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1 TITLE PAGE

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Clinical Trial Protocol [CBYL719CIN01] / NCT05631795

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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List of Abbreviations

ABC	Advanced Breast Cancer
AE	Adverse Event
AI	Aromatase Inhibitor
AKT	Protein Kinase B
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/GPT
ARA	Acid Reducing Agents
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/GOT
ATC	Anatomical Therapeutic Chemical Classification System
AUC0-6h	Area Under the Curve 0-6h
b.i.d.	bis in diem (twice a day)
BAL	Broncho-alveolar Lavage
BAP	Bone-specific Alkaline Phosphatase
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CDK4/6	Cyclin-Dependent Kinases 4 and 6
CI	Confidence Interval
CK	Creatine Kinase
Cmin	Minimum Concentration
CNS	Central Nervous System
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal cross linking telopeptide of type I collagen
CYP	Cytochrome P
DCGI	Drugs Controller General of India
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DS&E	Drug Safety and Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture

EGFR	Epidermal Growth Factor Receptor
EM	Erythema Multiforme
EOT	End of Treatment
ER	Estrogen Receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography FISH Fluorescence In Situ Hybridization
FPG	Fasting Plasma Glucose
FSH	Follicle-stimulating Hormone
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GWAS	Genome Wide Association Studies
HbA1c	Glycosylated Hemoglobin
HDL	High Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
HFHC	High-fat high-calorie
HIV	Human Immunodeficiency Virus
HLA	Human Leukocytes Antigen
HR	Hormone Receptor
HR.	Hazard Ratio
i.v.	intravenous(ly)
IB	Investigator Brochure
IC50	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IIT	Investigator Initiated Trial
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Tests
LLOQ	Lower Limits of Quantitation
LFLC	Low-fat low-calorie
LVEF	Left Ventricular Ejection Fraction
MBC	Metastatic Breast Cancer
MCF7	Michigan Cancer Foundation-7

MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDR1	Multi Drug Resistance
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRP2	Multi-drug Resistance Protein-2
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
NCCN	National Comprehensive Cancer Network
NCDS	Novartis Clinical Data Standards
NCI-CTCAE	National Cancer Institute Common Terminology Criteria Adverse Event NGS Next Generation Sequencing
NDCT	New Drugs and Clinical Trials
NSAI	Non-Steroidal Aromatase Inhibitors
NTCP	Sodium Taurocholate Co-transporting Polypeptide
o.d.	omnia die (once a day)
PET/CT	Positron Emission Tomography/Computed Tomography PFS Progression-Free Survival
PgR	Progesterone Receptor
PHI	Protected Health Information
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Phosphatidylinositol-4,5-biphosphonate 3-kinase catalytic subunit alpha
PK	Pharmacokinetics
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SJS	Stevens - Johnson syndrome
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
t.i.d.	Ter in die (3 times a day)
Tc99	Technetium-99
UGT1A9	UDP-glucuronosyltransferase 1 family, polypeptide A9
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1.1 Glossary of Terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study Participant
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the participant (total daily or weekly etc.)
Enrollment	Point/time of participant entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug"
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment arms of a study
Other study treatment	Any drug administered to the participant as part of the required study procedures that was not included in the investigational treatment
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Enrolment number	A unique treatment identification code assigned to each enrolled participant
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the participant came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs administered to the participant (Participant) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when participant permanently stops taking study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Withdrawal of consent	Withdrawal of consent occurs only when a participant does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Amendment 3 (Released 30-Apr-2025)

Study status

The first participant was enrolled on 16-Aug-2022. As of 14-Apr-2025, the study is ongoing; 40 participants were enrolled, 19 participants discontinued, and 16 participants completed the study.

Amendment rationale

- The main purpose of this protocol amendment is to update the sample size from 100 to 40 participants based on the DCGI (Health Authority) approval received on 27-Jan-2025.

Changes to the protocol

The following sections are changed in the amended protocol:

- Editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency.
- Protocol summary has been aligned with changes applicable in Amendment 3.
- Section 4: Study Design
    - Updated text related to the total number of participants to be included in the study.
- Section 12.6: Sample Size calculation
    - Updated sample size to 40 and provided sample size justification for this new sample size.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Health Authorities for approval. The changes herein affect the Informed Consent. Sites are required update and submit a revised Informed Consent for approval that takes into account the changes described in this protocol amendment.

Summary of previous Amendments

Amendment 2 (Released 03-Mar-2023)

Study status

The first patient was enrolled on 16-Aug-2022 and as of 06-Feb-2023, the study is ongoing and we have enrolled two subjects in the study. One subject was discontinued due to withdrawal of consent.

Amendment rationale

The main purpose of this protocol amendment is:

- To update and clarify inclusion criterion #2 to ensure participants with confirmed *PIK3CA* mutant ABC/MBC whose disease has progressed on or after endocrine based treatment will be included in the study
- To update inclusion criterion #4 related to clarify that the assessment of adequate bone marrow and organ function is per Investigator's clinical judgement in alignment with the latest Prescribing Information for Pivikto® (alpelisib) in India.
- To revise the section on Prohibited Medications by including herbal medications in this section rather than the section on Permitted Concomitant Therapy Requiring Caution and/or Action.
- To revise the SAE reporting procedure as per the latest NDCT 2019 rules as suggested by the local safety team.
- To update and ensure uniformity across the protocol to mention that both advanced and metastatic breast cancer (ABC or MBC) patients will be included in the study in line with the latest Prescribing Information for Pivikto® (alpelisib) in India.
- To clarify that the tumor sample for *PIK3CA* testing will be performed at central laboratory within days -35 to -1 of the screening period. This is applicable only for patients who have not undergone *PIK3CA* testing previously. For patients with PIK3CA reports, the patients can start with main screening. However, molecular pre-screening and main screening will be allowed to be conducted simultaneously, if desired by the Investigator, instead of sequentially in order to reduce the time from molecular pre-screening to randomization, if needed.

Other Updates

- To clarify fulvestrant 500 mg will be administered intramuscularly as two 5 mL injections 250 mg each, one in each buttock
- To clarify that the study is a single arm study
- To update and clarify that coagulation parameters (PT, INR and aPTT) will be done in the local laboratory of the site instead of central laboratory
- To update and clarify that ECHO may be performed locally only at the Investigator's discretion in patients with abnormal ECG findings.
- To update that for re-screening participants, a new number will be assigned and not the initially assigned number.

- To clarify that during pre-screening (molecular screening), details on screen failures that reported SAEs (and no AEs) will be documented in the eCRF. However, for main study screen failures, both AEs and SAEs will be documented in the eCRF.
- To clarify that if there is an SAE due to study treatment misuse/abuse, details are to be captured in the SAE form.
- To clarify that at the conclusion of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the CRO.
- Some language and formatting changes, and typographical corrections have been done throughout the protocol.

Changes to the protocol

The following sections have been changed in the amended protocol:

- Editorial revisions, clarifications and corrections as per the Amendment 2 are made throughout the protocol to improve consistency.
- Protocol summary has been aligned with changes applicable in Amendment 2.
- Section 6.1: Inclusion Criteria
    - Updated and clarified inclusion criterion #2 to ensure completeness in the text mentioning participants with confirmed *PIK3CA* mutant ABC/MBC whose disease has progressed on or after endocrine based treatment will be included in the study
    - Updated inclusion criterion #4 related to clarify that the assessment of adequate bone marrow and organ function is per the Investigator's clinical judgement in alignment with the latest Prescribing Information for Pivikto® (alpelisib) in India.
- Section 7.2.1.1: Permitted Concomitant Therapy Requiring Caution and/or Action and Section 7.2.2: Prohibited Medications
    - Revised the section on Prohibited Medications by including herbal medications in this section rather than the section on Permitted Concomitant Therapy Requiring Caution and/or Action.
- Section 7.3.2: Treatment Assignment, Randomization
    - Clarified that the study is a single arm study
- Section 10.1.2: Serious Adverse Events
    - Revised the SAE reporting procedure as per the latest NDCT 2019 rules as suggested by the local safety team.
- Table 8-1: Assessment Schedule in Section 8: Visit Schedule and Assessments
    - Clarified in the footnotes that the tumor sample for *PIK3CA* testing will be performed at central laboratory within days -35 to -1 of the screening period. However, molecular pre-screening and main screening will be allowed to be conducted simultaneously, if desired by the Investigator.
- Section 8.4.1: Laboratory Evaluations
    - Clarified that coagulation parameters (PT, INR, and aPTT) will be done in the local laboratory of the site instead of central laboratory

IRB/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities for approval. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (Released 29-Nov-2021)

Study status

The study was in start-up phase.

Amendment rationale

The main purpose of this protocol amendment was for formatting changes and typographical corrections. Editorial revisions, clarifications and corrections as per the Amendment 1 were made throughout the protocol to improve consistency.

Changes to the protocol

- Glossary term section was updated as per protocol requirement. e.g. Participant Number, Randomization Number.
- List of abbreviation section was updated in line with protocol. i.e. AESI deleted.
- Formatting was done to rectify the error of Inclusion Criterion #4.
- Exclusion criteria # 4: Cross reference mentioned in Exclusion criteria #4 has been corrected from Inclusion Criteria # 6 to Inclusion criteria # 7. Erroneously mentioned as #6, has been corrected to #7.

  "Exclusion Criteria# 4: Participant with type I diabetes or not controlled type II (based on FPG and HbA1c, see Inclusion Criterion 7)"
- Exclusion criteria# 10 was deleted and moved to Inclusion Criteria as a Note.

  "Active, bleeding diathesis, or on oral anti-vitamin K medication (except low dose warfarin and acetylsalicylic acid or equivalent, as long as the INR is ≤ 2.0."
- Exclusion criteria# 11 - Any severe and/ or uncontrolled medical conditions - has been deleted due to repetition.
- Exclusion criteria# 05 was updated with "done at Investigator's discretion" for better clarity.
- Section 7.5.2 Dose Modification: Below statement was deleted as there is no PK in the study, which was erroneously mentioned.

  "Consider collecting a time-matched PK sample and record time and date of last study drug intake."
- Section 7.6.3 Emergency breaking of assigned treatment code: The section was not applicable and has been mentioned accordingly in the Protocol.
- Section 8 Visit schedule and assessments, Table 8-1; Section 8.4.1 Laboratory evaluations, Table 8-2: The Table was modified for better understanding and to maintain the consistency of text in the Table and in the Protocol.
- Section 9.2, Section 10, Section 11, Section 13 and Section 14 including subsections: It was erroneously hidden with Instruction text of the template, so formatting corrected.

- Section 12: As there were hidden section in template, the numbering was erroneous, so formatting corrected
- Appendix 16: Numbering of Appendices and formatting was done.

IRB/IECs

A copy of this amended protocol and Informed Consent document was submitted to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities for approval.

1.2 Protocol Summary

Title	ALpelisib PhIV 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 treatment.
Brief title	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.
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine 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-based treatment.
Primary Objective(s) and Key Secondary Objective	The primary objective is to determine the safety of alpelisib in combination with fulvestrant for participants with HR-positive, HER2-negative, ABC or MBC with a PIK3CA mutation.
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.
Population	The study will include approximately 40 men and postmenopausal women with HR+, HER2-negative ABC or MBC, who progressed on or after endocrine/CDK4/6i treatment.
Key Inclusion criteria	The investigator or designee must ensure that only participants who meet all of the inclusion and none of the exclusion criteria are offered treatment in the study. 1. Written informed consent obtained before any trial related activities and according to local guidelines. 2. Participants with confirmed PIK3CA mutant ABC or MBC whose disease has progressed on or after endocrine based treatment 3. Postmenopausal females and males ≥18 years old with confirmed HR-positive, HER2-negative ABC or MBC. • Postmenopausal status is defined either by: • Prior bilateral oophorectomy • Age ≥60 y • Age <60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and Follicle-stimulating Hormone (FSH) and estradiol in the postmenopausal range per local normal range Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status (NCCN.2.2015). Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression in this trial.

	4. Participant has adequate bone marrow and organ function that is considered appropriate to receive study treatment, as per the Investigator's clinical judgement. 5. Adequate liver function as shown by: • In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN. • If the Participant has liver metastases, ALT and AST ≤ 5 × ULN (elevated AST or AST values must be stable for 2 weeks, without evidence of biliary obstruction by imaging done at Investigator's discretion). • Total bilirubin < 2 × ULN (any elevated bilirubin should be asymptomatic at enrollment) except for Participants with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN 6. Adequate renal function as shown by: • Creatinine Clearance ≥ 35 mL/min using Cockcroft-Gault formula 7. Fasting plasma glucose (FPG) ≤140 mg/dL (7.7 mmol/L) and glycosylated hemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met) 8. ECOG (Eastern Cooperative Oncology Group) Performance Status < 2 9. Fasting Serum amylase ≤ 2 × ULN and Fasting Serum lipase ≤ ULN 10. Potassium within normal limits, or corrected with supplements 11. Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ grade 1 if judged clinically not significant by the investigator
Key Exclusion Criteria	1. Known hypersensitivity to alpelisib or fulvestrant, or to any of the excipients of alpelisib or fulvestrant 2. Participant ineligible for endocrine therapy per the investigator's judgment 3. Participant has received prior treatment with any PI3K inhibitors and / or mTOR inhibitor 4. Participant with type I diabetes or not controlled type II (based on FPG and HbA1c, see inclusion criterion 7) 5. Participant has a concurrent malignancy or malignancy within 3 years of study screening period, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer 6. Participant has not recovered to grade 1 or better from related adverse effects of prior anti-cancer therapy (with the exception of alopecia) 7. Participants receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry except in cases outlined below: Topical applications, inhaled sprays, eye drops or local injections are allowed. Participants on stable low dose of corticosteroids for at least two weeks prior to enrollment are allowed 8. Bilateral diffuse lymphangitic carcinomatosis 9. Participants with a known history of HIV seropositivity. Screening for HIV infection at baseline is not required 10. Active, bleeding diathesis, or on oral anti-vitamin K medication 11. Participant with severe liver impairment (Child Pugh score B/C) 12. Participant has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs 13. Participant has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate patient participation in the clinical study 14. Participant has documented pneumonitis/interstitial lung disease which is active and requiring treatment 15. Participant has active cardiac disease or a history of cardiac dysfunction 16. Participants with unresolved osteonecrosis of the jaw 17. Participant has a history of severe cutaneous reactions like Stevens-Johnson-Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

18. Participant is a nursing (lactating) or pregnant woman
19. Participant is a woman of child-bearing potential defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study treatment and at least for 1 week (for alpelisib) or 1 year (for fulvestrant based on prescribing label) after the last dose of each study drug (whichever comes later).

    Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the Participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female Participants on the study the vasectomized male partner should be the sole partner for that Participant
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS) without hormonal component.

    Use of oral (estrogen and progesterone), injected or implanted combined hormonal method of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormonal vaginal ring or transdermal hormone contraception. In case of use or oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Note: Women are considered postmenopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 6 weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
20. Participant is a sexually active male unwilling to use a condom during intercourse while taking study treatment, and for 1 week (for alpelisib) or 1 year (for fulvestrant based on prescribing label) after stopping each study drug (whichever comes later). A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm during study and up to the time period specified above.

Investigational and reference therapy

The Participants will receive following treatments:

Study treatment & Dose	**Pharmaceutical form and route of administration**	**Frequency and/or Regimen**
Fulvestrant- 500 mg	Injection for i.m. administration (500 mg should be administered intramuscularly slowly (1 - 2 minutes per injection) as two 5 mL injections 250 mg each, one in each buttock)	Dosed every 28 days (Cycle 1 Day 1) with 1 additional dose on Day 15 of Cycle 1
Alpelisib- 300 mg	Tablet for oral use	Once daily

Safety assessments	● Incidence of AEs, including SAEs and ADRs after treatment initiation ● 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
Data analysis	The assessment of safety will be based mainly on the percentage of patients with at least one on-treatment adverse event and on the number of laboratory values that fall outside of pre-determined ranges
Key words	● HR+, HER2-negative, ABC or MBC, alpelisib, fulvestrant, PI3K, CDK4/6 inhibitor, Phase IV, ER+, PgR+, men, postmenopausal, aromatase inhibitor.

2 INTRODUCTION

2.1 Background

Breast cancer (BC) is the most common cancer in women, with about 900,000 new cases annually. It is estimated that worldwide over 508,000 women died in 2011 due to breast cancer (Global Health Estimates, WHO 2013). Breast cancer in men is a more rare disease and makes up <1% of all cases of breast cancers, but its treatment is based on the guidelines for female breast cancer (Foerster 2014, Agrawal 2007, Patten 2013, Giordano 2002).

Breast cancer is now the most common cancer in women in India. The annual percentage change in the incidence ranged from 0.46 to 2.56 for breast cancer. In 2015, there will be an estimated 155,000 new cases of breast cancer and about 76,000 women in India are expected to die of the disease (Rangarajan et al 2016). Subtypes of breast cancer are distinguished by expression of estrogen receptors (ER), progesterone receptors (PgR) and human epidermal growth factor receptor-2 (HER2), as well as by distinct gene expression profiles (Perou et al 2000; Sotiriou and Pusztai 2009). Within these subtypes 60-70% of breast tumors are HR-positive HER2-negative. Expression of the ER and/or PgR is one of the most important prognostic factors in invasive breast cancer. Estrogen deprivation therapy is the core treatment modality in patients with HR-positive advanced breast cancer. Endocrine therapy options for postmenopausal women with ER+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer (MBC) include selective ER modulators (SERM; tamoxifen), ER antagonists (fulvestrant), selective nonsteroidal AIs (NSAI; anastrozole and letrozole) and steroidal AIs (exemestane). Blocking estrogen signaling with tamoxifen has been the main approach in treatment for ER+ breast cancer for over 35 years. In postmenopausal women, AIs reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens in non-ovarian tissues; synthesis in these tissues is the primary source of estrogens in postmenopausal women. AIs are generally used as the first line of therapy for women with HR-positive breast cancer (Beslija 2009; NCCN 2.2015).

2.2 The PI3K Pathway

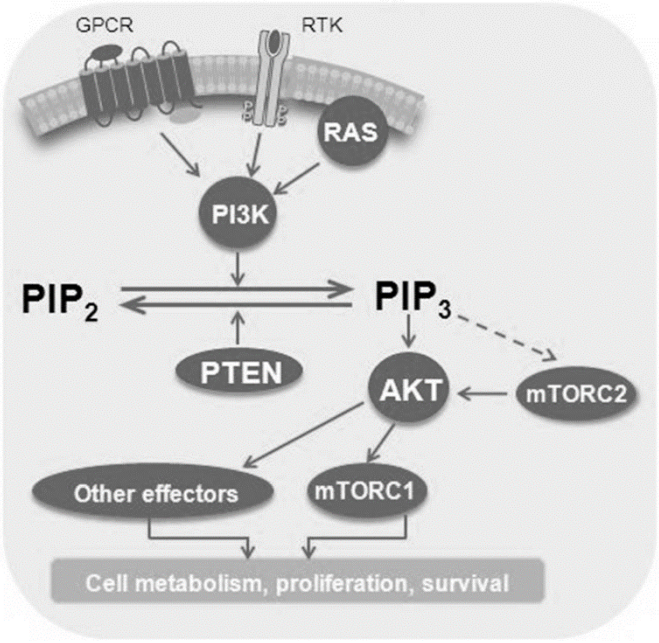
The phosphatidylinositol-3-kinase (PI3K) signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso 2001). PI3K signaling also serves a central role in the pathogenesis of numerous forms of neoplasia. Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors and in many tumor types (Liu 2009). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006).

Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to:

- Gain-of-function mutations of PI3K subunits (*PIK3CA* encoding the PI3K catalytic subunit p110α; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (e.g., HER2, EGFR, RAS, Src-family proteins) or
- Loss-of-function mutations or epigenetic alterations affecting negative regulators of PI3K signaling (e.g., loss of Phosphatase and Tensin Homolog (PTEN) expression or function) (Chow 2006, Cully 2006).

A schematic representation of these PI3K components is shown in Figure 2-1.

Figure 2-1 Schematic Representation of the PI3K Pathway



2.3 PI3K Pathway in HR-Positive Breast Cancer

PI3K pathway is frequently altered in HR-positive breast cancer. Gain-of-function mutations in *PIK3CA* have been observed in about up to 45% of HR-positive breast cancer patients using next generation sequencing (NGS) approach (Table 2-1). Inactivation of the tumor suppressor gene PTEN via loss-of-function mutations, gene deletion or transcriptional down-regulation also leads to PI3K pathway activation and has been reported in approximately 13% of HR-positive breast cancer patients (Table 2-1).

The overlap between *PIK3CA* and PTEN alteration appears relatively rare (Cancer Genome Atlas Network 2012).

Table 2-1 PI3K Signaling Pathway Mutations and Alterations in Breast Cancer

	***PIK3CA* Mutation**	**PTEN mutation/loss**
All breast tumors	36%	NR
HR-positive HER2- negative	45%	13%
Triple Negative	9%	35%
HER2- positive	39%	4%
(Cancer Genome Atlas Network 2012)		

PIK3CA mutations occur in approximately 40% of patients with HR– positive, HER2–negative breast cancer. The PI3Kα-specific inhibitor alpelisib has shown antitumor activity in early studies and landmark phase III study SOLAR-1 (André et al 2019).

A total of 572 patients underwent randomization, including 341 patients with confirmed tumor-tissue PIK3CA mutations. Using a median follow-up time (between randomization and the data cut-off date of 12-Jun-2018) of 20 months for the cohort of patients with PIK3CA-mutated cancer, median progression-free survival per investigator assessment was 11.0 months (95% confidence interval [CI], 7.5 to 14.5) in the alpelisib+fulvestrant group, as compared with 5.7 months (95% CI, 3.7 to 7.4) in the placebo+fulvestrant group (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; one-sided p-value < 0.001).

PFS in the cohort without PIK3CA-mutated cancer did not meet the proof-of-concept criteria; the hazard ratio was 0.85 (95% CI, 0.58 to 1.25; posterior probability of hazard ratio <1.00, 79.4%). At the time of final PFS analysis, overall survival was not mature, with 92 of the required 178 deaths for the final OS analysis reported.

Overall response rate among all the patients in the cohort with PIK3CA-mutated cancer was greater with alpelisib+fulvestrant than with placebo+fulvestrant (26.6% vs. 12.8%); among patients with measurable disease in this cohort, the percentages were 35.7% and 16.2%, respectively. In the overall population, the most frequent adverse events of grade 3 or 4 were hyperglycemia (36.6% in the alpelisib+fulvestrant group vs. 0.7% in the placebo+fulvestrant group) and rash (9.9% vs. 0.3%). Diarrhea of grade 3 occurred in 6.7% of patients in the alpelisib+fulvestrant group, as compared with 0.3% of those in the placebo+fulvestrant group; no diarrhea of grade 4 was reported. The percentages of patients who discontinued study drug due to adverse events were 25.0% and 4.2%, respectively for the alpelisib and placebo arms.

2.4 Purpose

The purpose of this study is 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 in Indian participants.

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 Drugs Controller General of India (DCGI)/ Health Authority and the requirement to conduct a local Phase IV safety study.

Efficacy of alpelisib has been already evaluated in a randomized, Phase III trial where alpelisib (at a dose of 300 mg per day) plus fulvestrant (at a dose of 500 mg every 28 days and once on day 15) was compared with placebo plus fulvestrant in patients with HR-positive, HER2-negative ABC or MBC who had received endocrine therapy. Patients were enrolled into two cohorts on the basis of tumor-tissue PIK3CA mutation status.

The primary endpoint was progression-free survival as assessed by the investigator per RECIST1.1 in the cohort with a PIK3CA mutation; progression-free survival was also analyzed in the cohort without PIK3CA mutation as a secondary endpoint. Additional secondary endpoints included overall survival, overall response rate and safety. Treatment with alpelisib plus fulvestrant prolonged progression-free survival among patients with HR-positive, HER2-negative, ABC or MBC with a PIK3CA mutation who had received endocrine therapy previously.

3 OBJECTIVES AND ENDPOINTS

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the safety of alpelisib plus fulvestrant	• Percentage of patients with at least one on-treatment AE
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the safety of alpelisib plus fulvestrant	• Percentage of patients with SAEs & with ADRs

4 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-based treatment.

The study will include approximately 40 participants. During the treatment phase, treatment will be administered 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.

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).

5 RATIONALE

5.1 Rationale for Study Design

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 (Health Authority) and the requirement to conduct a local Phase IV safety study.

PIK3CA mutations occur in approximately 40% of tumors in patients 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).

This is a Phase IV, prospective, multicenter, open-label, non-comparative, interventional study to assess the safety of alpelisib plus fulvestrant, in patients with HR-positive, HER2-negative ABC or MBC with a PIK3CA mutation that has progressed on or after endocrine treatment (with or without CDKi).

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 patients so far.

5.2 Rationale for Dose/Regimen and Duration of Treatment

Selection of the alpelisib 300-mg daily dosing schedule was based on the results of the first in-human study where alpelisib was administered both as a single agent and in combination with fulvestrant. In Study X2101, 134 adult participants with advanced solid malignancies whose tumors had an alteration (mutation or amplification) of the PIK3CA gene were treated until the 22-Mar-2017 data cut-off date. These participants received treatment with increasing doses of oral alpelisib (30 mg to 450 mg orally once daily or 120 mg to 200 mg orally b.i.d.) and the maximum tolerated dose (MTD) for alpelisib monotherapy was determined to be 400 mg. In the dose expansion phase, eighty-seven participants with heavily pretreated HR-positive, HER2-negative metastatic breast cancer were treated with alpelisib (300 mg, 350 mg, and 400 mg once daily) in combination with fulvestrant (500 mg administered on Days 1 and 15 of the first cycle and Day 1 of subsequent cycles). The MTD for alpelisib in combination with fulvestrant was declared at 400 mg. The recommended dose for expansion (further development) was determined to be 300 mg as a result of its acceptable safety profile, lower risk for hyperglycemia or rash compared with 400 mg, adequate exposure, and preliminary evidence of clinical activity.

Therefore, the combination of alpelisib 300 mg administered orally once daily with fulvestrant (500 mg) was selected for further evaluation in the Phase III registration Study C2301 that included participants from India. This is also the dose as per the approved US FDA prescribing information (May 2019); additionally, it has been approved in 10 countries. Alpelisib received approval from DCGI (Health Authority, India on 3 January 2020.

Therefore, in this study, alpelisib 300 mg orally daily plus fulvestrant 500 mg i.m. on Days 1 and 15 of Cycle 1 and Day 1 of every cycle thereafter will be administered where a cycle is defined as 28 days ± 3 days.

5.3 Rationale for Choice of Drugs

Not applicable.

5.4 Purpose and Timing of Interim Analyses/Design Adaptations

Not applicable.

5.5 Risks and Benefits

Participants in this study will be carefully monitored for key toxicities that have been observed with alpelisib and fulvestrant when administered in combination. The following assessments will be performed (see Section 8): periodic laboratory test including renal and liver function tests, urinalysis, and ECGs.

Risk will be minimized by adherence to inclusion/exclusion selection criteria (see Section 6), avoidance of prohibited medication (see Section 7.2.2), close safety monitoring, and alpelisib dose adjustment guidelines (see Section 7.2 and current fulvestrant prescribing information [Faslodex® prescribing information, 2011]).

6 POPULATION

The study will include 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-based treatment.

The investigator or designee must ensure that only participants who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

The participants are not permitted to participate in additional parallel investigational drug or device studies.

6.1 Inclusion Criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent obtained before any trial related activities and according to local guidelines.
2. Participants with confirmed PIK3CA mutant ABC or MBC whose disease has progressed on or after endocrine based treatment
3. Postmenopausal females and males ≥ 18 years old with confirmed HR-positive, HER2-negative ABC or MBC.

   Postmenopausal status is defined either by:
   - Prior bilateral oophorectomy
   - Age ≥60 y
   - Age <60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and Follicle-stimulating Hormone (FSH) and estradiol in the postmenopausal range per local normal range

Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status (NCCN.2.2015). Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression in this trial.

4. Participant has adequate bone marrow and organ function that is considered appropriate to receive study treatment, as per the Investigator's clinical judgement.
5. Adequate liver function as shown by:
   - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 × ULN.
   - If the participant has liver metastases, ALT and AST ≤ 5 × ULN (elevated AST or AST values must be stable for 2 weeks, without evidence of biliary obstruction by imaging done at Investigator's discretion).
   - Total bilirubin < 2 × ULN (any elevated bilirubin should be asymptomatic at enrollment) except for Participants with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
6. Adequate renal function as shown by:
   - Creatinine Clearance ≥ 35 mL/min using Cockcroft-Gault formula

7. Fasting plasma glucose (FPG) ≤140 mg/dL (7.7 mmol/L) and glycosylated hemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met)
8. ECOG (Eastern Cooperative Oncology Group) Performance Status < 2
9. Fasting Serum amylase ≤ 2 × ULN and Fasting Serum lipase ≤ ULN
10. Potassium within normal limits, or corrected with supplements
11. Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ grade 1 if judged clinically not significant by the investigator

6.2 Exclusion Criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Known hypersensitivity to alpelisib or fulvestrant, or to any of the excipients of alpelisib or fulvestrant
2. Participant ineligible for endocrine therapy per the investigator's judgment
3. Participant has received prior treatment with any PI3K inhibitors and/or mTOR inhibitor
4. Participant with type I diabetes or not controlled type II (based on FPG and HbA1c, see inclusion criterion 7)
5. Participant has a concurrent malignancy or malignancy within 3 years of study screening period, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer
6. Participant has not recovered to grade 1 or better from related side effects of prior anti-cancer therapy (with the exception of alopecia)
7. Participants receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry except in cases outlined below: Topical applications, inhaled sprays, eye drops or local injections are allowed. Participants on stable low dose of corticosteroids for at least two weeks prior to enrollment are allowed
8. Bilateral diffuse lymphangitic carcinomatosis
9. Participants with a known history of HIV seropositivity. Screening for HIV infection at baseline is not required
10. Active, bleeding diathesis, or on oral anti-vitamin K medication
11. Participant with severe liver impairment (Child Pugh score B/C)
12. Participant has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs
13. Participant has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate participation in the clinical study
14. Participant has documented pneumonitis/interstitial lung disease which is active and requiring treatment
15. Participant has active cardiac disease or a history of cardiac dysfunction
16. Participants with unresolved osteonecrosis of the jaw

17. Participant has a history of severe cutaneous reactions like Stevens-Johnson-Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
18. Participant is a nursing (lactating) or pregnant woman
19. Participant is a woman of child-bearing potential defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study treatment and at least for 1 week (for alpelisib) or 1 year (for fulvestrant based on prescribing label) after the last dose of each study drug (whichever comes later).

    Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the Participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female Participants on the study the vasectomized male partner should be the sole partner for that Participant
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS) without hormonal component.

    Use of oral (estrogen and progesterone), injected or implanted combined hormonal method of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormonal vaginal ring or transdermal hormone contraception. In case of use or oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Note: Women are considered postmenopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 6 weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
20. Participant is a sexually active male unwilling to use a condom during intercourse while taking study treatment, and for 1 week (for alpelisib) or 1 year (for fulvestrant based on prescribing label) after stopping each study drug (whichever comes later). A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm during study and up to the time period specified above.

7 TREATMENT

7.1 Study Treatment

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).

7.1.1 Investigational and Control Drugs

All eligible participants will receive (refer to Table 7-1 for dose & treatment schedule):

Alpelisib and fulvestrant

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.

Table 7-1 Alpelisib and Fulvestrant Dose and Treatment Schedule

Study Drug	Pharmaceutical form & route of administration	Max Dose & unit	Min Dose & unit	Frequency
Alpelisib	Film coated tablet for oral use	300 mg	150 mg	Daily (continuous) starting C1D1
Fulvestrant	Injection for i.m. administration (500 mg should be administered intramuscularly slowly (1 - 2 minutes per injection) as two 5 mL injections 250 mg each, one in each buttock)	500 mg		Days 1, 15 on Cycle 1 and Day 1 at each cycle thereafter

Dose reduction levels for alpelisib will be administered accordingly. For example, alpelisib 250 mg should preferentially be administered as 1 × 50 mg tablets + 1 × 200 mg tablet

7.1.2 Additional Study Treatments

No other treatment beyond alpelisib and fulvestrant are included in this trial.

7.1.3 Treatment Arms/Group

This is an open-label study and all participants will be offered alpelisib 300 mg p.o. + fulvestrant 500 mg i.m.

7.1.4 Treatment Duration

The planned duration of treatment is six (6) months. Participants may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the participant.

7.1.5 Post-Trial Access

Every effort will be made by Novartis to continue provision of study treatment via Post-Trial Access (PTA) to the patients who will be

- receiving study treatment till the end of the planned duration of study and in the opinion of the investigator, is still deriving clinical benefit from alpelisib and are
- willing to continue study treatment.

The investigator will also certify and the patients will provide the consent that the sponsor will have no liability for post-trial use of the study treatment and the same has been notified/approved by the Ethics Committee for clinical trial.

7.2 Other Treatment(s)

Not applicable

7.2.1 Concomitant Therapy

Medications required to treat adverse events, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed, except if specifically prohibited.

The participant must be told to notify the investigational site about any new medications she/he takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, physical therapy and blood transfusions) administered within 30 days of screening and during the study must be listed on the Concomitant medications/Significant non-drug therapies CRF.

7.2.1.1 Permitted Concomitant Therapy Requiring Caution and/or Action

Medications which are sensitive substrates for CYP3A4, CYP2C8, CYP2B6, CYP2C9 or CYP2C19 and/or which have a narrow therapeutic index are to be used with caution. The Investigator may contact the Medical Monitor for any questions regarding the use of permitted concomitant therapy requiring caution and/or action. These medications can be given based on Investigator’s judgment as appropriate.

7.2.2 Prohibited Medication

The following medications are prohibited during combined alpelisib and fulvestrant treatment in this study:

- Strong inducers of CYP3A4: avoid coadministration of alpelisib with a strong CYP3A4 inducers as it could potentially reduce the effectiveness of alpelisib
- Inhibitors of BCRP efflux transporter: avoid the use of BCRP inhibitors in subjects treated with alpelisib. If unable to use alternative drugs, closely monitor for increased adverse reactions.
- Other investigational and antineoplastic therapies

In addition, the use of herbal preparations/medications and dietary supplements (except for vitamins) are prohibited throughout the study, as a potential drug-drug interaction is possible. Herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng. Participants should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

As far as possible avoid co-administering QT prolonging drugs (or any other drug with the potential to increase the risk of drug-related QT prolongation e.g. via a potential drug-drug interaction increasing the exposure of the study drug or the exposure of the QT prolonging drug). If during the course of the study, concomitant administration of drugs with a known potential to cause Torsades de Pointe is required and cannot be avoided, study drug must be interrupted until an assessment of the potential safety risk has been performed. A definitive list of drugs associated with QT prolongation and/or Torsades de Pointe is available online at www.crediblemeds.org. If, based on the investigator assessment and clinical need study treatment is resumed, close ECG monitoring is advised.

7.2.3 Rescue Medication

Not applicable

7.3 Participant Numbering, Treatment Assignment, Randomization

7.3.1 Participant Numbering

Each Participant is identified in the study by a Participant Number (Participant No.), that is assigned when the Participant is first enrolled for screening and is retained as the primary identifier for the Participant throughout his/her entire participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential Participant number suffixed to it, so that each Participant is numbered uniquely across the entire database. Upon signing the informed consent form (ICF), the Participant is assigned to the next sequential Participant No. available.

7.3.2 Treatment Assignment, Randomization

No randomization will be performed in this study as its open-label, single arm study.

7.4 Treatment Blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the clinical trial team.

7.5 Dose Escalation and Dose Modification

7.5.1 Dose Escalation Guidelines

No dose escalation is planned in the study.

7.5.1.1 Starting Dose

Alpelisib at a dose of 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 i.m. at day 1 of enrollment.

Alpelisib is dosed on a flat scale of mg/day and not by weight or body surface area. There will be no breaks between dosing cycles.

7.5.2 Dose Modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the participant to continue the study treatment. These changes must be recorded on the Dosage Administration Record CRF.

Fulvestrant

The established clinical dose of fulvestrant (500 mg) will be used and no dose modification of fulvestrant is planned in this study. For information on fulvestrant and management of related AEs refer to the Faslodex® SmPC or local Prescribing Information.

Alpelisib

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of alpelisib therapy. A maximum of 2 dose reductions will be allowed, after which the participant will be discontinued from treatment with alpelisib. Dose reduction should be based on the worst preceding toxicity.

Please refer to Table 7-2 and Table 7-3 for guidance.

Table 7-2 Dose reduction sequential steps for alpelisib

Alpelisib dose level	Dose and schedule	Number of tablets & strength
Starting dose	300 mg/day continuously	1 × 200 mg tablet and 2 × 50 mg tablet or 2 × 150 mg tablets
Dose level -1	250 mg/day continuously	1 × 200 mg tablet and 1 × 50 mg tablet
Dose level -2	200 mg/day continuously	1 × 200 mg tablet

Recommendations for dose reduction or dose interruption of alpelisib in the management of adverse reactions are summarized in Table 7-2. No dose modification for fulvestrant is permitted. Clinical judgment of the treating physician, including confirmation of lab values if deemed necessary, should guide the management plan of each participant based on individual benefit/risk assessment.

However, treatment must be discontinued as indicated in Table 7-3.

After treatment is resumed at a lower dose:

If the same toxicity recurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration.

Once the alpelisib dose has been reduced, no re-escalation will occur, even upon resolution of AE.

If alpelisib dosing is held for > 28 days since planned dose or fulvestrant is held for more than 35 days since a planned injection, then participant should be withdrawn from the study. Participants who have been withdrawn from the study due to study drug discontinuation (i.e. either fulvestrant or alpelisib) should be scheduled for an End of Treatment visit (EOT). Once withdrawn from study, patients may receive treatment outside of the study as per routine management and PI discretion.

Table 7-3 Criteria for interruption and re-initiation of alpelisib treatment

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Investigations (Fasting Glucose)	
Hyperglycemia Always consider consultation with a diabetologist and recommend/reinforce on lifestyle changes as per ADA,i.e. exercise and dietary advice (e.g. small frequent meals, low carb, high fiber, balancing carbs over the course of the day. Three small meals and 2 small snacks rather than one large meal). Note: this table provides dose management recommendations. The preferred option for treating alpelisib- induced hyperglycemia is metformin, given its wide availability and well characterized safety profile. However, in case of intolerance to or unavailability of metformin, investigator's judgment should be exercised and other insulin sensitizers such as thiazolidinediones or dipeptidyl peptidase-4 Inhibitors can be used.	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For participants with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this apply only for values > 140 mg/dL (7.7 mmol/L)	Maintain dose level, and remind participant on lifestyle changes*. • If FPG < 140 mg/dL, consider adding metformin as per guidance below or in cooperation with diabetologist • If FPG 140-160 mg/dL, start/intensify metformin as per guidance below or in cooperation with diabetologist • Metformin 500 mg once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg bid, with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. • Monitor FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every two

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
	weeks until FPG is within baseline values
Grade 2 (> 160 – 250 mg/dL) [> 8.9 - 13.9 mmol/L]	**Maintain dose level** and remind participant on lifestyle changes*, exclude confounding factors like e.g. urinary tract infection, consider consultation with a diabetologist and start oral- antidiabetic treatment, e.g. metformin 500 mg bid with breakfast and dinner. If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Titrate to the maximum tolerated dose over a period of 3 weeks. • If FPG is still rising on maximum tolerated dose of metformin or persistently > 160mg/dl (> 8.9 mmol/L), add an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose). • Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1 • If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib by 1 dose level • Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG >250mg/dL.
Grade 3 (> 250 - 500 mg/dL) [> 13.9 – 27.8 mmol/L]; hospitalization indicated	**Omit alpelisib** and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors like e.g. urinary tract infection and consider consultation with a diabetologist. • Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate. Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of alpelisib-induced hyperglycemia given the short half-life of alpelisib. • Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1. • If FPG resolves to ≤ Grade 1 within 3-5 days, while off study treatment and on metformin, re-start alpelisib and reduce 1 dose level, continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG > 250 mg/dl

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
	• If FPG does not resolve to Grade 1 within 3-5 days while off study treatment and on metformin, consult a diabetologist for management of diabetes is strongly recommended. If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue participant from alpelisib treatment.
Grade 4 ((> 500 mg/dL) [≥ 27.8 mmol/L]; life-threatening consequences	**Omit alpelisib**, confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors like e.g. urinary tract infection. Consider cooperation with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours. • If grade improves then follow specific grade recommendations • If FPG is confirmed at Grade 4 and confounding factors could be excluded, permanently discontinue participant from alpelisib.
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 × 10^9/L) Grade 2 (ANC < 1.5 - 1.0 × 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 × 10^9/L) Grade 4 (ANC < 0.5 × 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 × 10^9/L, with a single temperature of ≥ 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour)	Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 × 10^9/L) Grade 2 (PLT < 75 - 50 × 10^9/L)	Maintain dose level

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 3 (PLT < 50-25 × 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 × 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Investigations (Renal)	
Creatinine increased	
Grade 1 (> 1 – 1.5 x baseline; > ULN – 1.5 × ULN)	Maintain dose level
Grade 2 (> 1.5 – 3.0 x baseline; 1.5 – 3.0 × ULN)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (>3.0 x baseline; > 3.0 – 6.0 × ULN)	Permanently discontinue participant from alpelisib
Grade 4 (> 6.0 × ULN)	Permanently discontinue participant from alpelisib
Investigations (Hepatic)	
Isolated total Bilirubin elevation (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	
Blood bilirubin increased	
Grade 1 (> ULN - 1.5 × ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 × ULN)	Omit dose. Monitor LFTs[b] weekly or more frequently if clinically indicated, until resolved to ≤ Grade 1, then: • If resolved in ≤ 14 days, then maintain dose level • If resolved in > 14 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 × ULN)*	Omit dose. Monitor LFTs[b] weekly or more frequently if clinically indicated, until resolved to ≤ Grade 1, then: • If resolved in ≤ 14 days, ↓ 1 dose level • If resolved in > 14 days discontinue participant from alpelisib. The participant should be monitored weekly

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
	(including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks
Grade 4 (> 10.0 × ULN)*	Permanently discontinue participant from alpelisib The participant should be monitored weekly (including LFTs[b]), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.
Isolated AST or ALT Elevation Confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorders, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction	
Grade 1 (> ULN – 3.0 × ULN)	Maintain dose level with LFTs[b] monitored per protocol
Grade 2 (> 3.0 - 5.0 × ULN) • For participants with baseline value ≤ 3.0 × ULN	• Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN
• For participants with baseline value > 3.0-5.0 × ULN	• Maintain dose level

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 3 (> 5.0 - 20.0 × ULN) **> 5.0 - 10.0 × ULN** • For participants with baseline value ≤ 3.0 × ULN	Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 × ULN Then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, ↓ 1 dose level
• For participants with baseline value > 3.0-5.0 × ULN	• Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b], weekly, or more frequently if clinically indicated, until resolved to ≤ 5.0 × ULN If resolved in ≤ 21 days, maintain dose level If resolved in > 21 days and confounding factors have been excluded, ↓ 1 dose level
> 10.0 - 20.0 × ULN	• Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ baseline. Then ↓ 1 dose level.
Grade 4 (> 20.0 × ULN) • For participants deriving clinical benefit upon investigator's judgement	• Omit dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3 × ULN (or ≤ 5 × ULN for participants with baseline value > 3.0 -5.0 × ULN), then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed; if reoccurs at > 5 × ULN, discontinue participant from alpelisib.
For all other participants	• Discontinue participant from alpelisib Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to baseline or stabilization over 4 weeks
Combined[c] elevations of AST or ALT and total Bilirubin	

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion

Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
• For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 × ULN and combined with total bilirubin > 2.0 × ULN	• Permanently discontinue alpelisib
• or participants with elevated baseline AST or ALT or total bilirubin value [AST or ALT > 2 × baseline AND > 3.0 × ULN] OR [AST or ALT > 8.0 × ULN], combined with [total bilirubin > 2 × baseline AND > 2.0 × ULN	• Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b], or more frequently if clinically indicated, until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks.

All dose modifications should be based on the worst preceding toxicity.

[a.] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03)

[b] Core LFTs include albumin, ALT, AST, total bilirubin ([direct and indirect], if total bilirubin > 2.0 × ULN), alkaline phosphatase (, if alkaline phosphatase is > Grade 2) and GGT. For participants with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin ([direct and indirect] if total bilirubin > 2.0 × ULN), alkaline phosphatase (if alkaline phosphatase is > Grade 2) and GGT).

[c.] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction.

[d] "Cholestasis" defined as ALP elevation (> 2.0 × ULN and R value < 2) in participants without bone metastasis, or elevation of ALP liver fraction in participants with bone metastasis

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values.

It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R > 2 and < 5) liver injury

* Note: If total bilirubin > 3.0 × ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.

Investigations (Cardiac)

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Cardiac – QTc prolongation	
Grade 1 (QTc 450-480 ms) Grade 2 (481-500 ms)	Maintain dose level
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs Grade 4 (QTc ≥ 501 ms or > 60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	First Occurrence: • Assess the quality of the ECG recording and the QT value and repeat if needed • Interrupt study treatment • Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment. • Review concomitant medication use for other causes for QT prolongation (refer to crediblemeds.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation • Check study drug dosing schedule and treatment compliance After confirming ECG reading at site, if QTcF > 500 ms or > 60 ms change from baseline • Interrupt study treatment • Repeat ECG and confirm ECG diagnosis by a cardiologist If QTcF confirmed > 500 ms or > 60 ms change from baseline • Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT • Consult with a cardiologist (or qualified specialist) • Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 ms or < 60ms change from baseline. • After resolution to ≤ 480 ms /60 ms change from baseline, consider re-introducing treatment at reduced dose, and increase ECG monitoring • If QTcF remains ≤ 500 ms/60 ms change from baseline after dose reduction, continue planned ECG monitoring during subsequent treatment If QTcF recurs > 500 ms/60 ms change from baseline after dose reduction, discontinue participant from alpelisib.

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Cardiac - Left Ventricular Systolic Dysfunction	
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	• Maintain dose level, and continue alpelisib with caution • Repeat LVEF within 4 weeks or as clinically appropriate
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	• Omit alpelisib until resolved* (as defined below), then ↓1 dose level • LVEF measurement to be repeated, if not resolved* within 28 days permanently discontinue participant from alpelisib treatment
Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue participant from alpelisib
*the event is considered resolved when the participant is asymptomatic, has a resting ejection fraction ≥ 40% and ≤ 20% decrease from baseline	
Other Cardiac Events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue participant from alpelisib
Investigations (Gastrointestinal)	
Diarrhea or Colitis (see also Appendix 16.1) Diarrhea is defined as a disorder characterized by frequent and watery bowel movements. Colitis is defined as a disorder characterized by inflammation of the colon.	
Grade 1 (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline) OR Asymptomatic colitis; clinical or diagnostic observations only; intervention not indicated	Maintain dose level but initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental Activities of Daily Living (ADL)) OR	• Omit dose until resolved to ≤ Grade 1, then restart at same dose. • If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then decrease 1 dose level

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Abdominal pain; mucus or blood in stool	• Initiate or intensify appropriate medical therapy and monitor as clinically indicated. For Grade 2 colitis consider additional treatment, such as steroids.
Grade 3 (Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL) OR Severe abdominal pain; peritoneal signs	• Omit dose until resolved to ≤ Grade 1, then decrease dose level. • Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated. For Grade 3 colitis consider additional treatment, such as steroids.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	• Discontinue participant from treatment. • Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.
Investigations (Pancreatic)	
Pancreatitis	
Grade 2 (enzymatic elevation or radiologic findings only)	Omit dose until resolved to Grade ≤ 1, then resume treatment at □ 1 dose level. If toxicity recurs, permanently discontinue participant from alpelisib
Grade 3 (Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support) For participants deriving clinical benefit upon investigator's judgement: For other participants:	• Omit dose until complete resolution of symptoms and lipase resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed. • If recovery to ≤ Grade 1 is greater than 28 days, the participant must be discontinued from the study. • If toxicity reoccurs, permanently discontinue participant from alpelisib Permanently discontinue participant from alpelisib
Grade 4 (Life threatening consequences; urgent intervention indicated)	Permanently discontinue participant from alpelisib

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Stomatitis/Oral mucositis (see also Appendix 16.2)	
Grade 1 (Asymptomatic or mild symptoms; intervention not indicated)/Tolerable Grade 2 (moderate pain; not interfering with oral intake; modified diet indicated)	Maintain dose level. Non-alcoholic or salt water mouth wash.
Intolerable Grade 2 (moderate pain; not interfering with oral intake; modified diet indicated) or Grade 3 (severe pain; interfering with oral intake)	First occurrence: hold until ≤ Grade 1 and ↓ 1 dose level (if stomatitis is readily manageable with optimal management, re- introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until ≤ Grade 1 and ↓ 1 dose level.
Grade 4 (life threatening consequences; urgent intervention indicated)	Permanently discontinue participant from alpelisib.
Skin and subcutaneous tissue disorders	
Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib- induced skin toxicity. Dermatologist consultation is mandated for serious cutaneous reactions (i.e. fulfilling seriousness criteria for AE Reporting) and for severe cutaneous reactions like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme.	
Grade 1 (< 10% body surface area (BSA) with active skin toxicity*)	**Maintain dose level** • Initiate topical corticosteroids 3-4 × daily, preferred compounds to use are Triamcinolone, Betamethasone as long as skin toxicity is active, during maximum 28 days For participants with symptoms like burning and/or pruritus add non- sedating anti-histamine, consider adding a sedating anti- histamine at night If active rash is not resolved within 28 days of appropriate treatment, consider adding low dose systemic corticosteroid (20- 40 mg/d)
Grade 2 (10-30% BSA with active skin toxicity*)	**Maintain dose level**. • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone as long as skin toxicity is active, during max. 28 days • Consider adding systemic corticosteroids 20-40mg/d If rash resolves to ≤ Grade 1 within 10 days systemic

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
	corticosteroid may be discontinued For participants with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine, consider adding a sedating anti- histamine at night
Grade 3 (> 30% BSA with active skin toxicity*)	**Omit alpelisib** dose until rash /skin toxicity is no longer active but fading (Grade 1), consider exploratory skin biopsy for central assessment • Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone for at least 28 days • Add systemic corticosteroids 20-40mg/d If rash resolves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued For participants with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine during day time, consider adding a sedating anti-histamine at night Re-start alpelisib dose once rash /skin toxicity is no longer active but fading (Grade 1): • at same dose in case of first occurrence, at reduced dose level in case of second occurrence • If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re- challenge with alpelisib; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued For participants with symptoms like burning, stinging and/or pruritus antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib.
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	• Permanently discontinue participant from alpelisib Consult a dermatologist, ensure documentation by imaging like photographs, and obtain a skin biopsy for central assessment Treatment may follow guidelines for Grade 3 above with the exception of rechallenge. Additional measures may be taken as per local treatment guidance
Any Grade of Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis or other SJS/TEN like severe skin reactions	• Permanently discontinue participant from alpelisib • Consult a dermatologist, ensure documentation by imaging like photographs, and obtain a skin biopsy for central assessment Follow local treatment guidelines for SJS/TEN

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
*"Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.	
Investigations (Pulmonary disorders)	
Pneumonitis (any grade): Immediately interrupt alpelisib for any case of suspected pneumonitis. Fulvestrant may be continued if clinically indicated. Obtain appropriate imaging (high resolution CT scan) and consider BAL and biopsy if appropriate based on clinical judgment. Treatment for pneumonitis should be initiated based on institution guidelines and generally includes high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Alpelisib should be permanently discontinued in all patients with confirmed pneumonitis.	
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 × ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 × ULN)	Maintain dose level
Grade ≥ 3 (> 2.0 × ULN)	Omit dose until resolved to baseline, then • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, then ↓ 1 dose level. Note: In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess amylase)
Note: Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Investigations (any other)	
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held, at the investigators discretion	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 4	Permanently discontinue from alpelisib Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)

7.5.3 Follow-Up for Toxicities

All participants must be followed up for safety (AEs and serious adverse events [SAEs]) for 30 days following the last dose of study treatment (alpelisib and/or fulvestrant). Participants whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first which includes all study assessments appropriate to monitor the event.

7.6 Additional Treatment Guidance

7.6.1 Treatment Compliance

Compliance will be assessed by the investigator and/or study personnel at each participant visit and information provided by the participant and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each participant visit.

7.6.2 Recommended Treatment of Adverse Events

Refer Appendix 16.1 and Appendix 16.2.

7.6.3 Emergency Breaking of Assigned Treatment Code

Not Applicable.

7.7 Preparation and Dispensation

Participants will be provided with an adequate supply of alpelisib for self-administration at home, including instructions for administration, until at least their next scheduled study visit for the study duration i.e. six months. Participants will receive alpelisib on an outpatient basis.

Fulvestrant 500 mg will be administered intramuscularly as two 5 mL injections 250 mg each, one in each buttock.

The investigator or responsible site personnel must instruct the participant or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the participant by authorized site personnel only. All dosages prescribed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

7.7.1 Handling of Study Treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated

site personnel have access. Upon receipt, study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure (IB). Clinical supplies will be dispensed only in accordance with the protocol. Technical complaints will be reported to the respective Novartis CO Quality Assurance.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to CRO address provided in the investigator folder at each site.

8 VISIT SCHEDULE AND ASSESSMENTS

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF.

Table 8-1 Assessment Schedule

	Screening			Cycle 1**			Cycle 2**		Subsequent Cycles**(Cycle 3 to Cycle 6)	End of study treatment (EoT)/Early discontinuation**	Post treatment Follow-up phase
Day of cycle	**-35 to -1[#]**	**-28 to -1[#]**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**		**30 days after last dose for safety**
Obtain Informed Consent	X	X									
Participant History											
Demography		X									
Inclusion/exclusion criteria		X									
Eligibility checklist (within IRT)			X								
Relevant medical history/current medical conditions		X									
Diagnosis and extent of cancer		X									
ER/PgR status		X									
PIK3CA mutation testing	X										
HER2 status		X									
Prior antineoplastic therapy		X									
Prior/concomitant medications		X		Continuous up to 30 days after last dose of study treatment							
Physical Examination											
Performance status (ECOG)			X				X		X	X	
Height			X								

	Screening			Cycle 1**			Cycle 2**		Subsequent Cycles**(Cycle 3 to Cycle 6)	End of study treatment (EoT)/Early discontinuation**	Post treatment Follow-up phase
Day of cycle	**-35 to -1#**	**-28 to -1#**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**		**30 days after last dose for safety**
Weight			X				X		C3D1 and then as clinically indicated	X	
Vital signs			X	X		X	X	X	X	X	
Physical examination			X		X	X	X	X	X	X	
Laboratory Assessments											
Hematology			X			X	X	X	X	X	
ECG*			X	As clinically indicated X						X	
Fasting Chemistry (Full)			X				X		X	X	
Fasting Chemistry (Partial)						X		X			
Fasting Glucose			X		X	X	X	X	X	X	
HbA1c			X				C2D1 and then every 3 cycles X			X	
Fasting Lipid Panel			X							X	
Coagulation			X				C2D1 and then every 2 cycles X			X	
Fasting Lipase, Fasting Amylase			X		X			X		X	

	Screening			Cycle 1**			Cycle 2**		Subsequent Cycles**(Cycle 3 to Cycle 6)	End of study treatment (EoT)/Early discontinuation**	Post treatment Follow-up phase
Day of cycle	**-35 to -1#**	**-28 to -1#**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**		**30 days after last dose for safety**
Urinalysis (macroscopic)			X	As clinically indicated X						X	
ECHO*			As clinically indicated								
Study Drug Administration											
Alpelisib				Daily							
Fulvestrant				X		X	X		Day 1 of each cycle X		
Safety											
Adverse events	X	Continuous, up to 30 days after the last dose of study treatment									
Hospitalizations		Continuous, up to 30 days after the last dose of study treatment									

If required, tumor sample for *PIK3CA* testing should be obtained and sent locally within Day -35 to Day -1 of the screening period. After confirming the *PIK3CA* mutation status, all other screening assessments will be done within Day -28 to Day -1 of the screening period and prior to assignment of treatment. Molecular pre-screening and main screening to be conducted simultaneously, if desired by the Investigator.

***:** In case of ECG abnormalities, ECHO can be performed as required.

****** . The visit window is ±3 days for all the visits. EOT to be performed within 14 days after treatment discontinuation

X = assessment to be recorded in the clinical database or received electronically from a vendor

***: Post treatment follow-up can be done either telephonic or as an onsite visit

8.1 Screening

After signing the study ICF, the tumor sample (refer Section 5.1) should be sent to central laboratory within days - 35 to -1 of the screening period for *PIK3CA* testing; else if the participant has a confirmed PIK3CA testing already and fits the inclusion criteria, can be considered for screening and subsequent inclusion. If block is rejected or QC is failed, re-biopsy may be performed. It is recommended to wait for the *PIK3CA* testing results before conducting other screening assessments. All other screening assessments will be done within 1 to 28 days prior to assignment of treatment (see Table 8-1 for the list of assessments to be performed).

Re-screening of participants is only allowed once per participant if the participant was not registered as entering the treatment phase before. In this case, the Participant No. assigned to the participant initially will not be used and the participant will be given a new number at re-screening.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the participant will be considered a screening failure. In case re-screening occurs, all evaluations re-assessed should meet the eligibility criteria.

8.1.1 Information to be Collected on Screening Failures

Participants who signed an ICF but are found not eligible for any reason will be considered as screening failures, and data will be handled in the same manner.

The following CRFs must be completed for a screen failure participant:

Screening phase disposition page of CRF (including reason for not being started on treatment)

Informed Consent, including additional biomarker ICF, if relevant

Inclusion/Exclusion Criteria

Demography

AEs (only if the participant experienced a SAE during the screening period after signing the ICF)

Withdrawal of informed consent, if applicable

Death, if applicable

For Screen failure patients including pre-screening (molecular screening) failures: If a screen failure participant experiences an AE, details about the AE will be recorded only in the Investigator's source documents. If the AE meets SAE criteria, details will be captured in eCRF.

In case of a SAE, the SAE report must be submitted to Novartis within 24 hours after becoming aware of it.

No other data will be entered into the clinical database for participants who are screen failures.

8.2 Participant Demographics/Other Baseline Characteristics

The data that will be collected on participant characteristics at screening includes:

Diagnosis and extent of cancer

Medical history (e.g., important medical, surgical, and allergic conditions from the participant's medical history which could have an impact on the participant's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History CRF should include the toxicity grade.

ER, PgR and HER2 status

All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.

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.

Furthermore the following assessments will be performed:

PIK3CA mutation status

Vital signs

Height, weight

Physical examination

Performance status (ECOG)

Laboratory evaluations (e.g., hematology, coagulation, biochemistry, fasting plasma glucose/ /serum lipid profile/HbA1c/lipase/amylase, urinalysis)

ECG

8.3 Efficacy

Efficacy / Pharmacodynamics are not measured in this study.

8.4 Safety

Safety will be monitored by assessing physical examination, vital signs, performance status evaluation, ECG, cardiac imaging, laboratory evaluations for hematology and biochemistry including glucose monitoring as well as collecting AEs at every visit.

If one of the study drugs is being held due to toxicity, scheduled visits and assessments should still be performed as described in Table 7-1.

8.4.1 Laboratory Evaluations

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 and collection plan outlined respectively in Table 8-1.

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.

Table 8-2 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)

8.4.2 Appropriateness of Safety Measurements

The safety assessments selected are standard for this indication/Participant population.

9 STUDY DISCONTINUATION AND COMPLETION

9.1 Discontinuation

9.1.1 Discontinuation of Study Treatment

Participants may voluntarily discontinue from alpelisib and/or fulvestrant for any reason at any time. If a participant decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the participant's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue alpelisib and/or fulvestrant for a given participant if, she/he believes that continuation would be detrimental to the participant's well-being.

Study treatment must be discontinued under the following circumstances:

AE or laboratory abnormalities

Pregnancy

Lost to follow-up

Physician decision

Participant/guardian decision

Death

Progressive Disease (clinical and radiological progression as per PI discretion)

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

The appropriate personnel from the site and Novartis will assess whether alpelisib plus fulvestrant treatment should be discontinued for any participant for any reason.

If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified.

In addition to the general withdrawal criteria, if alpelisib dosing is held for > 28 days since planned dose or fulvestrant is held for more than 35 days since a planned injection, then participant should be withdrawn from the study.

Participants who have been withdrawn from the study due to study drug discontinuation (i.e. either fulvestrant or alpelisib) should be scheduled for an EOT visit. Once withdrawn from study, patients may receive treatment outside of the study as per routine management and investigator's discretion.

If the decision to withdraw the participant occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the participant return for an additional visit.

An end of phase disposition CRF page called “End of Treatment” disposition page should be completed, giving the date and primary reason for discontinuation.

At a minimum, all participants who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

The investigator must determine the primary reason for a participant’s premature withdrawal from the study and record this information on the relevant end of phase disposition CRF page.

9.1.1.1 Replacement Policy

Patients will not be replaced. Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

Does not want to participate in the study anymore, and

Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject’s decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject’s study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject’s samples until the time of withdrawal) according to applicable law.

9.1.2 Lost to Follow-Up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.3 Early Study Termination by the Sponsor

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the participant should be seen as soon as possible and the assessments described in Table 8-1 for a

discontinued or withdrawn participant should be performed. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

9.2 Study Completion and Post-Study Treatment

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

All enrolled and/or treated patients should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the patient should be recorded in the source documentation. Patients transitioning to PTA will also have to complete the EOS Visit assessment after the last dose administration of alpelisib as a part 6 months of treatment for the current study.

10 SAFETY MONITORING AND REPORTING

10.1 Definition of Adverse Events and Reporting Requirements

10.1.1 Adverse Events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

For subjects whose PIK3CA status is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 10.1.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured as adverse events.

Subjects whose PIK3CA status is known will sign the main study ICF.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

Adverse events will be assessed and graded according to the CTCAE Version 4.03.

1. 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).
2. In case an AE in related to the study agent, the degree of relatedness should be reported as per following:

Related:	There is a reasonable causal relationship between the study agent administered and the AE
Not Related:	There is no reasonable causal relationship between the study agent administered and the AE

Not Assessable: The relatedness between the study agent administered and the AE cannot be assessed

3. Its duration (start and end dates or ongoing) and the outcome must be reported. The outcome of the AE will be assessed and recorded as per the following categories:
   - Not recovered / Not resolved / Unchanged
   - Condition deteriorating
   - Recovered / resolved
   - Improving / recovering / resolving
   - Recovered with sequelae
   - Fatal
   - Unknown
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose continued unchanged
   - Dose reduced/increased
   - Drug interrupted/permanently discontinued
   - Study Drug withdrawn
   - Unknown
6. Its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the package insert.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

they induce clinical signs or symptoms

they are considered clinically significant

they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values that are considered to be non-typical in patient with the underlying disease.

10.1.2 Serious Adverse Events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening
- Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately

life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred (Section 10.1.5).

10.1.3 SAE Reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis safety, licensing authority i.e. DCGI (Health Authority) and the IRB/IEC immediately, without undue delay, under no circumstances later than within 24 h of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Initial SAE form containing full written summary detailing relevant aspects of the SAE will follow the initial notification and will be submitted to the sponsor, IRB/IEC, DCGI (Health Authority), and the CRO within 24 hours of receipt of additional information. The report of the SAE, after due analysis shall be forwarded by the investigator to the Novartis safety, DCGI (Health Authority), IRB/IEC, Head of Institution (HOI) within 14 calendar days of reporting of SAE or as per local regulations.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting.

All SAEs will be collected and reported by sponsor to the regulatory authority and to respective ethics committees via Principal Investigator. Additionally, bi-annual blinded SUSAR Listings will also be submitted to all the participating sites.

Any SAEs experienced after the 30 days period should be reported to Novartis Patient Safety and other relevant stakeholder by Principal Investigator in accordance with current local regulation till the end of the trial.

10.1.4 Pregnancy Reporting

Not Applicable.

10.1.5 Reporting of Study Treatment Errors Including Misuse/Abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded in the appropriate CRF irrespective of whether or not associated with an AE/SAE as mentioned in Table 10-1, and reported to Novartis Patient Safety and other relevant stakeholders (i.e. EC, HA, Sponsor etc.) if associated with an SAE. Misuse or abuse will be collected and reported to the Patient safety team and other relevant stakeholders if it being associated with an SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

Not applicable.

11 DATA COLLECTION AND DATABASE MANAGEMENT

11.1 Data Collection

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database Management and Quality Control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis/sponsor employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and

to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 DATA ANALYSIS AND STATISTICAL METHODS

The data will be analyzed by Novartis and/or a designated CRO. Any data analysis carried out independently by an investigator should be submitted to Novartis before publication or presentation. The data from all centers that participate in this study will be combined in the final safety analysis.

12.1 Analysis Sets

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).

12.2 Participant Demographics and Other Baseline Characteristics

Baseline data (including disease characteristics) will be listed and summarized for each participant. Descriptive summary statistics (e.g. frequency, mean, median, range and standard deviation) will be used to present numeric data.

12.3 Treatments

Duration of study treatment exposure (months), cumulative dose (mg), dose intensity (mg/day), relative dose intensity (%), and the number (%) of participants with dose reductions/interruptions along with reasons for the dose reduction/interruption will be presented. The safety set will be used for the tables and listings.

12.4 Analysis of the Primary Endpoint(S)

For safety analyses, the safety set will be used and listings and tables will be presented.

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., ECG, vital signs) will be considered as appropriate. All safety data will be listed.

12.4.1 Definition of Primary Endpoint(S)

The percentage of patients with at least one on-treatment adverse event.

12.4.2 Statistical Model, Hypothesis, 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 percentage of patients with at least one on-treatment adverse event will be summarized with corresponding two-sided exact 95% CI (Clopper and Pearson 1934).

Refer to Section 12.6 for sample size considerations.

12.4.3 Handling of Missing Values/Censoring/Discontinuations

Not applicable

12.4.4 Safety Endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented for the safety set.

Safety summaries (tables, figures) include only data from the on-treatment period (i.e. means up to 30 days after last dose of study drug) with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on-treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

Adverse Events

The assessment of safety will be based mainly on the frequency of AEs, which includes all serious AEs. All AEs will be summarized using frequencies, percentages and corresponding two-sided exact 95% CIs (Clopper and Pearson 1934) by system organ class and preferred term, and severity. In addition, causal relationship 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.

AEs will be classified by MedDRA, graded based on CTCAE. A summary of AEs not mentioned in the label will also be produced.

[redacted]

12.5 Interim Analyses

Not applicable.

12.6 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 patients 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 patients 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 12-1).

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 12-1).

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 12-2).

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 12-2).

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 12-1 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 12-2 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%

13 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

13.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented, executed, and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

The Contract Research Organization (CRO) will review ICF to ensure it complies with the ICHE6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Prescribing Information or Pack Insert. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an

aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

13.4 Publication of Study Protocol and Results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Novartis has the right at any time to publish the results of the study. For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.6 Patient Engagement

Not Applicable

14 PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study patients.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a

protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 APPENDICES

16.1 Appendix 1: Guidelines for the Treatment of Study Drug Combination Induced Diarrhea

Mild to moderate diarrhea has been reported within the ongoing studies of single-agent BYL719. In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, participant education as well as proper management of diarrhea is mandatory. The following section outlines the recommended algorithm for management and treatment of BYL719 induced diarrhea (Benson et al 2004; Kornblau et al 2000; Wadler et al 1998).

The algorithm for treatment for diarrhea management is based on (Wadler et al 1998; Kornblau et al 2000).

Participant History of Diarrhea

At screening, the participant's history of diarrhea should be reviewed and the participant should be appropriately informed of potential study drug-induced diarrhea and its management:

Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;

Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;

Instruct participants regarding risk of developing diarrhea;

Explain the frequency of diarrhea and its relationship to NCI CTCAE 4.03 grading.

NCI CTCAE version 4.03 grading of diarrhea for participants without colostomy

Toxicity		1	2	3	4	5
Diarrhea		Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea is defined as a disorder characterized by frequent and watery bowel movements.						

First Report of Diarrhea

Obtain history of onset and duration of diarrhea

Description of number of stools and stool composition (e.g. watery, blood, mucus in stool)

Assess participant for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)

Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)

Proactively look for occurrence of diarrhea. If no problems occur, instruct the participant to call when a problem does arise.

Management of diarrhea

General recommendations:

Stop all lactose-containing products, alcohol

Stop laxatives, bulk fiber (e.g. Metamucil®) and stool softeners (e.g. docusate sodium, Colace®)

Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)

Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade®, broth)

Eat frequent small meals (e.g. bananas, rice, apple sauce, toast)

In addition, Investigators could manage diarrhea as per their local standard of care. For study treatment recommendation refer to Section 7.5.2.

It is recommended that participants are provided with loperamide tablets at the start of each cycle. Participants should be instructed on the use of loperamide at Cycle 1 in order to manage signs or symptoms of diarrhea at home. Participants should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the site should ensure that the participant understands the instruction. At the beginning of each cycle, each participant should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the site should question the participant regarding the actions taken for these symptoms.

Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. Note that all concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications/Non-drug Therapies eCRF.

Loperamide is the first-line treatment of diarrhea (any Grade) in this recommended algorithm. Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms. Another first-line treatment for diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide however it is important to note that loperamide and diphenoxylate hydrochloride/atropine sulfate must not be used in conjunction with one another due to the risk of developing paralytic ileus. Upon treatment with any antidiarrheal agents, the participant's response to treatment should be observed and appropriately documented in the source document and eCRF.

Treatment of Diarrhea CTCAE Grade 1 or 2

Diarrhea CTCAE grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) or after each unformed stool).

Diarrhea Resolved

Continue instructions for dietary modification

Gradually add solid foods to diet

Discontinue loperamide after 12 hrs diarrhea-free interval

Diarrhea Unresolved

Persisting diarrhea CTCAE grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of participants condition to rule out dehydration, sepsis, ileus) medical check and selected workup if participant does not need hospitalization (see section Diarrhea workup and additional test in the particular trial protocol). Observe participant for response to antidiarrheal treatment.

Persisting diarrhea CTCAE grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs) and addition of opium tincture (DTO) or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of participants condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe participant for response.

After Again 12-24 Hrs:

Diarrhea Resolved

Continue instructions for dietary modification

Gradually add solid foods to diet

Discontinue loperamide and/or other treatment after 12 hrs diarrhea-free interval

Diarrhea Unresolved

If diarrhea still persisting (CTCAE grades 1 and 2), after 2 × 24 hrs with high dose loperamide and opiates then admit to hospital and employ measures as for CTCAE grade 3 and 4 until diarrhea resolved.

If diarrhea still persisting and progressed to CTCAE grades 3 and 4, employ measures described below.

Treatment of Diarrhea CTCAE Grade 3 Or 4

Severe diarrhea CTCAE grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of participants

condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section Diarrhea workup and additional test in the particular trial protocol). Observe participant for response.

After 12-24 hrs:

If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 µg tid)

Continue IV fluids and antibiotics as needed

If diarrhea CTCAE grade 3 or 4 still persists participants should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.

If diarrhea CTCAE grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg TID) should be administered.

To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea Workup

Perform appropriate tests (Fine et.al.1999).

Spot Stool Analysis

Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)

Blood

Fecal leukocytes (Wright's staining and microscopy) or

Clostridium difficile toxin

Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed participants), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic Examinations

Endoscopic examinations may be considered **only if absolutely necessary**. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis
- Biopsy: Histopathological examination of colonic mucosa and immunophenotyping may be performed to confirm the etiology of colitis.

16.2 Appendix 2 - Guidelines for the Treatment of Study Drug Induced Stomatitis/Oral Mucositis

General guidance and management include participant awareness and early intervention. Evaluation for herpes virus or fungal infection should be considered.

Participants should be informed about the possibility of developing mouth ulcers/oral mucositis and instructed to report promptly any signs or symptoms to their physician,

Participants should be educated about good oral hygiene, instructed to avoid spicy/acidic/salty foods, and should follow the following guidelines:

For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.

For more severe toxicity (grade 2 in which case participants have pain but are able to maintain adequate oral alimentation, or grade 3 in which case participants cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with alpelisib metabolism.