NOVARTIS

Clinical Development

BYL719/ Alpelisib /Piqray®

CBYL719A03201 / NCT04862143

Open-label, multicenter, pilot-trial evaluating the safety and utility of a hybrid decentralized clinical trial (DCT) approach using a TELEmedicine platform in patients with HR-positive/HER2-negative advanced breast cancer with a PIK3CA mutation treated with alpelisib – fulvestrant

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Final 2.0
Release date:	11-Oct-2022
Number of pages:	36

Template Version 4.0, Effective from 23-Apr-2021

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
07-Mar-2022	Prior to DB lock	Creation of final version	N/A - First version	NA
06-Oct-2022	Prior to DB lock	Trial closeout early due to low rate of enrollment; SAP has been updated to align with synoptic CSR.	First amendment	All

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferease
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
CRS	Case Retrieval Sheet
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse events
DAR	Drug Administration Record
DCO	Data Cut-off
DCT	Decentralized Clinical Trial
DFI	Disease Free Interval
DI	Dose Intensity
DMS	Document Management System
DRL	Drug Reference Listing
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EOT	End Of Trial
ET	Endocrine Therapy
FAS	Full Analysis Set
HR	Hormone Receptor
HER2	Human Epidermal Growth Factor Receptor 2
HLGT	High Level Group Terms
HLT	High Level Terms
IA	Interim Analyses
ICF	Informed Consent Form
LHRH	Luteinizing Hormone-Releasing Hormone
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NMQ	Novartis MedDRA Queries
OFS	Ovarian function suppression
PD	Pharmacodynamics
PDI	Planned Dose Intensity
PDS	Programming Datasets Specifications
PFS	Progression Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set

PR	Progesterone Receptor
QOL	Quality Of Life
RAP	Reporting & Analysis Process
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SGLT2	sodium glucose co-transporter 2
SOC	System Organ Class
SMQ	Standardized MedDRA Queries
TBIL	Total bilirubin
TFLs	Tables, Figures, Listings
TFQ	Trial Feedback Questionnaire
ULN	Upper Limits Of Normal
WHO	World Health Organization

1 Introduction

This document describes the detailed statistical methodology to be used for the Clinical Study Report (CSR) for the analysis of study CBYL719A03201, open-label, multicenter, pilot-trial evaluating the safety and utility of a hybrid decentralized clinical trial (DCT) approach using a TELEmedicine platform in patients with HR-positive/HER2-negative advanced breast cancer with a PIK3CA mutation treated with alpelisib – fulvestrant.

The content of this SAP is based on CBYL719A03201 Protocol Amendment version 01, dated 15Jun2021). All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

CSR deliverables (shells for tables, figures, listings) and further programming specifications are described in Tables Figures and Listings (TFL) shells and Programming Datasets Specifications (PDS) documents, respectively.

This study terminated early due to very low rate of enrollment, which made it no longer feasible to continue with the trial; which meant there was insufficient data to perform the planned statistical analyses so study data will be listed only. This SAP amendment was issued after the decision to terminate the study; therefore, the changes to planned analyses are reflected in this document.

1.1 Study design

This is an open-label, single arm, multi-center, Phase II interventional pilot trial conducted to evaluate if a DCT using a telemedicine platform offers a satisfactory, safe and suitable management for HR-positive/HER2-negative patients with ABC harboring a PIK3CA mutation and treated with alpelisib plus fulvestrant.

In this pilot trial, approximately 20 participants living in a geographically well-defined region in Sweden will be treated with alpelisib plus fulvestrant after progression on an endocrine-based therapy. Upon enrollment in the trial (i.e., completion of the informed consent form [ICF]), participants will attend on-site visits for screening and on Cycle 1, Day 1. During the Cycle 1, Day 1 visit, participants will be trained on using the telemedicine platform and other monitoring devices to be used during remote participation: a glucometer and a smartphone with the telemedicine application installed. During this visit, participants will initiate treatment with alpelisib plus fulvestrant. Pre-menopausal women will be treated with goserelin, a luteinizing hormone-releasing hormone (LHRH) agonist, concomitantly with alpelisib plus fulvestrant. Participants with risk factors for developing hyperglycemia and participants who had a first fasting glucose level above the normal range (onset of hyperglycemia) may be treated, at the investigator's discretion, with sodium glucose co-transporter 2 (SGLT2 inhibitors) with or without metformin if needed, as prophylactic treatment to prevent hyperglycemia.

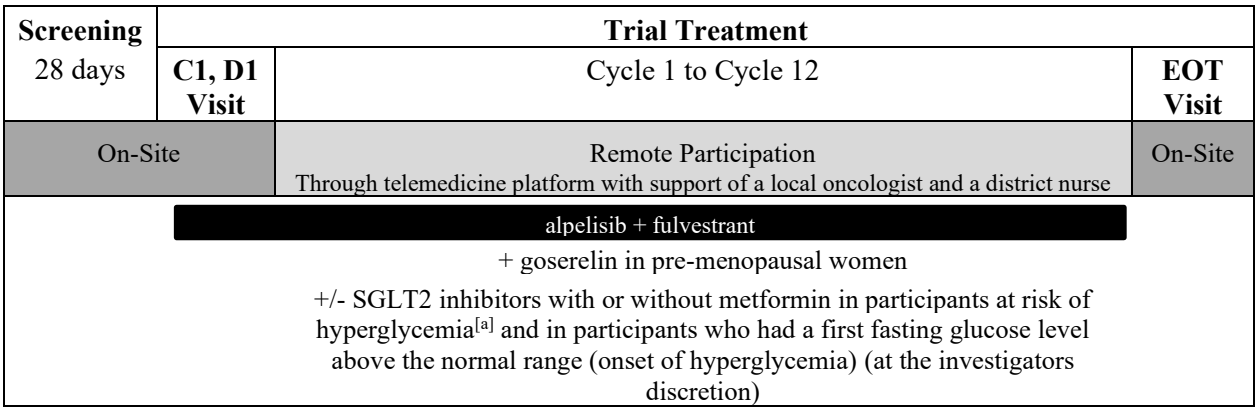
Following this visit, investigators will transition participants to remote participation enabled by the telemedicine platform with support of local healthcare providers under the investigator’s oversight (Refer Section 8 of clinical study protocol(CSP) “Visit schedule and assessments” for

additional details on visit schedule during remote participation). Treatment with alpelisib plus fulvestrant will continue until end of trial, disease progression, intolerable toxicity or participants/investigators' decision. Participants will be followed remotely up to 12 cycles of treatment or until treatment discontinuation, death, withdrawal of consent, or loss to follow-up, whichever occurs first. Discontinuation of remote participation is not a reason for trial discontinuation. Participants who do not wish to continue with remote participation will have the option to attend on-site visits. For each participant, the trial will conclude with an on-site end of trial (EOT) visit.

Throughout the trial, investigators will be asked to provide their inputs on DCT approach on a regular basis.

The study design is summarized in Figure 1-1.

Figure 1-1 Study design



[a] baseline BMI ≥30, baseline age ≥75 years, and baseline diabetic and pre-diabetic status have been found to be risk factors for hyperglycemia in patients treated with alpelisib.
BMI= body mass index, C1, D1 = Cycle 1, Day 1; EOT= End of trial; SGLT2= sodium glucose co-transporter 2

1.2 Study objectives, endpoints and estimands

The study objectives and corresponding endpoints as specified in the protocol are provided in Table 1-1

Table 1-1 Objectives and related endpoints

Objectives	Endpoints	Analysis
Primary Objective • To assess participant satisfaction with the DCT experience	**Endpoint for primary objective** • Participant satisfaction, assessed at the start of the trial, every 12 weeks, and at the end of trial through the Trial Feedback Questionnaire (TFQ)	Refer section 2.4.1
Secondary Objectives • To explore patient retention on DCT approach	**Endpoints for secondary objectives** • Proportion of participants on remote monitoring at 3, 6, 12 months for participants still on treatment. *Statistical assumptions (descriptive): targeted proportion of patients remaining on remote monitoring after 6 months, 75%* *Note: unscheduled in-clinic visit does not exclude for DCT monitoring*	• Refer section 2.5.1
• To explore if the DCT approach ensures safe and suitable remote management of patients	• Total number of unscheduled in-clinic visits because of safety reasons • Total number of unscheduled in-clinic visits and the reason • Number of unscheduled in-clinic visits per participant in the study	• Refer section 2.5.1

	• Discontinuation rate related to adverse events *Note: Visits initially planned to be performed remotely but finally performed on site and unscheduled visits on site or at the local oncologist's (regional hospital) will be considered as unscheduled in-clinic visits. Visits that require treating oncologists or district nurses assessments are considered unscheduled visits.*	
• Patient compliance to treatment	• Overall compliance	• Refer section 2.3.2.5
• To assess AEs (Adverse Event) of special interest (AESIs) and AEs leading to in-clinic visits	• Type, frequency and severity of AESIs (hyperglycemia, rash, and diarrhea) per Common Terminology Criteria for Adverse events (CTCAE) v4.03 (incidence proportion) • Number and proportion of AEs leading to in-clinic visits	• Refer section 2.6.1
• To evaluate participant-reported global health status, quality of life (QOL) and pain	• Change in scores of participant reported outcome (PRO) questionnaire (within same participant) from baseline to each time point of questionnaire administration (every 12 weeks)	• Refer section 2.9
• To assess the effectiveness of alpelisib plus fulvestrant	• PFS according to RECIST 1.1	• Refer section 2.5.1

1.2.1 Primary estimand(s)

Primary estimands have not been described as trial is not planning any hypothesis testing.

1.2.2 Secondary estimand(s)

Secondary estimands have not been described as trial is not planning any hypothesis testing.

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis according to the data analysis section 12 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

Statistical analysis will be performed using Statistical Analysis System (SAS)® (SAS Institute, North Carolina), Version 9.4 or higher.

Summary statistics for continuous variables will generally include the number of patients (n), mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. Summary statistics will also be presented graphically wherever applicable. For discrete (categorical or binary) variables, the number and percentage of patients in each category will be presented. 95% CIs presented will be 2-sided unless otherwise specified. No formal statistical testing of hypothesis are planned to be performed.

All statistical analyses will be performed under the direction of Novartis personnel. It is planned that the data from all centers that participate in this study will be used. Trial duration is planned to be 12 cycles of 28 days of treatment each. Cut-off date will be Last Patient Last Visit (LPLV) is scheduled as per trial.

The statistical results will be displayed using tables, figures and listings (TFLs). Listings will include all data collected in the eCRF. When dates are imputed, a flag should be provided to show that this is imputed rather than an actual date. In listings, the imputed dates are reported in their original format before imputation. In general, patient listings will be sorted by patient number and assessment date (and time), if applicable.

2.1.1 General definitions

2.1.1.1 Study drug and study treatment:

Study drug is defined as alpelisib.

Study treatment is defined as alpelisib plus fulvestrant.

2.1.1.2 Date of first administration of study drug/treatment

The date of first administration of study drug is defined as the first date when a nonzero dose of study drug is administered and recorded on the Dose Administration Record (DAR) eCRF/eDiary. The date of first administration of study drug will also be referred to as start of study drug. Similar definitions apply for the other components of study treatment.

The date of first administration of study treatment is defined as the first date when a nonzero dose of any component of study treatment is administered and recorded on the DAR eCRF/eDiary. The date of first administration of study treatment will also be referred to as the start of study treatment.

2.1.1.3 Date of last administration of study drug/treatment

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered and recorded on the DAR eCRF. Similar definitions apply for the other components of study treatment.

The date of last administration of study treatment is defined as the last date when a nonzero dose of any component of study treatment was administered and recorded on the DAR eCRF.

2.1.1.4 Study day

Study day on first study drug intake date is 1.

The study day will be calculated as:

The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date + 1 if event is on or after the reference start date;

The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g., adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) is the start of study treatment. (Note: if an adverse event starts before the start of study treatment the study day displayed on the listing will be negative).

The reference start date for all other, non-safety assessments (e.g., tumor assessment, death, disease progression, tumor response, and patient reported outcomes (PRO)) is the start of study treatment. In other words, all efficacy time -to-event variables (e.g., progression-free survival) will be calculated from start of study treatment.

2.1.1.5 Baseline

For efficacy evaluations, the last available assessment on or before start date of study treatment will be used as the "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include ECOG performance status and patient-reported outcomes. For RECIST based endpoint PFS, within 28 days prior to start of trial treatment (Day −28 to Day −1 prior to Cycle 1, Day 1). A window of 28 days from the start of study treatment will be allowed, i.e., the investigators will be maintained and baseline considered valid if the baseline assessment is within 28 days of treatment start date.

For safety evaluations (e.g., laboratory assessments and ECG), the last available assessment before or at date of start of study treatment will be used as the 'baseline' assessment.

Assessments specified to be collected post-dose on the first date of treatment are not considered as baseline values.

If patients have no value as defined above, the baseline results will be considered missing.

2.1.1.6 On-treatment assessment/event

Safety summaries and selected summaries of deaths will summarize only on-treatment assessments/events. An on-treatment assessment/event is defined as any assessment/event in the following time interval:

[date of first administration of study treatment, date of last administration of study treatment + 30 days], i.e., including the lower and upper limits. (Note: However, the calculation of study treatment duration will use different rules as specified in Section 2.3.2.5).

An AE started in the screening phase and ongoing in the on-treatment phase will not be considered as an on-treatment AE unless it has worsened.

If the last date of study treatment is missing, any assessment/event occurring after the start of study treatment will be considered as on-treatment.

Data listings will include all assessments/events, flagging those which are not on-treatment.

Note: The date of first administration of study treatment and the date of last administration of study treatment are defined in Sections 2.1.1.2 and 2.1.1.3, respectively.

2.2 Analysis sets

Enrolled Set: The enrolled set consists of all patients who signed the inform consent.

Full Analysis Set: The Full Analysis Set (FAS) consists of all enrolled set patients who received at least one dose of any component of study treatment.

Safety Set: The Safety Set consists of all enrolled set patients who received at least one dose of any component of study treatment and have at least one post-baseline safety assessment.

2.2.1 Subgroup of interest

Not applicable

2.3 Patient disposition, demographics and other baseline characteristics

Enrollment by study sites and local oncology clinics will be summarized on enrolled set. The reasons for screen failure will also be summarized.

2.3.1 Patient disposition

Patient disposition for all patients will be summarized based on enrolled set.

- Number (%) of patients treated/untreated
- Number (%) of patients who are still on-treatment (based on the absence of the 'End of treatment' page)
- Number (%) of patients who discontinued study treatment (based on the 'End of Treatment' page)
- Reasons for study treatment discontinuation (based on 'End of Treatment' page).
- Number (%) of patients who enroll into 15 year follow up protocol

End of Screening Phase Disposition with subject status for all patients will be summarized based on enrolled set.

2.3.2 Demographics and other baseline characteristics

The FAS will be used for all baseline disease characteristics and demographic summaries and data listings.

2.3.2.1 Demographics

Demographic data will be listed in detail. Quantitative data (e.g., age) will be summarized by appropriate descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

2.3.2.2 ECOG status

ECOG performance status will be summarized (n and %, missing if any).

2.3.2.3 Diagnosis and extent of cancer

Diagnosis and extent of cancer for each patient will be listed. This listing will include the following: primary site of cancer, histological grade, stage at initial diagnosis, time since initial diagnosis, time from initial diagnosis to first recurrence/progression, stage at time of study entry, presence/absence of target and non-target lesions, number and type of metastatic sites involved, HER-2 / estrogen / progesterone receptor status, number of de novo patients. disease free interval (DFI) for non-de novo patients and prior endocrine therapy status (ET).

Estrogen and progesterone receptor status summary will be combined into 3 categories (ER+ PR+, ER+ PR-, ER- PR+).

2.3.2.4 Medical History

Medical history and ongoing conditions, including cancer-related conditions, will be listed. Medical history/current medical conditions are coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of the analyses. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable listings.

2.3.2.5 Study treatment

Duration of study treatment exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized. The number of patients with dose reductions/interruptions, and the reasons, will be summarized and listed. Details of the derivations and summaries are provided in the following sections.

The safety set will be used for all summaries and listings of study treatment.

Duration of study treatment exposure

The duration of exposure to study treatment will be calculated as Duration of exposure to study treatment (days) = (last date of exposure to any study treatment component) – (date of first administration of study treatment) + 1.

Duration of exposure to alpelisib (days) = (last date of exposure to alpelisib) – (date of first administration to alpelisib) + 1.

Duration of exposure to fulvestrant (days) = (last date of exposure to fulvestrant) – (date of first administration to fulvestrant) + 1.

The last date of exposure is defined as follows for the study treatment components:

For alpelisib: the last date of exposure is defined as the date of last administration of the corresponding medication;

For fulvestrant, the last date of exposure is defined as following:

If patient discontinues fulvestrant before C2D1 dose, then:

- Last date of exposure = last date of administration + 13 days.

If patient died or lost to follow-up within last date of administration + 13 days,

- then last date of exposure is date of death or last contact date, respectively.

If patient discontinues fulvestrant after C2D1 dose, then:

- Last date of exposure = last date of administration + 27 days.

If patient died or lost to follow-up within last date of administration + 27 days,

- then last date of exposure is date of death or last contact date, respectively.

The duration of exposure includes the periods of temporary interruption (of any component of the study treatment for any reason). The duration of study treatment exposure will be summarized. In addition, the duration of exposure to study treatment will be categorized into time intervals (. < 1 month, 1- 2 months, 2 to 3 months, 3 to 4 months, 4 to 6 months, 6 to 8 months, 8 to 10 months and >= 10 months); frequency counts and percentages will be presented for the number of patients in each interval.

Cumulative dose and average daily dose

Cumulative dose for any component of study treatment is defined as the total dose of the medication given during the study treatment exposure.

Average daily dose is defined as [Cumulative dose (mg) / Number of dosing days]; drug free day(s) are not counted as dosing days.

Cumulative dose and average daily dose will be summarized using descriptive statistics for each component of study treatment. Patients with no exposure to the study treatment component will be excluded from the corresponding summary.

Dose intensity and relative dose intensity

Dose intensity (DI) for alpelisib for patients with non-zero duration of exposure to alpelisib is defined as follows:

DI (mg / day) = Cumulative dose (mg) / duration of exposure to alpelisib (day),

Planned dose intensity (PDI) is defined as the assigned dose by unit of time planned to be given to patients as per protocol. The PDI for alpelisib is displayed in Table 2-2. Note that DI for alpelisib will also be calculated and will be reported in the units displayed in Table 2-2, whereas duration of exposure itself will be summarized in months.

Table 2-2 Planned dose intensity

Medication	PDI (dose unit/unit of time)
alpelisib	300mg/day

Alpelisib relative dose intensity (RDI) is defined as: RDI = DI (dosing unit / unit of time) / PDI (dosing unit / unit of time).

Fulvestrant RDI is defined as:

RDI = actual cumulative dose / planned cumulative dose, where planned cumulative dose is defined as 500* (# completed D1 in a 28-days cycle) and added by 500 mg if patients completed C1D15.

DI for alpelisib and RDI for alpelisib and fulvestrant will be summarized separately for each of the study treatment component.

Dose reductions, interruptions and delays

The number and percentage of patients with dose reductions, interruptions or delays, and the reasons, will be summarized.

Interruption: An interruption is defined as a 0 mg dose given on one or more days during the period where a patient is not on the "off" part of a treatment cycle, after which > 0mg dose resumes. For patients who had dose interruption checked but never resumed non-zero dose, the dose interruption will not be counted. For example, in the sequence of 300 mg – 0mg (dose break) -0mg (dose interruption) – 0 mg (dose permanently discontinuation) the 0mg (dose interruption) will not be counted as dose interruption. Interruptions will be summarized for each component of the study treatment. Delay: A special case of alpelisib interruption occurs at the start of a new cycle, after a planned rest period. It will be determined based on alpelisib dose administration record where a planned dose break is followed by a dose interruption. Such instances will be identified as a subset of the interruptions and will be summarized separately as dose delays.

Reduction: A reduction is defined as a decrease from the previous non-zero dose to another non-zero dose less than protocol planned dose, even if this decrease has been directly preceded by an interruption. For example, in the sequence of alpelisib 300mg – 0mg – 150mg, the 150mg dose will be counted as a reduction.

If due to dosing error, a patient took a dose during the dosing with a dose that is lower than the previous dose, this will not be considered as dose reduction. For example, a patient took 300 mg from day 1-15, and mistakenly took 150 mg per day on day 15-28 which is supposed to be 300 mg per day. The patient resumed 300 mg dosing on day 29. This will not be considered as dosing reduction.

Dose reductions and interruptions will be tabulated separately. No dose escalations or dose modifications are allowed with fulvestrant. No dose escalation will be allowed for alpelisib as alpelisib is to be started at the maximum recommended daily dose according to the SmPC. Thus, Dose escalations are not allowed according to the protocol and will not be counted in these summaries.

Missing data: If dose is recorded but frequency is missing or entered as 'none', it is assumed that the study drug was taken as per-protocol.

Discontinuation of study treatment components

The reasons for discontinuation of alpelisib will be summarized, based on the information on the alpelisib DAR eCRF/eDiary for patients who have the "dose permanently discontinued" box checked.

Partial discontinuation: A partial discontinuation is defined as the event when the last nonzero dose of alpelisib is more than 21 days before the last non-zero dose of fulvestrant when the permanent discontinuation checkbox is checked in the alpelisib DAR page. Partial discontinuation of alpelisib will be summarized.

Prohibited Medication

Refer clinical study protocol Section 16.1.2 for the list of Prohibited Medication.

Treatment with the prohibited substances mentioned clinical study protocol Section 16.1.2 will be identified in the database as protocol deviations.

Some patients may take Prohibited substances during the treatment period so these concomitant medications will be selected via programming and tabulated and listed in the Clinical Study Report.

Number of patients who are receiving prohibited medication with percentage will be summarized. Clinical review of individual study data will be performed in order to identify those anti-neoplastic medications which are considered disallowed.

2.3.3 Prior, concomitant and post therapies

Prior anti-neoplastic therapy

Any prior anti-neoplastic medications, radiotherapy or surgery (biopsy and non-biopsy separately) will be listed for each patient.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Concomitant therapy

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that were administered to a patient, coinciding with the study assessment period (even if started before the study assessment period).

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Any anti-neoplastic therapy administered concomitantly with study treatment will be listed. .

2.3.4 Protocol Deviations

The number and percentage of patients in the FAS and safety with any protocol deviation will be tabulated by deviation category (as specified in Data Management Plan of the study).

All protocol deviations as well as protocol deviations leading to exclusion from FAS and SAF will be listed.

2.4 Analysis supporting primary objective(s)

All efficacy analyses will be performed on the set of Full Analysis Set. Primary efficacy and safety analyses will be conducted at the end of study.

2.4.1 Primary endpoint(s)

The primary objective of the trial is the participant satisfaction with the DCT experience.

The Trial Feedback Questionnaire (TFQ) is a brief, validated patient questionnaire designed to capture patient trial experience independent of disease and treatment.

Participants will be asked to complete the TFQ to provide feedback on their clinical trial experience. TFQ is divided in 3 parts: Part A – Participant experience before they started the trial; Part B – Participant experience during the trial; and Part C – Participant experienced at the end of the trial.

Participant satisfaction will be assessed at the start of the trial, every 12 weeks or monthly in between visits when full questionnaire is not dispensed during conduct, and at the end of the trial through the TFQ. All of the questions:

Question with five point Likert scale responses: Strongly disagree to Strongly agree;

Question with three point Likert scale responses: Many difficulties to no difficulties;

Question with three point Likert scale responses: Too little/too much and acceptable;

And question with two point Likert scale responses: Yes and no range in score from 1 to 5.

Question with five point Likert scale responses will be scored as 1(worst response), 2, 3, 4 and 5 (best response). Question with three point Likert scale responses will be scored from as 1(worst response), 3 and 5 (best response). Question with two point Likert scale responses will be scored as 1(worst response) and 5(best response). Question A3a and C4a will not have score as question asked in subjective manner.

2.4.2 Statistical hypothesis, model, and method of analysis

No formal statistical tests will be performed. No imputation procedures will be applied for missing items or missing assessments.

TFQ scores for each patient for each timepoint will be listed.

2.4.3 Handling of intercurrent events

Not applicable.

2.4.4 Handling of missing values not related to intercurrent event

Not applicable.

2.4.5 Sensitivity analyses

Not applicable.

2.4.6 Supplementary analyses

Not applicable.

2.5 Analysis supporting secondary objectives

2.5.1 Secondary endpoint(s)

The secondary efficacy objectives in this study are to

- To explore patient retention on DCT approach
- To explore if the DCT approach ensures safe and suitable remote management of patients
- Patient compliance to treatment
- To assess AEs of special interest (AESIs) and AEs leading to in-clinic visits
- To evaluate participant-reported global health status, quality of life (QOL) and pain
- To assess the effectiveness of alpelisib plus fulvestrant

Patient retention on DCT approach

Unscheduled in-clinic visits and the reason will be listed.

Unscheduled in-clinic visits because of safety reasons will be listed.

The enrolled set will be used for unscheduled in-clinic visits with safety reasons data listings.

Discontinuation related to adverse events will be listed.

All visit data by participant will be listed for enrolled set.

Patient compliance to treatment

Refer section 2.3.2.5.

AEs of special interest (AESIs) and AEs leading to in-clinic visits

Refer section 2.6.1.

Participant-reported global health status, quality of life (QOL) and pain

Refer section 2.9.

The effectiveness of alpelisib plus fulvestrant

Progression free Survival:

The efficacy endpoints based on the tumor assessments will be derived according to the RECIST guideline version 1.1 (see [Novartis guideline version 3.1 (Appendix 3) based on RECIST 1.1] for details). The tumor endpoint derivation is based on the sequence of overall lesion responses at each assessment/time point. However, the overall lesion response at a given assessment/time point may be provided from different sources as illustrated in Table 2-3 .

Table 2-3 Sources for overall lesion response

Sources	Description
investigators and site personnel	Imaging will be performed on-site at screening and at EOT.
investigators and site personnel	During the remote participation period, imaging will be performed at the local oncologist facilities. Once available, source imaging data will be made accessible to investigators and site personnel.

The investigator reported overall lesion response at each assessment/time point will be used to derive the efficacy endpoint, PFS.

Implementation of RECIST

Response and progression evaluation will be performed according to the Novartis RECIST guideline which is based on the RECIST 1.1 guidelines (Eisenhauer et al 2009). The text below gives instructions and rules to provide details needed for programming.

If CT or MRI scan available before signing of ICF but within 28 days of first dose, no need to repeat the procedures for baseline assessment. Any imaging assessments obtained after treatment initiation cannot be considered as baseline images.

Overall lesion responses for patients with only non-measurable lesions at baseline

Patients with at least one predominantly lytic bone lesion but not having measurable disease per RECIST 1.1 are allowed to enter the study. For patients with non-measurable lesions only at baseline, the overall lesion response will be based solely on non -target lesion response or an occurrence of a new lesion. Non-measurable lesions will be entered as non-target lesions. Therefore, the best overall response is determined from non-target lesion response and presence of new lesions (refer to RECIST Novartis guidelines).

Note: Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless there is unequivocal progression of existing non-target lesions or a new lesion.

Disease progression

Progressive disease should only be assigned if it is confirmed by an assessment method as per RECIST 1.1 guidelines (e.g., CT scan photos for skin lesions, etc.). If a new lesion is detected using an objective assessment method other than radiologic scan then it should also be entered

on the 'New lesion' RECIST eCRF with appropriate method. Discontinuation due to disease progression (Progressive disease) or death due to study indication in death CRF page, without corresponding supportive data in the RECIST eCRF (as defined above), will not be considered as progressive disease in the analysis of PFS.

Change in imaging modality

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g., keeping the same technique, like CT, but switching from with to without contrast use or vice versa, regardless of the justification for the change) or a major change in technique (e.g., from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in an UNK (unknown) overall lesion response based on the Novartis calculation as per Novartis calculated response. However, a response from the investigator that differs from the Novartis calculated UNK is acceptable if a definitive response assessment can be justified based on the available information.

Potential discrepancies between the modality used and overall lesion response (e.g., change in modality but response is different from 'Unknown') will be queried during the data validation process.

Determination of missing adequate assessments

The term 'missing adequate assessment' is defined as assessments that are not done or assessments for which the overall lesion response equals 'Unknown'. The 'missing adequate assessment' is also referred to as 'missing assessment'.

PFS censoring and event date options depend on the presence and the number of missing tumor assessments. An event occurring after two or more missing assessment is censored at the last adequate tumor assessment.

PFS based on site radiology assessment is the efficacy variable in this study. PFS is defined as the time from the start date of study treatment to the date of the first documented disease progression or death due to any cause. If a patient has not progressed or died at the analysis cutoff date, PFS will be censored at the time of the last adequate tumor assessment before the cut-off date.

Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition page) without supporting objective evidence (as defined in Section 2.5.1) satisfying progression criteria per RECIST will not be considered disease progression for PFS derivation.

2.5.2 Statistical hypothesis, model, and method of analysis

No formal statistical tests will be performed. No imputation procedures will be applied for missing items or missing assessments.

The PFS analysis will be performed on the FAS and will use the default censoring and event date. For the analysis, in this study, PFS will not be censored if a new antineoplastic therapy is started.

PFS will be listed for each patient.

Overall DCT experience

Summary of qualitative research on the overall DCT experience from the Investigators and Clinical Trial Team will be also added in the Clinical Study Report.

2.5.3 Handling of intercurrent events

Not Applicable

2.5.4 Handling of missing values not related to intercurrent event

Not Applicable

2.5.5 Sensitivity analyses

Not Applicable

2.5.6 Supplementary analyses

Not Applicable

2.6 Safety analyses

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

All safety outputs will use the safety set. The safety summary tables will include ‘on -treatment’ events/assessments, i.e., those collected on or after the first date of study treatment and collected no later than 30 days after the date of last study treatment administration. The AEs started before the first dose but worsening during the treatment period are also considered as ‘on - treatment’ events. All safety events/assessments will be listed and those collected outside of the on treatment window will be flagged.

2.6.1 Adverse events (AEs)

General rules for AE Reporting: AE summaries will include all AEs starting on or after study Day 1 (i.e., on or after the day of the first intake of study treatment) and starting no later than 30 days after the last administration of study treatment (see section 2.1.1.6). All AEs will be listed. AEs starting prior to study Day 1 and AEs starting later than 30 days after the last treatment date will be flagged in the listings.

AEs will be summarized by presenting the number and percentage of patients having at least one AE, having at least one AE in each primary system organ class, and for each preferred term using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the AE category.

Separate AE summaries will be presented by primary system organ class, preferred term, and maximum grade. A patient with multiple grades for an AE will be summarized under the maximum grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The frequency of grade 3 and 4 AEs will be summarized separately. Any information collected (e.g., grades, relationship to study treatment, action taken etc.) will be summarized and listed as appropriate.

AE summaries:

The following adverse event summaries will be produced:

- Summary of adverse events
- Adverse events, irrespective of causality, by primary system organ class, preferred term and maximum grade
- Adverse events with suspected relationship to study treatment by primary system organ class, preferred term and maximum grade
- Grade 3 or 4 adverse events, irrespective of causality, by primary system organ class, preferred term and maximum grade
- Grade 3 or 4 adverse events with suspected relationship to study treatment by primary system organ class, preferred term and maximum grade
- Serious adverse events, irrespective of causality, by primary system organ class and preferred term and maximum grade
- Adverse events leading to study drug discontinuation, irrespective of causality, by primary system organ class, preferred term and maximum grade
- Adverse events leading to study drug reductions, irrespective of causality, by primary system organ class, preferred term and maximum grade
- Adverse events leading to study drug interruptions, irrespective of causality, by primary system organ class, preferred term and maximum grade
- All AEs, and SAEs will be listed.

AEs of special interest will also be summarized. See Section 2.6.1.1 for the grouping details.

2.6.1.1 Adverse events of special interest / grouping of AEs

AESI are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the alpelisib, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLTs (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines

a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, the number and percentage of patients with at least one event of the AESI occurring during the on-treatment period will be summarized.

Summaries of these AESIs will be provided, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, etc.).

All AESIs will be listed.

A Case Retrieval Sheet (CRS) with the exact composition of the AE groupings is to be used to map reported AEs to the AESI groupings. This file may be updated (i.e., it is a living document) based on review of accumulating trial data, and therefore the groupings are also subject to potential change. Table 2-4 provides the latest groupings at the time of the finalization of the SAP, from the CRS dated DDMmmYYYY. The most up-to-date version of the CRS will be used at the time of the analysis.

The following AESIs are defined for this on the basis of results from the SOLAR-1: hyperglycemia, rash, and diarrhea. For additional detail, refer to Section 4.5.3 of CSP "Risk Management Strategies".

Table 2-4 AESI groupings

AESI grouping	MedDRA category
Hyperglycemia	SMQ? SOC? HLT? and PT?
Rash	SMQ? SOC? HLT? and PT?
Diarrhea	SMQ

2.6.2 Deaths

All deaths will be listed.

2.6.3 Laboratory data

On analyzing laboratory data, data from all sources (central and local laboratories) will be combined. All laboratory assessments will be listed and those collected later than 30 days after the last treatment date will be flagged in the listings.

Laboratory data will be classified (by biostatistics/statistical programming) into CTC grades according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3. The calculation of laboratory CTC grades will be based on the observed laboratory values only; clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests-where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges. The criteria to assign CTC grades in this study are given in Appendix 1.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following listings will be produced for the laboratory data:

- Listing of patients with CTC grade 3 or 4 laboratory abnormalities;
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

All lab data will be listed.

2.6.4 Other safety data

2.6.4.1 ECG and cardiac imaging data

ECG

A standard 12-lead ECG will be performed on-site at screening and thereafter only if clinically indicated. ECG data will be listed.

The following parameters will be assessed: QT, QTcF, RR, PR, and QRS intervals in msec, heart rate (bpm), and the overall interpretation if clinically significant abnormalities are present.

A newly occurring ECG abnormality is defined as an abnormal post-baseline ECG finding that is not present at Baseline. Baseline is defined as the last ECG measurement (taken on or before date of first dose of study treatment).

Cardiac imaging data

Cardiac assessments will only be performed if clinically indicated by the investigator or the local oncologist. Cardiac imaging (MUGA or ECHO) overall interpretation will be provided. Percentages will be based on all patients in the Safety set.

A listing of patients with newly occurring clinically significant abnormality will be produced.

2.6.4.2 Physical examination

The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the trial site if the visit is an onsite visit or at the practice of the local oncologist. Once available, source documents from the practice of the local oncologist will be made accessible to investigators and site personnel per current practice as allowed per country regulation. Additional details on transfer of source documents will be detailed in a separate operational manual.

Significant findings that were present prior to the signing of ICF must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after signing of ICF must be recorded on the AE page of the participant's CRF.

Listing of patients with physical examination data will be produced.

2.6.4.3 Vital signs

Vital signs assessments are performed in order to characterize basic body function. The parameters expected to be collected include: height, weight, temperature, pulse rate, and systolic and diastolic blood pressure.

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic blood pressure (BP): ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
- Temperature: ≥ 39.1°C
- Pulse rate: ≥ 120 bpm with increase from baseline of ≥15 bpm

Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Temperature: ≤ 35°C
- Pulse rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm

The following two listings will be produced by participant, and visit/time:

- Patients with clinically notable vital sign abnormalities.
- All vital sign assessments will be listed by vital sign parameter and if ranges are available.

2.7 Pharmacokinetic endpoints

Not applicable.

2.8 PD and PK/PD analyses

Not applicable.

2.9 Patient-reported outcomes

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0) and the EuroQoL 5-level instrument (EQ-5D-5L, Version 4.0) will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms and treatment-related side effects. The BPI-SF will be used to assess patient's subjective assessment of pain.

The PRO instruments except TFQ are planned to be administered during screening, cycle 4 day 1, cycle 7 day 1, cycle 10 day 1 and the end of treatment. PRO assessments will continue to be collected during the efficacy follow-up after the end of treatment.

The following electronic participant-reported outcomes (ePROs) EORTC QLQ-C30, EQ-5D-5L and BPI-SF will be used to evaluate participant-reported outcome measures of health-related quality of life, functioning, disease symptoms, treatment-related side effects, global health status, and cancer related pain.

The following time based intervals will be used to group the PRO data over time. Day is defined as date of PRO assessment date – treatment start date + 1.

Table 2-5 Time windows for patient reported outcomes

	Time interval
Baseline	Screening and Cycle 1, Day 1, before trial treatment administration
Cycle 4, 7 until cycle 10 Day 1	During treatment period, questionnaires to be performed in the week preceding Day 1 of Cycle 4, Cycle 7, and Cycle 10. i.e., days (1, 113] for Day 1 of cycle 4 (2nd assessment) i.e., days (114, 197] for Day 1 of cycle 7 (3rd assessment) i.e., days (198, 281] for Day 1 of cycle 10 (4th assessment)
End of treatment	Assessment taken at the end of treatment visit

If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the assessment obtained prior to target date will be used. If the closest assessment to the target date has two questionnaires filled out on the same date, then the worst score of these assessments will be used for each subscale score.

The FAS will be used for all PRO listings.

2.9.1 EORTC QLQ-C30

The EORTC QLQ-C30 contains 30 items and is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale (Aaronson et al 1993).

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high/healthy level of functioning; a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual (Fayers 2001).

2.9.2 EQ-5D-5L

The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Whatever the version of the EQ-5D questionnaire, the EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine.

The EQ-5D descriptive system comprises of the 5 following dimensions: mobility, self- care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Scoring of raw data and methods for handling missing items or missing assessments will be handled according to scoring manuals for each respective patient questionnaire (Oemar and Janssen 2013; Cleeland 2009).

2.9.3 Brief Pain Inventory

The BPI-SF is a self-administered assessment tool validated to assess pain (Atkinson et al 2011; Philip et al 1998). The basic aim of the BPI is to provide the information on the intensity of pain, along with the degree to which the pain interferes with the everyday functioning of life. The BPI uses simple numeric rating scales from 0 to 10. Since pain can vary to a considerable measure over a day, the BPI asks the patients to rate their pain at the time of responding to the questionnaire. In addition, the questionnaire also asks the respondent to specify the pain at its worst, least and average over the previous week.

No scoring algorithm have been developed for the BPI, but "worst pain" or the arithmetic mean of the four severity items can be used as measures of pain severity; the arithmetic mean of the seven interference items can be used as a measure of pain interference.

Analysis of PRO

EORTC QLQ-C30, EQ-5D-5L and Brief Pain Inventory data will be listed.

2.9.4 TFQ

For TFQ analysis, please refer Section 2.4.2

2.10 Biomarkers

Not applicable.

2.11 Other Exploratory analyses

Not Applicable.

2.12 Interim analysis

Not Applicable.

3 Sample size calculation

As this is a pilot trial to evaluate the use of DCT, there is no formal calculation of sample size. Approximately 20 participants will be included based on feasibility.

4 Change to protocol specified analyses

Not Applicable.

5 Appendix

5.1 Imputation rules

Throughout the study reasonable attempts will be made to limit the amount of missing data. However missing data will not be imputed, unless imputation is needed to perform specific analyses (e.g., for a dose administration record (DAR) with missing end date or end date after the cut-off date, the cut-off last contact date needs to be imputed as an end date to allow for calculation of treatment exposure duration and dose intensity). If it is required to impute an end date, the imputed date will be displayed and flagged in the appropriate listing, if produced. Imputation rules for missing dates (if applied) will be defined in the PDS before the database lock.

5.1.1 Study drug

The default rule for missing/partial start date or end date of study drug imputation is the following:

- Day missing will be replaced by 15;
- Day & month missing will be replaced by 1 July;
- No imputation if day, month and year are missing.

Imputed dates will not be displayed in listings except when required.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and study day, and any corresponding durations will be presented based on the imputations specified in the following paragraphs of this section.

5.1.2 AE date imputation

Missing or partial AE dates will not be imputed.

5.1.3 Concomitant medication date imputation

5.1.3.1 Prior therapies date imputation

In order to define prior medications/therapies, missing or partial start and stop dates will be handled as described in Section 5.1.1.

5.1.3.2 Post therapies date imputation

In order to define post/concomitant medications/therapies, missing or partial start and stop dates will be handled as described in Section 5.1.1.

5.1.3.3 Other imputations

Imputation of missing or partial dates for medical/disease history will be handled as described in Section 5.1.1.

Partial date imputation is allowed for event (death)/censoring coming from 'Death information' eCRF.

For rare cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then date of death is imputed as max [(1 mmm-yyyy), min(last contact date +1, cutoff date)].
- If both day and month are missing, then date of death is imputed as max [(1 Jan-yyyy), min (last contact date +1, cutoff date)].

5.2 AEs coding/grading

Adverse events are coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE v4.03 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death.

If CTCAE grading does not exist for an adverse event, grades 1 – 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE grade 5 (death) will not be used in this study; if an AE results in death it will be documented in the outcome ("fatal"). Information on deaths will also be collected on the 'Death' CRF.

5.3 Laboratory parameters derivations

CTC grades for laboratory values in Novartis Oncology (based on CTCAE v4.03 – Month YEAR)

Table for CTCAE v4.03

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Not Applicable.

5.4.2 Analysis supporting secondary objective(s)

Not Applicable.

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of deviation	Exclusion in analyses	Severity Code
IC01	Participant is an adult ≥ 18 years old at the time of consent	Include in all analyses	49
IC02	Participant with ABC (loco-regionally recurrent or metastatic) not amenable to curative therapy.	Include in all analyses	49
IC03	Participant with a histologically and/or cytologically confirmed diagnosis of ER-positive and/or PR-positive breast cancer by local laboratory.	Include in all analyses	49
IC04	Participant with a confirmed HER2-negative ABC (see Protocol definition)	Include in all analyses	49
IC05	Participant with a pathology report confirming PIK3CA mutant status by a certified laboratory using a validated PIK3CA mutation assay (from either tissue or blood).	Include in all analyses	49
IC06	Participant had progression of disease during or after endocrine-based therapy	Include in all analyses	49
IC07	Participant has a Performance Status at screening and at Cycle 1, Day 1 visit lower than or equal to 1 (ECOG/WHO PS ≤ 1)	Include in all analyses	49
IC08	Participant has adequate bone marrow and organ function as defined in the following laboratory valued (as assessed by site laboratory for eligibility) - see protocol	Include in all analyses	49
IC09	Participant is a man or a pre- or post-menopausal woman (for Pre and Post-menopausal se Protocol definition)	Include in all analyses	49
IC10	Participant is willing to operate a smartphone including the telemedicine application and a medical device (glucometer)	Exclude from all analyses	8
IC11	Participant is willing to follow the requirements for remote participation	Exclude from all analyses	8
IC12	Participant has signed ICF before any trial related activities and according to local guidelines.	Exclude from all analyses	8
E01	Participant has received prior treatment with any PI3K, mTOR, or AKT inhibitor.	Include in all analyses	49

E02	Participant with known hypersensitivity to alpelisib or fulvestrant, or to any of the excipients of alpelisib or fulvestrant.	Include in all analyses	49
E03	Participant has had major surgery within 14 days prior to trial treatment start and/or has not recovered from major side effects.	Include in all analyses	49
E04	Participant with inflammatory breast cancer at screening.	Include in all analyses	49
E05	Participant with an established diagnosis of diabetes mellitus type I or not controlled type II (based on fasting glucose [FG] and HbA1c, see inclusion criterion 8)	Include in all analyses	49
E06	Participant with impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of the trial treatments (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) based on investigator discretion.	Include in all analyses	49
E07	Participant has currently documented pneumonitis/interstitial lung disease (the chest Computerized Tomography (CT) scan performed at baseline for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).	Include in all analyses	49
E08	Participant with Child Pugh score B or C.	Include in all analyses	49
E09	Participant with uncontrolled hypertension defined by a Systolic Blood Pressure ≥ 160 mmHg and/or Diastolic Blood Pressure ≥ 100 mmHg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.	Include in all analyses	49
E10	Participant with clinically significant, uncontrolled heart disease and/or recent cardiac events (see Protocol version 01 for definition)	Include in all analyses	49
E11	Participant with any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate participant participation in the clinical trial (e.g., chronic active hepatitis, [testing not mandatory unless required by local regulations or requirements] confirmed pneumonitis etc.).	Include in all analyses	49
E12	Participant is currently receiving any of the following medications and cannot be discontinued 7 days prior to the start of the treatment: - Strong cytochrome P (CYP)3A4 inducers	Include in all analyses	49

	- Inhibitors of breast cancer resistance protein (BCRP)		
E13	Participant has a history of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.	Include in all analyses	49
E14	Participant with unresolved osteonecrosis of the jaw.	Include in all analyses	49
E15	Participant has a history of severe cutaneous reactions like Stevens-Johnson-Syndrome, Erythema Multiforme, or Toxic Epidermal Necrolysis, or Drug Reaction with Eosinophilia and Systemic Symptoms.	Include in all analyses	49
E16	Participant with evidence of disease progression during the pre-trial induction therapy and prior to first dose of alpelisib	Include in all analyses	49
E17	Participant has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to trial treatment initiation, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia).	Include in all analyses	49
E18	Participant is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting trial treatment, or who have not fully recovered from side effects of such treatment. (see Protocol for definition)	Include in all analyses	49
E19	Participant participated in a prior investigational study within 30 days prior to the start of trial treatment or within 5 half-lives of the trial treatment, whichever is longer.	Include in all analyses	49
E20	Participant has not recovered from all toxicities related to prior anticancer therapies to NCI CTCAE version 4.03 Grade ≤ 1. Exception to this criterion: participants with any grade of alopecia are allowed to enter the trial.	Include in all analyses	49
E21	Participant has a concurrent malignancy or malignancy within 3 years of start of trial treatment, with the exception of adequately treated, basal or squamous cell carcinoma, nonmelanomatous skin cancer, or curatively resected cervical cancer	Include in all analyses	49
E22	Participant has central nervous system (CNS) involvement which was not previously treated and not fulfilling the following 3 criteria to be eligible for the trial: - Completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of trial entry and - CNS tumor is clinically stable at the time of screening and	Include in all analyses	49

	- Participant is not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.		
E23	Participant has a known history of Human Immunodeficiency Virus infection (testing not mandatory unless required by local regulations or requirements).	Include in all analyses	49
E24	Participant is not able to understand and to comply with trial instructions and requirements, including oral administration of trial treatment	Exclude from all analyses	8
E25	Participant is a nursing (lactating) or pregnant woman as confirmed by a positive serum (hCG) test prior to initiating trial treatment	Include in all analyses	49
E26	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 trial treatment and at least for 2 years after the last dose of any trial treatment. Highly effective contraception methods include: see Protocol definition	Include in all analyses	49
E27	Participant is a sexually active male unwilling to use a condom during intercourse while taking trial treatment, and for 2 years after the last dose of trial treatment. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of trial treatment via seminal fluid to their partner. In addition, male participants must not donate sperm during the trial and up to the time period specified above	Include in all analyses	49
E28	Participants with active infections, including a COVID-19-related diagnosis	Include in all analyses	49
S1	Study medication not administered	Exclude from safety analyses	5
O1	Study drug related toxicity triggering a dose modification, as per protocol, and participant receives the incorrect dose	Include in all analyses	49
O2	Study drug related toxicity triggering a dose interruption, as per protocol and participant not discontinued from treatment	Include in all analyses	49
O3	Participant concomitantly administered with a strong inducer of CYP3A or inhibitors of BCRP, as per protocol	Include in all analyses	49
O4	Missed questionnaires or e-diary, as per protocol	Include in all analyses	49

Table 5-2 Code Text

Code	Code text
5	Exclude from safety analyses

8	Exclude from all analyses
49	Include in all analyses

6 Reference

Aaronson NK, Ahmedzai S, Bergman B, et al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst; 85(5):365-76.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solidtumours: revised RECIST guideline (version 1.1). Eur J Cancer; 45(2):228-47.

Fayers PM (2001). Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer; 37(11):1331-4.

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.