatine Kinase
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCGI	Drugs Controller General of India
DMS	Document Management System
DLT	Dose Limiting Toxicity
FAS	Full Analysis Set
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form; the term CRF can be applied to either EDC or Paper
EOT	End of Treatment
FPG	Fasting Plasma Glucose
GGT	Gamma-glutamyl transpeptidase
HbA1c	Glycosylated Hemoglobin
HDL	High Density Lipoprotein
HR	Hormone Receptor
HER2	Human Epidermal Growth Factor Receptor 2
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IQR	Internal Quartile Range

LDH	Lactate dehydrogenase
LDL	Low Density Lipoprotein
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI-CTCAE	National Cancer Institute Common Terminology Criteria Adverse Event
	NGS Next Generation Sequencing
PD	Protocol Deviation
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Phosphatidylinositol-4,5-biphosphonate 3-kinase catalytic subunit alpha
PRO	Subject-reported Outcomes
PT	Preffered Term
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
WBC	White Blood Cells
WHODD	World Health Organization Drug Dictionary

1 Introduction

This document (Statistical Analysis Plan) provides the technical and detailed elaboration of the analytical details mentioned in the CBYL719CIN01, Phase IV, prospective, multicenter, open-label, non-comparative, interventional study to assess the safety of alpelisib plus fulvestrant, in men and post-menopausal women with HR-positive, HER2-negative, advanced or metastatic breast cancer (ABC or MBC) with a PIK3CA mutation, whose disease has progressed on or after endocrine treatment. The main objective of this plan is to provide detailed information of statistical methodology, data conventions, and processes used for the analysis of data from the study.

Study reference documents and versions:

- Protocol: cbyl719cin1-protocol-amendment-version-4-30-apr-2025_Clean
- CRF: Annotated eCRF CBYL719CIN01 (v_4_07Oct2024)

1.1 Study design

This is a Phase IV, prospective, multicenter, open-label, non-comparative, interventional study to assess the safety of alpelisib plus fulvestrant in men and post-menopausal women with HR-positive, HER2-negative, ABC or MBC with a PIK3CA mutation, whose disease has progressed on or after endocrine treatment.

The study will include a total of 100 participants. During the treatment phase, treatment will beadministered as alpelisib 300 mg orally once daily dosing schedule starting on Cycle 1 Day

1 in combination with fulvestrant (i.m.) 500 mg on Cycle 1 Day 1 and Day 15, and Day 1 of every cycle thereafter (± 3 days) in a 28 days cycle for 6 cycles.

The planned duration of treatment is 6 months. Participants may be discontinued from treatment earlier due to unacceptable toxicity, disease progression, or if treatment is discontinued at the discretion of the investigator or the participant. For participants who were ongoing on treatment at the end of the planned duration of study and, in the opinion of the investigator, are still deriving clinical benefit from alpelisib, every effort will be made to continue provision of study treatment via post trial access (PTA).

1.1.1 Study Design Rationale

The following study has been planned to evaluate the safety of alpelisib in combination with fulvestrant in Indian participants with HR-positive, HER2-negative, ABC or MBC whose tumor harbors a PIK3CA mutation in accordance with the approval granted by DCGI and the requirement to conduct a local Phase IV safety study.

PIK3CA mutations occur in approximately 40% of tumors in Subjects with HR-positive, HER2-negative ABC or MBC. The PI3K α-specific inhibitor, alpelisib, has shown antitumor activity in early studies and the landmark Phase III study, SOLAR-1 (CBYL719C23201; Study C2301) (André et al 2019).

The PIK3CA mutant status is to be defined as follows:

- PIK3CA mutation will be identified by validated test analyzing the PIK3CA gene for 11 hotspots (C420R, E542K, E545X* (A/D/G/K), E545K, E545G, E545D, Q546X* (E/K/R), Q546E, Q546R, H1047X* (L/R/Y), H1047R, H1047L, H1047Y) known to affect the PI3K function in exons 7, 9 and 20.
- These hotspots are anticipated to cover the majority of the PIK3CA mutations identified in HR-positive ABC or MBC Subjects so far.

1.1.2 Treatments

During treatment phase, alpelisib 300 mg will be administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in combination with fulvestrant 500 mg starting on Days 1 and 15 of Cycle 1 and Day 1 of every cycle thereafter (± 3 days) in a 28 days cycle. A complete cycle of treatment is defined as 28 days (± 3 days) of once daily continuous treatment of alpelisib in combination with fulvestrant. The last day of a complete treatment cycle is Day 28. Day 1 of the next cycle starts on Day 29. During the study period and until the end of the 30 day safety follow–up period, Subjects will undergo evaluations for safety and tolerability at every visit outlined in Table 8-1 of the protocol. This is an open-label study, so the investigator and participant will be aware of treatment. The storage conditions for the alpelisib will be described on the medication label.

Novartis Drug Supply Management or its designee will provide alpelisib as 50 mg, 150 mg and 200 mg tablets as individual participant supply, packaged in bottles. Alpelisib will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area.

Fulvestrant will be procured locally according to local practice and regulation, or supplied by Novartis (or its designee). Storage conditions are described in the medication label. Medication

labels will comply with the legal requirements of each country and be printed in the local language.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record Case Report Form (CRF).

1.2 Study objectives, endpoints

Objective(s)	End point(s)
Primary Objective	**Endpoint for primary objective**
• To assess the safety of alpelisib plus fulvestrant	• Percentage of Subjects with at least one on-treatment AE
Secondary Objective	**Endpoints for secondary objective**
• To assess the safety of alpelisib plus fulvestrant	• Percentage of Subjects with SAEs & with ADRs
Safety Assessments	• Physical examination • ECOG performance status • Height, weight, and vital signs • ECG • Laboratory assessments including hematology, biochemistry, lipid panel, Fasting Glucose and HbA1c, fasting lipase, fasting amylase, coagulation (via PT and INR, aPTT) and urinalysis

1.2.1 Primary estimand(s)

Not Applicable

1.2.2 Secondary estimand(s)

Not Applicable

2 Statistical methods

2.1 Data analysis general information

Analysis of the data will be performed by the Biostatistics and Statistical Programming team at [redacted]. All statistical analyses will be performed using SAS® Enterprise Guide® 7.1.

The following standard descriptive analyses will be presented for all analysis populations:

- Descriptive statistics for continuous data

  The continuous data will be summarized using the number of observations (n), arithmetic mean (mean), standard deviation (SD), median, IQR, minimum and maximum value.

  The number of observations (n) will be presented with no decimal place. Mean, median and IQR will be presented up to one decimal places from the original value, SD up to one decimal places from the mean value, minimum and maximum value as an original value.

- For categorical data

  The categorical variables will be summarized using the frequency count (n) and percentage (%) for each possible value. The frequencies will be presented up to no decimal places and percentage up to 1 decimal place.

2.1.1 General definitions

2.1.1.1 Baseline definition

Non-missing values collected at immediately prior to the first dose of study drug administration will be considered as baseline values.

Or

Baseline is defined as the pre-dose assessment on C1D1 before study treatment administration.

The assessments at unscheduled visits will also be considered for the baseline computations if it is collected prior to study treatment initiation.

2.1.1.2 Handling of Missing Data

As this is Phase IV non comparative study and primary endpoint is to estimate safety, missing data will not be imputed. All Subjects observed cases will be used for analysis. Missing data will not be imputed. Only data recorded in the CRF will be analyzed. All missing data or partial dates will be presented in the subject data listing, as they are recorded on the Case Report Form (CRF). Missing data will not be estimated or carried forward in any statistical analysis.

2.1.1.3 Pooling of Centers

Data of all Centers will be pooled together for final statistical analysis.

Enrolled Population: The participants who signed the ICF and also met the study specified eligibility criteria are considered as Enrolled Population.

2.2 Analysis sets

2.2.1 Safety Population

The Safety Set includes all participants who received at least one dose of any study treatment. (i.e. at least 1 dose of any component of alpelisib or fulvestrant).

All safety data will be analyzed using the Safety Population.

2.2.2 Subgroup of interest

Not Applicable

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

Disposition of Subjects:

The following data on subject disposition will be summarized across treatment :

- Number and percentages of Subjects pre screened.
- Number of Pre Screen Failures
- Reason for Pre Screen Failures
    - Gene Mutation (PIK3CA) Testing
    - Withdrew Consent
    - If Withdrawal by Subject, Specify
    - Other
    - If Other, Specify
- Number and percentages of subjects screened (i.e. who provided informed consent)
- Number and percentages of screen failures
- Reason for Screen failures
    - Screen Failure (not met inclusion criteria/met exclusion criteria)
    - Adverse Event
    - Death
    - Withdrawn by Subject
    - If Withdrawal by Subject, Specify
    - Lost to Follow-up

- Physician Decision
- Protocol Deviation
- Other
- If Other, Specify

- Number and percentages of subjects enrolled
- Number and percentages of subjects in Safety Population
- Number and percentages of subjects who completed the study
- Number and percentages of Subjects entered in safety followup.
- Number of Subjects who discontinued the study
- Reason for Discontinuation from the Study

  - Adverse event or laboratory abnormalities
  - Pregnancy
  - Lost to follow-up
  - Physician decision
  - Participant/guardian decision
  - Death
  - Progressive Disease
  - Study terminated by sponsor
  - Technical problems
  - Use of prohibited treatment and medications
  - Any other protocol deviation that results in a significant risk to the participant's safety
  - Withdrawal of consent
  - If Withdrawal of Consent, Reason
  - Other
  - If Other, Specify

Subject data listings will be provided by all enrolled.

Study completion is defined when all treated Subjects have completed treatment of 6 months.

2.3.2 Demographics and other baseline characteristics

The following Subject demographics will be summarized for Safety Analysis population:

- Age (years)
- Gender
  - Male
  - Female
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
  - BMI (<18.5)
  - BMI (18.5 - 22.9)
  - BMI (23 - 24.9)
  - BMI (>=25)
- Ethnicity
  - Caucasian
  - Hispanic
  - Black
  - Asian
  - Unknown
  - Other
    - If Others, Specify
- Subject post-menopausal
  - Yes
  - No
- Histological classification of Breast Cancer

    - Ductal carcinoma in situ
    - Lobular carcinoma in situ
    - Invasive ductal carcinoma (ductal breast cancer)
    - Invasive Lobular carcinoma
    - Medullary carcinoma
    - Mucinous (colloid) carcinoma
    - Tubular carcinoma
    - Papillary carcinoma
    - Metaplastic breast cancer
    - Phyllodes tumors
    - Mammary Paget disease (MPD)
    - Inflammatory breast cancer
  - Staging of Breast Cancer
    - Stage IIIA
    - Stage IIIB
    - Stage IIIC
    - Stage IV
- Estrogen Receptor Result
    - Positive
    - Negative
- Progesterone Receptor Result
    - Positive
    - Negative

Subject data listings will be provided

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Descriptive statistical summaries will be provided for the following variables:

- Overall Treatment Duration (months)

  Overall Treatment Duration=(Last Day of treatment dose taken-First day of treatment dose taken)+1

- Actual Treatment Duration (months)

  Actual treatment duration will be defined as overall treatment duration minus the number of days between first day and last day of intake where the subject did not take study drug, which means actual treatment duration is given by the sum of days with actual study drug intake,

  Actual treatment duration = sum of days with actual study drug intake > 0.

- Drug Exposure Until the First Occurrence of AE

  Drug Exposure Until the First Occurrence of AE=Start date of first occurrence of any AE-start date of treatment +1.

- Number of Cycles:

  The parameter will be summarized using descriptive statistics (n, mean, SD, median, IQR and min - max) for safety population. Categories as cycles 1, cycle 2, cycle 3, cycle 4, cycle 5 and cycle 6 will be summarized by number and percentage of subjects.

- Cumulative Daily Dose:

  Cumulative Daily Dose is presented by number and percentage of subjects who took the first-time dose of 300mg and/or followed by 250mg or 200mg, within each category, based on recommended dose reduction. One subject may have counted in more than one category but only once within one category.

- Dose Reduction:

  Dose reduction will be summarized by number and percentage of subjects who got recommended dose reduction from 300mg to 250mg and/or 250mg to 200mg for the first time within each category during the study.

- Average Dose Reduction

  Average dose reduction is summarized for number of times dose reduced per subject during the study.

- Overall Study duration (months):

  The parameter will be summarized using descriptive statistics (n, mean, SD, median, IQR and min - max) for safety population.

Study duration (days) = (Date of study termination/completion - Date of obtaining ICF) +1

- Compliance:

  The parameter will be summarized using descriptive statistics (n, mean, SD, median, IQR and min - max) for safety population.

  Compliance = (Total doses consumed / Total doses advised) x 100%.

- Adjusted Compliance:

  Adjusted Compliance = [{Total doses consumed / (Total doses advised – Doses omitted or reduced due to toxicity)} × 100]

  Total Doses Advised is the planned or advised doses over the study period, considering the original treatment schedule.

  Account for Interruptions:

  - Doses Consumed : Track the total doses actually administered or consumed.
  - Doses Omitted or Reduced: Document any doses that were omitted or adjusted due to toxicity.

- Any Dose Modification

  Total Dose modification during the study will be summarised by number and percentage of subjects in Safety population.

  Additionally, number and percentage of subjects will be presented for dose reduction, temporary interruptions, discontinuation of therapy, other, if other, specify and none as recorded in CRF.

- Reason for Dose Modifications

  Number and percentage of subject will be presented for Adverse Event, Other, and if Other, specify under Reason for Dose Modification category as per CRF.

- Dose intensity (mg/day)

  Dose Intensity: It is computed as the ratio of total dose received and actual duration.,

  where Actual Duration = [(Last dose date – First dose date) + 1]

- Relative dose intensity (%)

  Relative dose intensity: It is computed as the ratio of dose intensity and planned dose intensity (i.e. planned dose received/planned duration).

Subject data listings will be provided for safety population.

2.4.2 Prior, concomitant and post therapies

2.4.2.1 Medical History

All relevant medical history (excluding the study indication) and complete surgical history will be documented at the Screening Visit from subjects' medical records and records from the investigator's interviews as designated in the Schedule of Procedures. All medical and surgical history must be noted in the Medical History page of eCRF.

Medical history events will be coded using Medical Dictionary for Regulatory Affairs (MedDRA) dictionary (September 2023, Version 26.1). The frequency count (n) and percentage (%) of subjects will be summarized according to the coded terms of system organ class (SOC) and preferred term (PT) for the safety population.Summaries will be sorted by descending overall counts of system organ class and preferred term within system organ class and, in case of equal counts, alphabetically by system organ class and by preferred term within system organ class.

Subjects will be counted only once for each system organ class and preferred term.

Subject data listings will be provided for safety population.

2.4.2.2 Prior and Concomitant Medication

Medications other than study drug, if taken and stopped within 30 days before the first study drug administration in the study are defined as prior medications. Prior medications will be documented at screening visit.

Medications other than study medications, started prior and ongoing on the first treatment day and as those starting on the first treatment day or after are defined as concomitant medications. Concomitant medications will be documented at each visit.

All medications and significant non-drug therapies taken within 30 days before the first dose is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures CRF page and updated on a continual basis if there are any new changes to the medications.

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD) (September 2023, B3 format) which employs the Anatomical Therapeutic Chemical (ATC) classification system. For all prior medications, counts (n) & percentages (%) of subjects will be presented by ATC main group and preferred drug name/verbatim terms and will be sorted in descending order of frequency of ATC main group, preferred term within ATC main group in total for safety population and, in case of equal counts, alphabetically by ATC main group, preferred term within ATC main group.

Summary of Prior Radiotherapy will be presented using number and percentage of subject for Any Prior Therapy categorised under "Yes" and "No" as per CRF.

Summary of Prior Antioplastic Medications will be provided.

Listing will be provided for Prior and Concomitant Non-Drug Treatment separately.

Subjects will be counted only once for each ATC main group, and preferred term.

Subject data listings will be provided for safety population.

2.5 Analysis supporting primary objective(s)

The primary objective will be to assess the safety of Alpelisib.

2.5.1 Primary endpoint(s)

The primary endpoint is the percentage of Subjects with at least one on-treatment adverse event.

2.5.2 Statistical hypothesis, model, and method of analysis

No hypothesis testing and therefore no inferential statistical analysis is planned for this study. Only descriptive analysis will be used to understand the collected data and characteristics of studied population.

The primary analysis will be summarized by number and percentage of Subjects with at least one TEAEs with corresponding two-sided exact 95% CI using Clopper and Pearson method in the Safety Population.

Treatment-Emergent Adverse Events (TEAEs) are defined as the adverse events that occurred, or worsened, on treatment period (i.e. from first dose of treatment up to 30 days after last dose of study drug).

The following table will be provided:

- Summary of Subjects with at least one TEAE

2.5.3 Handling of intercurrent events

Not Applicable

2.5.4 Handling of missing values not related to intercurrent event

As this is Phase IV non comparative study and primary endpoint is to estimate safety, missing data will not be imputed. All Subjects observed cases will be used for analysis.

2.5.5 Sensitivity analyses

Not Applicable

2.5.6 Supplementary analyses

Not Applicable

2.6 Analysis supporting secondary objectives

All secondary analyses will be performed on the Safety population, unless otherwise specified. The secondary objective is to assess the safety of alpelisib plus fulvestrant.

2.6.1 Secondary endpoint(s)

The secondary endpoint is :

- Percentage of Subjects with SAEs & with ADRs.

2.6.2 Statistical hypothesis, model, and method of analysis

No hypothesis testing and therefore no inferential statistical analysis is planned for this study. Only descriptive analysis will be used to understand the collected data and characteristics of studied population.

Treatment-Emergent Adverse Events (TEAEs) are defined as the adverse events that occurred, or worsened, on treatment period (i.e. from first dose of treatment up to 30 days after last dose of study drug).

The TEAEs "Related to Study Drug" are equivalent to "Adverse Drug Reactions".

An overall summary of TEAEs will be presented with number and percentage of Subjects with corresponding two-sided exact 95% CI using Clopper and Pearson method and number of TEAEs in the Safety Population according to the following characteristics:

- Subjects with at least one TEAEs
- Subjects with at least one TEAEs by CTCAE Grade
    - Grade 1
    - Grade 2
    - Grade 3
    - Grade 4
    - Grade 5
- Subjects with at least one serious TEAE
    - Congenital Anomaly or Birth Defect
    - Persistent or Significant Disability/Incapability
    - Death
    - Hospitalization or Prolonged Hospitalization
    - Life-threatening criteria
    - Other Medically Important Event
        - Other Medically Important Event, Specify
- Subjects with at least one TEAE by Causal relationship to Study Agent
    - Related
    - Not Related
    - Not Assessible
- Subjects with at least one TEAE by Relationship to Fulvestrant
    - Related

  - Not Related
  - Not Assessible
- Subject with at least one TEAE leading to below Action Taken with Study Treatment
  - Drug Permanently Withdrawn
  - Drug Temporarily Delayed/Interrupted
  - Dose Reduced
  - Dose Not Changed
  - Dose Increased
  - Not Applicable
  - Unknown
- Subject with at least one TEAE leading to below Action Taken with Subject
  - Treatment Given
  - None
  - Withdrawn from the study
  - Other
    - If Other, Specify
- Subject with at least one TEAE leading to below Outcome
  - Not recovered / Not resolved / Unchanged
  - Condition deteriorating
  - Recovered / resolved
  - Improving / recovering / resolving
  - Recovered with sequelae
  - Fatal
  - Unknown

Number and percentage of Subjects will be summarized with corresponding two-sided exact 95% CI using Clopper and Pearson method and number of TEAEs in the Safety Population. Following tables will be provided:

- Overall Summary of Subjects with TEAEs and Frequency of TEAEs
- Summary of Subjects with TEAEs and Frequency of TEAEs by System Organ Class and Preferred Term
- Overall Summary of Subjects with Serious TEAEs and Frequency of TEAEs
- Summary of Subjects with Serious TEAEs and Frequency of TEAEs by System Organ Class and Preferred Term

- Overall Summary of Subjects with TEAEs of Adverse Drug Reactions and Frequency of TEAEs of Adverse Drug Reactions
- Summary of Subjects with TEAEs of Adverse Drug Reactions and Frequency of TEAEs of Adverse Drug Reactions by System Organ Class and Preferred Term

2.6.3 Handling of intercurrent events

Not Applicable

2.6.4 Handling of missing values not related to intercurrent event

Not Applicable

2.6.5 Sensitivity analyses

Not Applicable

2.6.6 Supplementary analyses

Not Applicable

2.7 Safety analyses

2.7.1 Adverse events (AEs)

Definition and Reporting of Adverse Events will be referred to section 10.1 of the protocol.

Treatment-Emergent Adverse Events (TEAEs) are defined as the adverse events that occurred, or worsened, on treatment period (i.e. from first dose of treatment up to 30 days after last dose of study drug).

The assessment of safety will be based on mainly on the frequency of AEs,which includes all serious AEs.All AEs will be summarized using frequencies, percentages and corresponding twp-sided exact 95% C.I. (Clopper and Perason 1934) by system organ class and preferred term, and severity.

In addition, causality of adverse events to the study drug will be determined at the discretion of the treating physician, of AE to the study drug, actions taken to the study drug and treatment given will also be summarized.SAEs with fatal outcomes will separately be analyzed describing with all the factors above.

A separate summary for death including on-treatment and post treatment deaths will be provided where post treatment deaths are defined as those occurring between first dose of study drug and during the study, even including deaths which occurred after 30 days of the last dose of study drug.

All Adverse Events (AEs) will be coded using MedDRA dictionary (September 2023, Version 26.1), graded based on NCI CTCAE 4.03 grading.A summary of AEs not mentioned in the label will also be produced.Summary statistics (number and percentage of Subjects, not of events) will be classified by MedDRA System Organ Class and Preferred Term with worst CTCAE grade in Safety Population.The following tables will be presented:

- Summary of Subjects with at least one TEAEs by System Organ Class , Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs by System Organ Class , Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs by System Organ Class , CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs Related to Study Treatment by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs Related to Study Treatment by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs Related to Fulvestrant by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs Related to Fulvestrant by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs by Action Taken with Study Treatment by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs by Action Taken with Study Treatment by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs and Treatment Given as Action Taken with Subject by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs and Treatment Given as Action Taken with Subject by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one TEAEs by Outcomes by System Organ Class, Preferred Term and worst CTCAE grade - Safety Population
- Summary of Subjects with at least one TEAEs by Outcomes by System Organ Class, CTCAE Term and worst CTCAE grade - Safety Population
- Summary of Subjects with at least one Serious TEAEs Leading to Death by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs Leading to Death by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs Leading to Death and Related to Study Treatment by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs Leading to Death and Related to Study Treatment by System Organ Class, CTCAE Term and worst CTCAE grade;

- Summary of Subjects with at least one Serious TEAEs Leading to Death and Related to Fulvestrant by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs Leading to Death and Related to Fulvestrant by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs Leading to Death by Action Taken with Study Treatment by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs Leading to Death by Action Taken with Study Treatment by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs Leading to Death with Treatment Given as Action Taken with Subject by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one Serious TEAEs Leading to Death with Treatment Given as Action Taken with Subject by System Organ Class, CTCAE Term and worst CTCAE grade;
- Summary of Subjects with at least one Post-Treatment AEs Leading to Death by System Organ Class, Preferred Term and worst CTCAE grade;
- Summary of Subjects with at least one Post-Treatment AEs Leading to Death by System Organ Class, CTCAE Term and worst CTCAE grade;

- Summary of Time to First Occurrence of AE

- Summary Of Subjects With Frequency Of Hyperglycaemia

- Summary of non-diabetic subjects at baseline developing new-onset diabetes during treatment
- Listing of Adverse Events: subject ID, System Organ Class/ Preferred Term/ Adverse Event Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, TEAE Flag, Seriousness Criteria, Causal Relationship to Study Agent, Relationship to Fulvestrant, Action Taken with Study Treatment, Action taken with Subject, Outcome.
- Listing of Serious Treatment-Emergent Adverse Events: subject ID, System Organ Class/ Preferred Term/ Adverse Event Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, Seriousness Criteria, Causal Relationship to Study Agent, Relationship to Fulvestrant, Action Taken with Study Treatment, Action taken with Subject, Outcome.

2.7.1.1 Adverse events of special interest / grouping of AEs

Not Applicable

2.7.2 Deaths

The following listing in the Safety Population will be provided:

- Listing of Treatment-Emergent Adverse Events Leading to on Treatment Death: subject ID, System Organ Class/ Preferred Term/ Adverse Event Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, Seriousness Criteria, Causal Relationship to Study Agent, Relationship to Fulvestrant, Action Taken with Study Treatment, Action taken with Subject, Outcome.
- Listing of Treatment-Emergent Adverse Events Leading to Post Treatment Death: subject ID, System Organ Class/ Preferred Term/ Adverse Event Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, Seriousness Criteria, Causal Relationship to Study Agent, Relationship to Fulvestrant, Action Taken with Study Treatment, Action taken with Subject, Outcome.
- Listing of Treatment-Emergent Adverse Events Leading to Study Treatment Withdrawal: subject ID, System Organ Class/ Preferred Term/ Adverse Event Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, Seriousness Criteria, Causal Relationship to Study Agent, Relationship to Fulvestrant, Action Taken with Study Treatment, Action taken with Subject, Outcome.

2.7.3 Laboratory data

Clinical laboratory analyses (hematology, fasting biochemistry (full or partial), fasting lipase, fasting amylase, fasting lipid panel/glucose, HbA1c, and urinalysis) are to be performed by the central laboratory. Coagulation tests: Prothrombin time/International normalized ratio (PT and INR) and Activated Partial thromboplastin time (aPTT) will be done in a local laboratory of the site. In case of urgent safety management of hyperglycemia, fasting glucose assessment may be allowed to be done locally according to the schedule of assessments.

Note: as hyperglycemia typically occurs within the first weeks of treatment, fasting plasma glucose at Days 8 and 15 of Cycle 1 should be performed both locally and centrally for rapid availability for safety evaluation and dose adjustments.

Unscheduled local laboratory assessments may be performed if medically indicated to assess a (potential) AE or when the treating physician cannot wait for central laboratory results for decision making (e.g. dose modifications). In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

Central clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology, - Differential (Basophils, Eosinophils, Lymphocytes, Monocytes,

	Neutrophils)
Fasting Chemistry (full)	Calcium, Magnesium, Potassium, Sodium, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, GGT, Total Protein, Albumin, Creatinine, Creatinine Clearance, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Lactate dehydrogenase (LDH)
Fasting Chemistry	Creatinine, ALT, AST, Total Bilirubin
Fasting Lipid panel	Total Cholesterol, LDL, HDL, Triglycerides
Urinalysis	Macroscopic Panel (Dipstick) (WBC, blood, protein and glucose)
Additional tests	Amylase fasting, Lipase fasting, HbA1c, FPG

Local clinical laboratory parameters collection plan included:

- Coagulation (Prothrombin time/International normalized ratio (PT/INR) and Activated Partial thromboplastin time (aPTT))
- ECG (in case of ECG abnormalities, ECHO may be performed as required)

All laboratory parameters will be summarized descriptively by n, mean (SD), median (IQR), min and max for continuous variables whereas by number and percentage will be reported for categorical variables.

2.7.4 Other safety data

2.7.4.1 ECG

Categorical data such as 12-lead ECG will be described at all available visits based on the overall interpretation of the ECG (normal / abnormal, clinical relevance (Abnormal NCS, Abnorma CS). Frequency counts n and % will be provided for above interpretation of 12 Lead ECG at all available visits.

2.7.4.2 Vital signs

Changes in vital signs will be obtained at each visit during the treatment and at end of treatment visit. Body weight (kg), Systolic / Diastolic BP (mmHg), Body temperature(°F), Pulse Rate (beats/minute) and Respiratory rate (breaths/min) will be summarized descriptively and change from baseline will be assessed at all available visits. If more than one baseline assessment was collected, the most recent one will be used.

2.8 Pharmacokinetic endpoints

Not Applicable

2.9 PD and PK/PD analyses

Not Applicable

2.10 Subject-reported outcomes

Not Applicable

2.11 Biomarkers

Not Applicable

[redacted]

2.13 Interim analysis

Not Applicable

3 Sample size calculation

The study will enroll approximately 40 participants.This is a descriptive study and no hypothesis testing will be conducted.The primary endpoint of the percentage of Subjects reporting at least one on-treatment AE will be presented with a 2-sided 95% exact CI (Clopper and Pearson 1934).

- In the SOLAR-1 study (BYL719C2301), the percentage of Subjects in the alpelisib+fulvestant treatment group reporting at least one on-treatment AE was 99%.

  Assuming the percentage of patients with at least one AE in this study in Indian patients should be approximately in the range of values previously observed for the globally conducted SOLAR-1 study, the operating characteristics are considered for potential underlying true AE incidences rate as 90, 95, and 99%.

Different sample size scenarios with different AE rate are presented in (Table 1).

A sample size of 40 provides sufficient precision for AE rate estimation, with a confidence interval width ranging from 10.7% to 20.9% when the true AE rate varies between 90% and 99% (Table 1).

For a 90% AE rate, the 95% CI would be 76.3% to 97.2%, while for a 99% AE rate, it would be 89.3% to 100% (Table 2).

With a sample size of 40, there is a reasonable likelihood of detecting at least one adverse event, with the probability ranging from approximately 33% to over 99% depending on the underlying incidence rate (from 1% to over 20%) (Table 2).

A sample size of 40 is considered sufficient to estimate AE rates with reasonable confidence, including those of lower incidence, suggesting the study is appropriately powered to observe relevant effects.

The sample size calculation is done using SAS version 9.4.

Table 1 The width and 95% confidence intervals with varying proportions of adverse Events

Sample Size (N)	Width	Proportion (P)	Lower 95% 2-sided CI	Upper 95% 2-Sided CI
20	0.305	0.9	0.683	0.988
20	0.247	0.95	0.751	0.999
20	0.186	0.99	0.814	1
25	0.27	0.9	0.713	0.983
25	0.216	0.95	0.782	0.998
25	0.155	0.99	0.845	1
30	0.244	0.9	0.735	0.979
30	0.193	0.95	0.803	0.996
30	0.134	0.99	0.866	1
35	0.224	0.9	0.751	0.975
35	0.176	0.95	0.819	0.995
35	0.118	0.99	0.882	1
40	0.209	0.9	0.763	0.972
40	0.163	0.95	0.831	0.994
40	0.107	0.99	0.893	1

Table 2 Probabilities of observing an adverse event with varying incidence rates and sample sizes

Sample Size (N)	Incidence Rate of AE	Probability of At Least One Event
20	1%	18.21%
25	1%	22.22%
30	1%	26.03%
35	1%	29.66%
40	1%	33.10%
20	5%	64.15%
25	5%	72.26%
30	5%	78.54%
35	5%	83.39%
40	5%	87.15%
20	10%	87.84%
25	10%	92.82%
30	10%	95.76%
35	10%	97.22%
40	10%	98.52%
20	>20%	>99%
25	>20%	>99%
30	>20%	>99%
35	>20%	>99%
40	>20%	>99%

4 Change to protocol specified analyses

Not Applicable

5 Appendix

- Mock tables
- Mock Listings

5.1 Imputation rules

Not Applicable

5.1.1 Study drug

For this study, the study drug is alpelisib. Fulvestrant is also being used in this study. Study treatment in this study refers to the combination of alpelisib and fulvestrant. This is an open-label study, so the investigator and participant will be aware of treatment. The storage conditions for the alpelisib will be described on the medication label.

Novartis Drug Supply Management or its designee will provide alpelisib as 50 mg, 150 mg and 200 mg tablets as individual participant supply, packaged in bottles. Alpelisib will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area.

Fulvestrant will be procured locally according to local practice and regulation, or supplied by Novartis (or its designee). Storage conditions are described in the medication label. Medication labels will comply with the legal requirements of each country and be printed in the local language.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record Case Report Form (CRF).

5.1.2 AE date imputation

Not Applicable

5.1.3 Concomitant medication date imputation

Not Applicable

5.1.3.1 Prior therapies date imputation

Not Applicable

5.1.3.2 Post therapies date imputation

Not Applicable

5.1.3.3 Other imputations

Not Applicable

5.2 AEs coding/grading

Adverse events will be assessed and graded according to the CTCAE Version 4.03. The CTCAE grade (Version 4.03). Adverse events will be assessed and graded according to the CTCAE Version 4.03. Grade 1 to 5 will be used to characterize the severity of the AE. For CTCAE Grade 5, determine whether Grade 5 will be used to capture death information or if instead the death information will be recorded elsewhere (e.g. on a dedicated CRF to record death).

5.3 Laboratory parameters derivations

Not Applicable

5.4 Statistical models

Not Applicable

5.4.1 Analysis supporting primary objective(s)

No hypothesis testing and therefore no inferential statistical analysis is planned for this study. Only descriptive analysis will be used to understand the collected data and characteristics of studied population.

5.4.2 Analysis supporting secondary objective(s)

No hypothesis testing and therefore no inferential statistical analysis is planned for this study. Only descriptive analysis will be used to understand the collected data and characteristics of studied population.

5.5 Rule of exclusion criteria of analysis sets

The Safety Set includes all participants who received at least one dose of any study treatment

Table 1 Criteria leading to exclusion

Analysis Set	Criteria that cause subjects to be excluded
Safety	With out taking at least 1 dose of any component of alpelisib or fulvestrant

6 Reference

- ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.
- Protocol: cbyl719cin1-protocol-amendment-version-4-30-apr-2025_Clean
- CRF: Annotated eCRF CBYL719CIN01 (v_4_07Oct2024)