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Novartis Research and Development

BYL719/Alpelisib

Clinical Trial Protocol 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 TELEPIK Trial

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List of abbreviations

ABC	Advanced Breast Cancer
ADA	American Diabetes Association
AE	Adverse Event
AESI	Adverse Event of Special Interest
AKT	Protein kinase B
ALT	Alanine aminotransferase
ASIH	Avancerad sjukvård i hemmet (Swedish acronym which means “advanced care at home”)
AST	Aspartate aminotransferase
AV	Atrioventricular
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BPI-SF	Brief Pain Inventory Short Form
C1	Cycle 1
CDK4/6i	Cyclin-dependent kinases 4 and 6 inhibitors
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central nervous system
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P
D1	Day 1
DCT	Decentralized Clinical Trial
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EMA	European Medicines Agency
EORTC QLQ C30	European Organization for Research and Treatment of Cancer’s core quality of life questionnaire
EOT	End of Trial
ePRO	Electronic participant reported outcome
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
ESO	European School of Oncology
EU	European Union

FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FG	Fasting glucose
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-Glutamyl Transferase
hCG	human chorionic gonadotropin
HCP	Healthcare Professional
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
LHRH	Luteinizing Hormone-Releasing Hormone
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MPA	Swedish Medical Product Agency
MRI	Magnetic Resonance Imaging
mTOR	mechanistic target of rapamycin
NCI	National Cancer Institute
NTI	Narrow Therapeutic Index
OFS	Ovarian function suppression
ONJ	Osteonecrosis of the Jaw
PFS	Progression-free survival
PIK3	Phosphatidylinositol-3-kinase
PIK3CA	Gene which encodes the p110alpha catalytic subunit of PI3K
PR	Progesterone receptor
PRO	Participant Reported Outcomes
PT	Preferred Term
QOL	Quality of life
RANK	Receptor activator of nuclear factor κ B
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SGLT2	Sodium Glucose Co-Transporter 2
SMBG	Self-monitoring blood glucose

SmPC	Summary of Product Characteristics
SOC	System Organ Class
TBIL	Total bilirubin
TFQ	Trial Feedback Questionnaire
ULN	Upper Limit of Normal
VAS	Visual Analysis Scale
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the trial
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a trial participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the trial treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Decentralized Clinical Trial (DCTs)	Trials executed through telemedicine and mobile/local healthcare providers, using processes and technologies that differ from the traditional clinical trial model. DCTs are conducted remotely, with participants remaining at home during a significant portion of the trial, also called partially decentralized or hybrid approaches, or all of the trial, called full DCTs.
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical trial data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant, i.e. the End of Trial (EOT) visit of the last ongoing patient (C12D28 or final visit for a patient early dropped)
Enrollment	Point/time of participant entry into the trial at which informed consent must be obtained
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the trial (i.e. concomitant or rescue therapy)
Part	A sub-division of a trial used to evaluate specific objectives or contain different populations. For example, one trial could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the trial for all data collected, sample labels, etc.

Patient-reported-Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition, without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the trial phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, trial information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the trial prior to the planned completion of all trial drug administration and/or assessments; at this time all trial drug administration is discontinued and no further assessments are planned
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgement as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location within a participant's locality
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the trial
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper
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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Trial treatment	Any drug or combination of drugs or intervention administered to the trial participants as part of the required trial procedures; includes investigational drug(s), control(s) or background therapy
Trial treatment discontinuation	When the participant permanently stops taking any of the trial drug(s) prior to the defined trial treatment completion date (if any) for any reason; may or may not also be the point/time of trial discontinuation
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the trial treatment.
Unscheduled in-clinic visit	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.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question.
Withdrawal of trial consent (WoC)	Withdrawal of consent from the trial occurs only when a participant does not want to participate in the trial any longer and does not allow any further collection of personal data

Amendment 1 (15-Jun-2021)

Amendment rationale

The protocol has been amended to address the request for supplementary information as described in the Deficiency letter received from the Swedish Health Authority (Medical Products Agency) on 22 April 2021 before the study started. The amended version is in accordance with the responses indicated by Novartis on 29 April 2021.

Changes to the protocol

Major changes to the protocol are listed below. Minor changes are highlighted in the track-change version.

- Section "Glossary of terms": definition of "participant-reported outcomes (PRO)", "Re-screening" and "Remote" were added to match the most updated version of the Oncology protocol template.
- Section 5.2 "Exclusion criteria": criterion #26 was amended to exclude hormonal therapy as possible contraception method.
- Section 6.2.2 "Prohibited medications": the section was updated to specify that hormonal contraception is contraindicated for patients with ER positive breast cancer; therefore, it is not to be considered as contraception method for the trial.
- Section 6.7 "Preparation and dispensation": the sentence "Each shipment will be for a maximum of one cycle of trial treatment" was eliminated to allow treatment continuity within the windows of assessments as per protocol.
- Section 8 "Visit schedule and assessments": section amended to include a clearer definition of local oncologists and district nurse, as well as the possibility to include other qualified healthcare professionals such as home-nursing professionals from ASIH (Swedish acronym meaning advanced care at home) performing standard of care procedures. Moreover, it was included the definition of "unscheduled visit" and the specification that, in case the participant cannot attend a final on site visit, they will be requested to return the study drug and the devices provided for the trial, through the courier.
- Table 1-1 "Assessment schedule": the assessment schedule was amended for the following assessments:
  - Included the continuous completion of e-diary by the participant.
  - e-PROs moved to Cycle 1, Day 1, specifying that they should be completed in the telemedicine platform, in the period between screening and Cycle 1, Day 1, before trial treatment administration.
  - for fasting plasma glucose (FPG) at Cycle 1, Day 1 and Cycle 1, Day 15, a note was added to reflect the last approved SmPC version (At Cycle 1, Day 1 and Cycle 1, Day 15, if accepted by local approved SmPC, FPG evaluation could be replaced by self-monitoring blood glucose (SMBG) assessment, and this will not be considered a protocol deviation).
  - SMBG: removed from screening and Cycle 1, Day 1, as FPG will be collected at those time points. SMBG will be started on Cycle 1, Day 2

  - Considering the remote logistics and the allowed time-windows for the different assessments, a note was added to specify that CxD1 of each cycle is to be considered as the day of fulvestrant injection.
  - Participant satisfaction: TFQ questionnaire was replaced by collection of "participant satisfaction" and a note was added to specify that participant satisfaction will be collected on a quarterly basis (Day 1 of Cycles 4, 7, and 10) through Novartis standard Trial Feedback Questionnaire (TFQ) and, on the other Cycle x, Day 1 timepoints, through dedicated questions in the e-diary.
- Sections 8.1, 8.2, 8.3, 8.4, and 8.5 were amended to reflect the above changes described in Table 8-1.
- Section 8.6 "DCT elements included in the trial" was added as a new section, to include more operational information on the responsibilities and operational processes necessary to conduct the decentralized procedures/visits for participants at an off-site location.
- Section 9.2 "Trial completion and post-trial treatment": included the definition of End of trial, to reflect what is included in the glossary.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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.

Summary of previous amendments

Not applicable. This is the first Protocol amendment.

Protocol summary

Protocol number	CBYL719A03201
Full title	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
Brief title	Study of safety and utility of a hybrid decentralized trial approach using a TELEmedicine platform in patients with HR-positive/HER2-negative advanced breast cancer with a PIK3CA mutation, treated with alpelisib – fulvestrant
Sponsor and Clinical Phase	Novartis Pharma AG Phase II
Investigation type	Other
Trial type	Interventional
Purpose and rationale	Novartis designed this pilot trial to answer Swedish Medical Product Agency's call for launching pilot DCTs to identify and register pragmatic, empirical, and practical observations and experiences in connection with planning and implementing decentralized, patient-centered clinical trials at a geographic distance with virtual elements.
Primary Objective	To assess participant satisfaction with the DCT experience
Secondary Objectives	• 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 adverse events (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 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.
Trial design	Open-label, single arm, multi-center, Phase II interventional pilot trial.
Trial population	Men, pre- and post-menopausal women with a HR-positive/HER2-negative ABC (loco-regionally recurrent not amenable to curative therapy or metastatic) with a PIK3CA mutation, which progressed on or after endocrine-based treatment.
Key Inclusion criteria	1. Participant is an adult ≥18 years old at the time of consent 2. Participant with ABC (loco-regionally recurrent or metastatic) not amenable to curative therapy. 3. Participant with a histologically and/or cytologically confirmed diagnosis of ER-positive and/or PR-positive breast cancer by local laboratory. 4. Participant with a confirmed HER2-negative ABC.

	5. Participant with a pathology report confirming PIK3CA mutant status by a certified laboratory using a validated PIK3CA mutation assay (from either tissue or blood). 6. Participant is a man or a pre- or post-menopausal woman. 7. Participant is willing to operate a smartphone compatible with the software of the medical device and willing to manage applications 8. Participant is willing to use the telemedicine platform and to follow the remote participant monitoring procedure. 9. Participant has signed an informed consent form before any trial related activities and according to local guidelines.
Key Exclusion criteria	1. Participant has received prior treatment with any PI3K, mTOR, or AKT inhibitor. 2. Participant with known hypersensitivity to alpelisib or fulvestrant, or to any of the excipients of alpelisib or fulvestrant. 3. 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.
Trial treatment	Participants will receive alpelisib 300 mg daily and fulvestrant 500 mg administered intramuscularly on Cycle 1, Day 1 and Cycle 1, Day 15, and on Day 1 of each cycle thereafter until Cycle 12. Pre-menopausal women will receive goserelin 3.6 mg on Day 1 of each cycle.
Treatment of interest	Participants with risk factors for developing hyperglycemia may be treated, at the investigator's discretion, with SGLT2 with or without metformin if needed, as prophylactic treatment to prevent hyperglycemia. Prophylactic use of antihistamines could be considered for the treatment of trial drug inducted skin toxicity.
Efficacy assessments	Tumor imaging
Key safety assessments	Adverse event monitoring, Physical examinations, Vital signs, Monitoring of laboratory markers in blood, Health related quality of life using Participants reported outcomes
Data analysis	All analyses will be descriptive.
Key words	Pilot, Decentralized clinical trial.

1 Introduction

1.1 Background

Historically clinical trials rely heavily on close and frequent on-site contact between participants and investigators. Access to trial sites has been a challenge for patients living in remote and rural areas. This has contributed to a bias towards inclusion of patients living in urban areas. Nowadays, another way of conducting clinical trials is emerging, decentralized clinical trials (DCTs). The United States Food and Drug Administration (FDA) defines DCTs as trials executed through telemedicine and mobile/local healthcare providers, using processes and technologies that differ from the traditional clinical trial model. DCTs offer flexibility to patients participating in trials where they can remain at home for some or all visits in a trial. DCTs can be either full DCTs, where all activities occur away from the trial site, or Hybrid DCTs, where some activities remain at the trial site. DCTs have the potential to offer benefits to both patients and sites, but industry adoption of the model has been slow. There are several barriers to the uptake of DCTs including limited experience with the approach, and the perception of regulatory barriers with implementing and using data from DCTs (Apostolaros et al 2020). Industry regulations have been written for traditional trial models and drugs approvals to date, such as for alpelisib, were based on data collected from traditional trials. In light of the COVID-19 pandemic, there is a critical need to ensure continued participant safety, study oversight, assurance of data integrity, and continuity of treatment which provided an impetus to accelerate towards more patient-centric DCTs. The most common DCT components implemented during the pandemic were telemedicine, electronic informed consent, digital data collection tools, remote site monitoring, direct to patient shipping, home health visits, and local community-based laboratory utilization. Future trials need to capitalize on the increased adoption and learning from the use of DCT components that occurred in this time of crisis.

On 28 May 2020, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending the granting of a marketing authorization for the medicinal product alpelisib (Piqray®). Alpelisib, an orally administered PI3K inhibitor that selectively inhibits the α-isoform of PIK3, p110α, was developed to answer the need to treat postmenopausal women, and men, with hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy. Marketing authorization was granted based on safety and efficacy data obtained through a traditional clinical trial, the SOLAR-1 trial. The SOLAR-1 trial was a randomized, double-blind, placebo-controlled Phase 3 trial where men and postmenopausal women with HR-positive/HER2-negative advanced breast cancer (ABC) were assigned to cohorts based on their tumor-tissue PIK3CA mutation status and randomized 1:1 to receive either treatment with alpelisib plus fulvestrant or placebo + fulvestrant. Participants in the SOLAR-1 trial were mandated to attend several on-site visits: Day 1, Day 8, and Day 15 of Cycle 1; Day 1 and Day 15 of Cycle 2; and Day 1 of subsequent cycles.

SOLAR-1 trial primary endpoint was progression-free survival (PFS) in the PIK3CA-mutated cohort, as assessed by the investigator according to response evaluation criteria in solid tumors (RECIST) version 1.1. The trial showed a statistically significant improvement in PFS in favor

of the alpelisib plus fulvestrant arm (hazard ratio = 0.65; 95% confidence interval [CI]: 0.50, 0.85), 1-sided $p < 0.001$). The median PFS was prolonged by 5.3 months, from 5.7 months (95% CI: 3.65, 7.36) in the placebo + fulvestrant arm to 11.0 months (95% CI: 7.5, 14.5) in the alpelisib plus fulvestrant arm. No PFS benefit was observed in patients without a PIK3CA mutation (Andre et al 2019).

The safety profile of alpelisib plus fulvestrant is based on the combined PIK3CA mutant and non-mutant cohort data of the SOLAR-1 trial. Medical dictionary for regulatory activities (MedDRA) preferred terms of any grade reported in at least 35% of the patients who received alpelisib plus fulvestrant were hyperglycemia (63.7%), diarrhea (57.7%), nausea (44.7%), decreased appetite (35.6%), and rash (35.6%) or maculopapular rash (14.1%). The most common adverse events (AEs) of grade 3 or 4, occurring in at least 5% of patients were hyperglycemia (36.6%), rash (9.9%), maculopapular rash (8.8%), and diarrhea (6.7%). Permanent discontinuation of alpelisib due to AEs occurred in 25.0% of patients receiving alpelisib plus fulvestrant. The most frequent AEs leading to the discontinuation of alpelisib were hyperglycemia (6.3%) and rash (3.2%) (Andre et al 2019).

1.2 Purpose

DCTs will enable more diversity in clinical trials and increase enrollment of historically underrepresented patients in clinical research. In Sweden, the distribution of ABC patients is widespread and often there are limited sites options for clinical trial participation. The purpose of this pilot trial is to describe if the hybrid DCT approach is satisfactory, safe and suitable for ABC patients treated with alpelisib, which has a balanced safety profile.

Additionally, the Swedish Medical Products Agency (MPA) is seeking to gain experience from DCT pilots with the aim to identify and register pragmatic, empirical, and practical observations and experiences in connection with planning and implementing decentralized, patient-centered clinical trials at a geographic distance with virtual elements. This trial was selected as a part of the MPA pilot program and is designed as a hybrid DCT.

2 Objectives, endpoints, and estimands

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
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)
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*
• 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 • 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
• To assess AEs 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
• 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)

Objectives	Endpoints
• To assess the effectiveness of alpelisib plus fulvestrant	• PFS according to RECIST 1.1

2.1 Primary estimands

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

2.2 Secondary estimands

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

3 Trial design

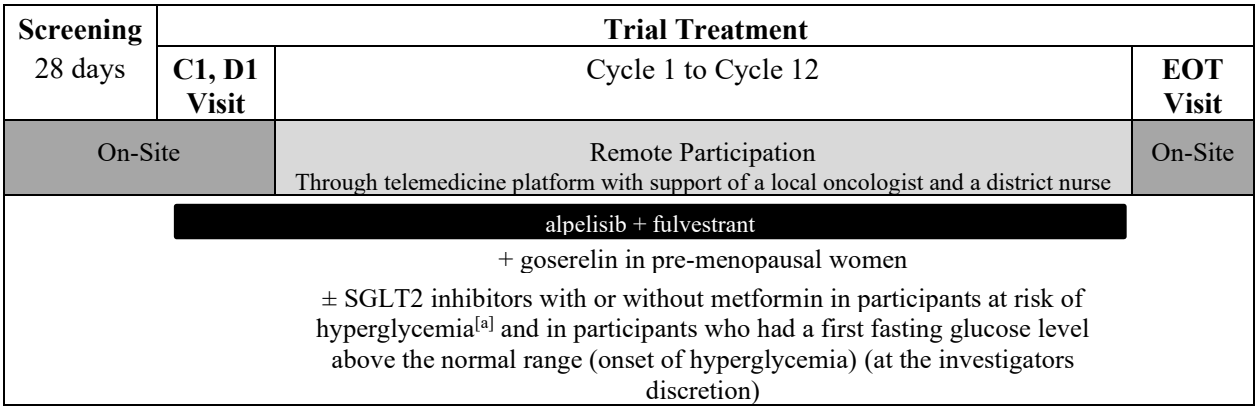
This is an open-label, single arm, multi-center, Phase II interventional pilot trial conducted to evaluate if a DCT using a telemedicine platform offers a satisfactory, safe and suitable management for HR-positive/HER2-negative patients with ABC harboring a PIK3CA mutation and treated with alpelisib 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 (see Section 8 "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.

Figure 3-1 Trial 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

4 Rationale

4.1 Rationale for trial design

This trial is a single arm, open-label trial conducted in HR-positive/HER2-negative patients harboring a PIK3CA mutation and treated with alpelisib plus fulvestrant. This trial included a hybrid DCT approach to reduce participant burden of traveling to sites and enable enrollment of patients living far from investigative sites that may not have consented to participate in traditional clinical trials. Expected benefits of using a decentralized approach are (1) reduced burden on participants by bringing visits, services, and supplies closer to them, leading to increased access to trial (see Section 4.5.1 "Potential benefits for participants"), (2) potential improvement of participant recruitment (e.g., geographic diversity of recruitment), (3) potential to increase adherence to protocol and participant retention.

Based on alpelisib safety profile, the following AESIs will be particularly looked at in this pilot trial: hyperglycemia, rash, and diarrhea. For hyperglycemia, a medical device will be used for blood glucose measurements. For rash, participants will take a photograph using the telemedicine application and upload the photograph to the platform for the investigator's evaluation. Investigators will refer participants to the local oncologists when required. For diarrhea, participants will be trained to recognize signs and symptoms and will be instructed to contact investigators whenever they occur.

Pain and health-related QOL will be surveyed using questionnaires administered through the telemedicine platform.

Participants at risk of 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 SGLT2 inhibitors with or without metformin as prophylactic treatment. Based on the data from the SOLAR-1 trial, baseline body mass index (BMI) $\geq$ 30, baseline age $\geq$ 75 years, and baseline diabetic and pre-diabetic status have been found to be risk factors for hyperglycemia in patients treated with alpelisib; these risk factors were present in 74.7% of patients with any grade of hyperglycemia and in 86.2% of patients with grade 3 or 4 hyperglycemia. As baseline diabetic and pre-diabetic status are defined based on baseline hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) values, these values will be closely monitored during the trial.

Following expert opinion of the European School of Oncology (ESO) and European Society for Medical Oncology (ESMO) (Cardoso et al 2020), and from the Swedish guidelines for treatment of metastatic breast cancer (Cancercentrum 2019), it is recommended that young women with ER-positive ABC should have adequate ovarian function suppression (OFS) or ovarian function ablation. These young women should then be treated in the same way as postmenopausal women. Pre-menopausal women will be eligible for the trial even though this is outside of alpelisib label. These women will receive goserelin a LHRH agonist, as a co-therapy to induce OFS.

Participants with prior endocrine-based therapy with or without cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6i) will be eligible for trial participation; even though participants previously treated with concomitant CDK4/6i treatments are outside of alpelisib label. Endocrine therapy are considered the standard of care for patients with ER-positive/HER2-negative ABC, since it achieves substantial PFS benefit, significantly

increases OS and either maintains or improves QOL. The BYLieve study was originally designed to investigate the benefit:risk ratio of PIK3CA inhibitor treatment following prior use of CDK4/6 inhibitor treatments. BYLieve trial is a Phase II, multicenter, open-label, 3-cohort, non-comparative study of Piqray plus endocrine therapy (fulvestrant or letrozole) in men and women with ER-positive/HER2-negative, PIK3CA-mutated advanced breast cancer whose disease has progressed after prior therapy, including CDK4/6i (Rugo et al 2018). Results from the cohort of patients with CDK4/6i +aromatase inhibitor as an immediate prior treatment and centrally confirmed PIK3CA mutation (n = 121) have been published (Rugo et al 2020). The primary endpoint was the proportion of patients who are alive without disease progression at 6 months (RECIST v1.1; local assessment). The AE analysis was based on preferred terms. Based on a median follow-up of 11.7 months, 50.4% of patients (95% CI: 41.2 to 59.6) met the primary endpoint. The most frequent all-grade AEs and grade ≥ 3 AEs in this BYLieve cohort were similar to those reported in SOLAR-1.

4.2 Rationale for dose/regimen and duration of treatment

As alpelisib is already marketed in Europe, this protocol will mandate dosing follows the recommendations per the summary product characteristics (Piqray® SmPC, Novartis). Based on the 11.0-month median PFS in the alpelisib plus fulvestrant group in the cohort of patients with PIK3CA-mutated cancer (Andre et al 2019), trial duration is planned to be 12 cycles of 28 days of treatment each.

4.3 Rationale for choice of combination drugs

Fulvestrant

Per alpelisib SmPC, alpelisib is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR-positive/HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy. The combination of alpelisib and fulvestrant demonstrated increased anti-tumor activity compared to either treatment alone in xenograft models derived from estrogen receptor positive, PIK3CA mutated breast cancer cell lines (Piqray® SmPC, Novartis).

Goserelin

Endocrine treatment is a standard treatment option for pre-menopausal women with ABC. As it is generally admitted that pre-menopausal women exhibit a more aggressive disease with a poorer prognosis than other women and given that, despite several treatment options, resistance to endocrine therapy and disease progression occur in pre-menopausal women, there is a need for new therapeutic options. International ESO-ESMO guidelines and Swedish guidelines for treatment of metastatic breast cancer state that pre-menopausal women should be treated like post-menopausal women upon OFS (Cancercentrum 2019; Cardoso et al 2020). OFS can be induced, among other options, by administration of LHRH agonist. It is recommended to give LHRH agonists on an every 4 weeks basis to optimize OFS (Cardoso et al 2020). In the phase Ib B-YOND trial, pre-menopausal women with HR-positive ABC were treated with alpelisib and buparlisib. Interim data conducted in a small group of 16 patients treated with alpelisib in combination with tamoxifen and goserelin achieved 44% clinical benefit rate with 7 (44%)

patients achieving partial response per RECIST v1.1 as best overall response. Safety profile was generally manageable. These interim results led to conclusion that these pathways should also be further explored in this pre-menopausal population (Lu et al 2017). As goserelin is currently approved for the palliative treatment of pre-menopausal and peri-menopausal ABC, pre-menopausal women will be offered the possibility to be treated off-label with alpelisib plus fulvestrant with the addition of goserelin in this pilot trial.

4.4 Purpose and timing of interim analyses/design adaptations

Not Applicable.

4.5 Risks and benefits

4.5.1 Potential risks to participants

This pilot hybrid DCT was designed using a registered drug with participants being managed according to clinical practice. Risks to participants will be limited as the investigator is able to anticipate possible reactions to trial treatment and efficiently manage any adverse drug reactions. For details on clinical safety, please refer to the latest version of alpelisib SmPC (Piqray® SmPC, Novartis) and fulvestrant SmPC (Faslodex® SmPC, Astra Zeneca). The addition of goserelin to premenopausal women is not expected to affect the metabolism of participants, or to be affected by co-administration of the other drugs (alpelisib in combination with fulvestrant), so no additional safety risks are expected with this combination. Risks will also be minimized by adherence to inclusion/exclusion selection criteria (see Section 5 "Trial Population"), avoidance of prohibited medication (see Section 6.2.2 "Prohibited medication"), close safety monitoring (see Section 6.5.1 "Follow-up for toxicities" and Section 10 "Safety monitoring and reporting"), adherence to dose adjustment guidelines (see Section 6.5 "Dose escalation and dose modification"), and training of site personnel. Participants will be trained to report symptoms via the telemedicine application as soon as possible as they occur. Safety management in a DCT is the same as in the traditional clinical trial. The investigator is responsible for identifying, managing, and assessing safety events reported and must use their medical judgment to determine the appropriate care needed to address any AEs. The platform will support the Investigator in overseeing the participant with summary reports and notifications.

The participant can return to on-site visits at any time at the investigator's and the participant's discretion.

Women of childbearing potential and sexually active males must be informed that taking this trial treatment may involve unknown risks to the fetus if pregnancy was to occur during the trial and up to the period required after the last dose of trial treatment. Based on findings in animals and its mechanism of action, alpelisib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of alpelisib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes, including embryo-fetal mortality (post-implantation loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures based on area under the curve that were ≥ 0.8 times the exposure in humans at the recommended dose of 300 mg/day. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus. Participants must therefore agree to adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the trial.

Sufficient training on the use of monitoring devices (glucometer and smartphone) is required to avoid any additional burden on participants. Participants in the SOLAR-1 trial had a median age of 63 years, the telemedicine platform was selected for its user-friendliness and specific inclusion criteria have been included to ensure that all enrolled participants will be able to adhere to the remote participation (see Section 4.5.3 "Risk management strategies" for additional details).

In DCTs, trial conduct is centered around the patient rather than the site, this means that each patient may have a different local oncologist and district nurse, to support care local to them. As such, this increases the number of parties that support data collection for the trial. Ensuring data privacy and security is essential, the telemedicine platform selected uses measures such as encryption, access controls and audit trails to ensure integrity, reliability and security of data flow (see Section 4.5.3 "Risk management strategies" for additional details).

4.5.2 Potential benefits for participants

The hybrid approach is expected to reduce participant burden associated with traditional clinical trials, which involve frequent and lengthy on-site visits. The introduction of remote visits (facilitated by telemedicine, home health visits and direct-to-patient shipping of the trial medication) reduces the travel burden for participants; saving in turn participant's time, effort, and possibly money. Use of remote visits can reduce geographic barriers to participation and allow for recruitment of a larger pool of participants, especially those in more remote (non-urban) areas and/or those who do not drive and/or have easy access to transportation. This is particularly true for a geographically large country, such as Sweden, where patients oftentimes need to travel long distances to attend visits.

It is anticipated that the reduced number of on-site visits will decrease participant burden and improve their satisfaction in taking part in this clinical trial, resulting in a lower drop-out rate. A survey conducted in 4,086 patients across the United States and Europe highlighted the importance for participants to keep relationships with site personnel and 40% of respondents indicated that they would prefer clinical trial tests to be performed through a hybrid design (Goller and Kinlaw 2020). The hybrid approach will allow participants to maintain contact with investigators, both face-to-face during clinic visits at site or through the telemedicine platform during remote participation. Participants will be closely monitored by the investigator via the telemedicine platform and the investigator will also have oversight of the local oncologist and district nurse. Investigators will keep the responsibility and authority to make decision for all aspects related to the management of participants during the entire clinical trial duration.

4.5.3 Risk management strategies

Processes have been implemented to efficiently manage risks related to participants' safety.

Training of investigative staff and participants will be critical to ensure the success of remote participation. Prior to site initiation, investigational sites will be trained on the telemedicine platform, including both site and participant facing components, how to use the glucometer, and on processes unique to this DCT. At the Cycle 1, Day 1 Visit, participants will be trained by site staff on how to use the telemedicine application, in particular how to use the features to communicate with the site, and on how to use the glucometer. Investigators will ensure that participants feel at ease with the telemedicine application and are comfortable with the use of the glucometer prior to remote participation. Protocol selection criteria ensure enrolled participants are comfortable with the concept of remote participation.

Processes mandated in the SmPC for patients with diabetes, pre-diabetes or a risk factor for hyperglycemia will be extended to all participants. Participants will be requested to perform daily self-assessment of their blood glucose levels using a glucometer during the first two weeks of treatment, or longer when the risk is higher, and to have their blood drawn for fasting plasma

glucose measurement at least once per cycle. Participants will be instructed to contact site personnel in case they identify a high glucose value using the glucometer (equal or higher than 8.9 mmol/L) and the investigator will be able to monitor all reported glucose values in the telemedicine platform. Laboratory confirmation of self-measured high glucose values may be requested if deemed necessary by the investigator. The investigator will use clinical judgment to guide the management plan for each participant based on an individual benefit/risk assessment. See Section 6.5.1.3 "Guideline for the treatment of alpelisib-induced hyperglycemia" for additional details.

Rash will be reported through the telemedicine platform. Site personnel will assess pictures of the rash uploaded by participants in the telemedicine platform. Site personnel will decide how the event should be managed or, if needed, will refer participants to the local healthcare provider for further assessment. See Section 6.5.1.2 "Guidelines for the treatment of trial drug induced skin toxicity".

Participants will be trained to recognize signs and symptoms of diarrhea and will be instructed to contact their investigator whenever they occur. Investigators will manage symptomatic treatment according to their current clinical practice. Process management of study drug to be followed in case of diarrhea is described in Table 6-3 "Criteria for dose reduction/interruption and re-initiation of alpelisib for adverse drug reactions".

Ensuring integrity, reliability and security of data flow is of the highest priority. Novartis assessed and qualified a telemedicine platform including direct capture of source data within a secure electronic environment. Data captured within this pilot trial will be stored in a robust and secure cloud-based back end; access to data will be role-based and restricted. The selected platform is a validated system complying with relevant International Conference for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. Specific measures are built into the telemedicine platform to ensure integrity and security or data flow and storage, access control measures, and audit trail functionality will be described in a separate operational manual that will be provided to investigators.

The glucometer that will be provided to participants is validated and CE marked, and will be employed in the study for its intended use.

In light of the most recent guidelines, risks associated with the COVID-19 pandemic were evaluated and no additional risks were identified for this DCT. A COVID-19 test will not be mandated, but patients with COVID-19 symptoms at screening will not be enrolled in the trial. Specific measures will be taken according to local guidelines to prevent Sars-Cov-2 contamination during home visits.

Based on key anticipated benefits and potential risks, the benefit-risk balance is anticipated to be positive for the target population of this trial.

4.6 Rationale for public health emergency mitigation

During a Public Health emergency declared by Local or Regional authorities, i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity should be implemented. Design of this protocol already meets Novartis guidelines in terms of Public Health Emergency Mitigation. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and

permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Trial population

The trial will include approximately 20 participants HR-positive/HER2-negative ABC (loco-regionally recurrent not amenable to curative therapy or metastatic) with a PIK3CA mutation (refer to alpelisib SmPC for details on PIK3CA mutation, (Piqray® SmPC, Novartis), which progressed on or after endocrine-based treatment. Participants will be enrolled in a geographically well-defined region in Sweden.

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

5.1 Inclusion criteria

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

1. Participant is an adult ≥ 18 years old at the time of consent
2. Participant with ABC (loco-regionally recurrent or metastatic) not amenable to curative therapy.
3. Participant with a histologically and/or cytologically confirmed diagnosis of ER-positive and/or PR-positive breast cancer by local laboratory.
4. Participant with a confirmed HER2-negative ABC.

   HER2-negative defined as a negative *in situ* hybridization test or an immunohistochemistry status of 0, 1+ or 2+. If immunohistochemistry is 2+, a negative *in situ* hybridization (Fluorescence *In Situ* Hybridization, Chromogenic *In Situ* Hybridization, or Silver *In Situ* Hybridization) test is required by local laboratory testing.
5. Participant with a pathology report confirming PIK3CA mutant status by a certified laboratory using a validated PIK3CA mutation assay (from either tissue or blood).

   It is recommended the tumor sample is collected after the most recent progression or recurrence.
6. Participant had progression of disease during or after endocrine-based therapy.

   Aromatase inhibitor therapy does not need to be the latest treatment regimen.
7. Participant has a Performance Status at screening and at Cycle 1, Day 1 visit lower than or equal to 1 (ECOG/WHO PS ≤ 1)
8. Participant has adequate bone marrow and organ function as defined in the following laboratory valued (as assessed by site laboratory for eligibility):
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - Platelets ≥ 100×10^9/L
   - Hemoglobin ≥ 9.0 g/dL
   - Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ Grade 1 according to National Cancer Institute (NCI)-CTCAE version 4.03 if judged clinically not significant by the investigator
   - International normalized ratio (INR) ≤ 1.5

- Creatinine Clearance ≥ 35 mL/min using Cockcroft-Gault formula
- Total bilirubin < 2 × upper limit of normal (ULN; any elevated bilirubin should be asymptomatic at enrolment) except for participants with Gilbert's syndrome who may only be included if total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
- Potassium within normal limits, or corrected with supplements
- 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 ALT or AST values must be stable for 2 weeks, without evidence of biliary obstruction by imaging)
- Fasting Serum amylase ≤ 2 × ULN
- Fasting Serum lipase ≤ ULN
- FPG ≤ 140 mg/dL (7.7 mmol/L) and Glycosylate Hemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met)

9. Participant is a man or a pre- or post-menopausal woman

   Post-menopausal status is defined either by:

   - Prior bilateral oophorectomy or
   - Age ≥ 60 or
   - Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and follicle-stimulating hormone (FSH) and/or estradiol in the post-menopausal range per local normal range. If patient is taking tamoxifen or toremifene and age < 60, then FSH and plasma estradiol levels should be in post-menopausal range per local normal range.

     Note: For women using therapy-induced amenorrhea other than ovarian radiation or goserelin, serial measurements (per local guidelines) of FSH and/or estradiol are needed to ensure menopausal status.

   Pre-menopausal status is defined as either:

   - Patient had last menstrual period within the last 12 months

     OR
   - If on tamoxifen or toremifene during the past 14 days, plasma estradiol and FSH must be in the premenopausal range per local normal range,

     OR
   - In case of therapy-induced amenorrhea, plasma estradiol and/or FSH must be in the premenopausal range per local normal range

10. Participant is willing to operate a smartphone including the telemedicine application and a medical device (glucometer)
11. Participant is willing to follow the requirements for remote participation.
12. Participant has signed ICF before any trial related activities and according to local guidelines.

5.2 Exclusion criteria

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

1. Participant has received prior treatment with any PI3K, mTOR, or AKT inhibitor.
2. Participant with known hypersensitivity to alpelisib or fulvestrant, or to any of the excipients of alpelisib or fulvestrant.
3. Participant has had major surgery within 14 days prior to trial treatment start and/or has not recovered from major side effects.
4. Participant with inflammatory breast cancer at screening.
5. 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)
6. 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.
7. 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).
8. Participant with Child Pugh score B or C.
9. Participant with uncontrolled hypertension defined by a Systolic Blood Pressure ≥ 160 mmHg and/or Diastolic Blood Pressure ≥ 100 mmHg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.
10. Participant with clinically significant, uncontrolled heart disease and/or recent cardiac events including any of the following:
    - History of angina pectoris, coronary artery bypass graft, symptomatic pericarditis, or myocardial infarction within 6 months prior to the start of trial treatment
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - History of Left Ventricular Ejection Fraction < 50%
    - Clinically significant cardiac arrhythmias, (e.g., ventricular tachycardia), complete left bundle branch block, high grade atrioventricular (AV) block (e.g. bifascicular block, Mobitz type II and third degree AV block without pacemaker in place)
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or Fredericia QT correction formula (QTcF) > 470 msec at screening
11. 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.).
12. 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

- Inhibitors of breast cancer resistance protein (BCRP)

13. Participant has a history of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.
14. Participant with unresolved osteonecrosis of the jaw.
15. 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.
16. Participant with evidence of disease progression during the pre-trial induction therapy and prior to first dose of alpelisib.
17. 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).
18. 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.

    Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
19. 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.
20. 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.
21. 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, non-melanomatous skin cancer, or curatively resected cervical cancer.
22. 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
    - Participant is not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
23. Participant has a known history of Human Immunodeficiency Virus infection (testing not mandatory unless required by local regulations or requirements).
24. Participant is not able to understand and to comply with trial instructions and requirements, including oral administration of trial treatment.
25. Participant is a nursing (lactating) or pregnant woman as confirmed by a positive serum (hCG) test prior to initiating trial treatment.

26a. 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:

- 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 trial 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 trial the vasectomized male partner should be the sole partner for that participant

  Note: Hormonal contraception is contraindicated for patients with ER positive breast cancer, therefore it is not to be considered as a contraception method for the trial.

  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. Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 6 weeks before starting trial 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.

  If local regulations to prevent pregnancy deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

27. 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.
28. Participants with active infections, including a COVID-19-related diagnosis.

6 Treatment

6.1 Trial treatments

Participants will be administered alpelisib 300 mg daily (2 × 150 mg film-coated tablets) for 12 cycles of 28 days and fulvestrant 500 mg administered intramuscularly on Cycle 1, Day 1 and Cycle 1, Day 15, and on Day 1 of each cycle thereafter until Cycle 12 (see Table 6-1).

Table 6-1 Trial treatments

Drugs	Pharmaceutical Form and route of administration	Dose	Frequency and/or regimen	MAH
Alpelisib (Piqray®)	Film coated tablet for oral use	300 mg	Daily (continuous) starting Cycle 1, Day 1	Novartis
Fulvestrant (Faslodex®)	Injection for intra-muscular administration	500 mg	Days 1 and Day 15 on Cycle 1 and Day 1 at each cycle thereafter	AstraZeneca AB

MAH= Marketing Authorization Holder

6.1.1 Additional trial treatments

Depending on menopausal status, women participants may be prescribed goserelin as co-therapy with alpelisib and fulvestrant to induce OFS (see Table 6-2).

Table 6-2 Co-therapies

Drugs	Pharmaceutical Form and route of administration	Dose	Frequency and/or regimen
Goserelin	Injection for intra-muscular administration	3.6 mg	Starting Cycle 1, Day 1 and Day 1 at each cycle thereafter

6.1.2 Treatment arms/group

All participants enrolled within this trial will receive the same treatment.

6.1.3 Treatment duration

The planned duration of treatment is 12 cycles of 28 days. Participants may be discontinued from treatment earlier than the planned treatment duration due to unacceptable toxicity, disease progression and/or decision made at the discretion of the investigator or the participant.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

6.2.1.1 Permitted concomitant medications

The use of any concomitant medications/non-drug therapies deemed necessary to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed, except if specifically prohibited (See Section 6.2.2 “Prohibited medication”).

All medications, procedures, and significant non-drug therapies (including vitamins, physical therapy, herbal/natural medications and blood transfusions) administered within 30 days prior to the start of trial treatment must be recorded on the appropriate electronic Case Report Form.

The investigator should instruct the participant to notify the trial site about any new medications and/or non-drug therapies/procedures he/she takes after signing the informed consent. Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is

already enrolled, contact Novartis to determine if the participant should continue participation in the trial.

Oral anti-diabetics

Participants who develop hyperglycemia during the trial should be treated according to the ADA (American Diabetes Association) guidance.

Consultation with a diabetologist or healthcare provider experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia. It is recommended to start treatment with metformin, however SGLT2 inhibitors may be a suitable alternative or add-on therapy to metformin. SGLT2 inhibitors are a class of diabetic medications that improve hyperglycemia primarily by promoting urinary glucose excretion.

In the SOLAR-1 study, among the 284 participants who were randomized to receive alpelisib plus fulvestrant, 190 participants (67%) developed hyperglycemia, with 18 patients (6%) discontinuing alpelisib treatment due to hyperglycemia, as of 30-Sep-2019.

Among those with hyperglycemia, 166 participants received concomitant anti-diabetic medications, primarily consisting of metformin (87%). However, in addition to metformin, 6 participants also received an SGLT2 inhibitor, consisting of empagliflozin, ipragliflozin, or dapagliflozin. All 6 participants had ≥ 1 risk factor at baseline for developing hyperglycemia, defined as prediabetes (n = 4; 1 of whom had documented history of type 2 diabetes), diabetes (n = 2), and obesity (n = 2). The most severe hyperglycemia in these participants was grade (G) 3 (n = 5). After initiating an SGLT2 inhibitor, all subsequent hyperglycemia events were G 1/2, except one G 3 event with steroids as a confounding factor. The duration of alpelisib ranged from 9.5 to 27.7 months in these 6 participants who discontinued alpelisib; and notably, 2 participants were continuing to receive alpelisib after 37.0 and 40.0 months, respectively. None of the 6 participants discontinued alpelisib due to hyperglycemia.

Based on these data, participants may benefit from the initiation of an SGLT2 inhibitor with metformin, which is available as a single oral combination pill or as two separate medications. Particularly in participants with at least one risk factor for the development of severe hyperglycemia, defined as prediabetes/diabetes, and/or obesity (BMI ≥ 30), and/or age ≥ 75 years, early or prophylactic initiation of an SGLT2 inhibitor alone or in combination with metformin may help to reduce the incidence and frequency of severe hyperglycemia events. The decision to initiate an SGLT2 inhibitor alone or in combination with metformin prophylactically or at the onset of hyperglycemia (first fasting glucose level above the normal range) is at the discretion of the investigator. Since SGLT2 inhibitors may increase the risk of euglycemic diabetic ketoacidosis, serum ketones levels will be assessed throughout the trial in participants treated with SGLT2 inhibitors at screening, Day 1 of each cycle, and at EOT. For additional details on management of alpelisib induced hyperglycemia, please refer to Section 6.5.1.3 “Guidelines for the treatment of alpelisib induced hyperglycemia”.

Participants receiving oral anti-diabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, should be monitored with respect to their effectiveness as alpelisib was found to be an inducer of CYP2C9 in vitro.

Gastric protection agents

Alpelisib is characterized by a pH-dependent solubility but can be co-administered with acid reducing agents (e.g. proton-pump inhibitors, H2-antagonists and antacids), as long as it is taken after food. In a joint food effect and acid reducing drug-drug interactions (DDI) study, food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH value leading to a net decrease in area under the curve of on average by 21% when administered after a meal.

Palliative radiotherapy

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. Participants requiring initiation of palliative radiotherapy during the course of the trial should be assessed by appropriate image modalities to exclude disease progression per RECIST 1.1 and the reason for its use must be clearly documented. If disease progression is documented, the participant should discontinue trial treatment. No dose modification of trial treatment is needed during radiotherapy.

Hematopoietic growth factors

Hematopoietic growth factors may be used according to American Society of Clinical Oncology guidelines.

Corticosteroids

Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone may prolong or aggravate hyperglycemia (steroid-induced diabetes). Hyperglycemia is a common adverse event for PI3K inhibitors like alpelisib, so corticosteroids should therefore be used with caution and participants should be closely monitored.

Rash Management

Prophylactic use of antihistamines could be considered, refer to Section 6.5.1.2 “Guidelines for the treatment of trial drug inducted skin toxicity”.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during combined alpelisib and combination drug in this trial are listed below and in Appendix 1 “Permitted medication to be used with caution”. This list is not comprehensive and is only meant to be used as a guide. The investigator may contact Novartis for any questions regarding the use of permitted concomitant therapy requiring caution and/or action.

These medications should be excluded from participant use if possible. If they must be given, based on the investigator’s judgment, then use with caution and consider an alpelisib and/or combination drug interruption, as appropriate, if the concomitant medication is only needed for a short time.

Medications to be used with caution:

- **CYP2C9 substrates with narrow therapeutic index (NTI) (e.g. anticoagulants)**: In vitro evaluations indicated that pharmacological activity may be reduced by the CYP2C9 induction effects of alpelisib. In the absence of clinical data, caution is recommended with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants as alpelisib may reduce the clinical activity of such drugs (Table 16-1 "List of CYP450 substrates to be used with caution"). Alternatively, therapeutic anticoagulation may be accomplished using low-molecular weight heparin or Direct Thrombin inhibitors, and Factor Xa inhibitors.
- **CYP2B6 sensitive substrates or CYP2B6 substrates with NTI**: Based on a static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib. In absence of clinical data, CYP2B6 sensitive substrates (e.g. bupropion, evafirenz) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib, as alpelisib may reduce the clinical activity of such drugs (Table 16-1 "List of CYP450 substrates to be used with caution").
- **Selected CYP3A4 substrates**: Alpelisib can be co-administered with sensitive CYP3A4 substrates (e.g. everolimus, midazolam) and CYP3A4 substrates with narrow therapeutic window (e.g. fentanyl). Caution is recommended when alpelisib is used in combination with CYP3A4 substrates that also possess an additional time dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. ribociclib, encorafenib, refer to Table 16-2 "List of prohibited strong inducers of CYP3A"). Systemic exposures of such CYP3A4 auto inhibitors and auto inducers may be either decreased or increased depending on the drug and nature of auto-perpetrator potential, respectively, when alpelisib is co administered, based on PBPK simulations.
- **Herbal Medications**: The use of herbal preparations/medications and dietary supplements are permitted with caution unless explicitly prohibited (see Section 6.2.2 "Prohibited Medication") for being strong inducers of CYP3A such as St. John's Wort (*Hypericum perforatum*) and avasimibe (see Table 16-2 "List of prohibited strong inducers of CYP3A") or BCRP inhibitors such as curcumin (see Table 16-3 "List of prohibited BCRP inhibitors"). Medications such as kava, ephedra (ma huang), *Gingko biloba*, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng should be avoided if possible due to their potential for complex interactions. Since cannabinoids have been shown to inhibit BCRP in vitro, medical cannabis should be used with caution. Participants closely monitored for increased adverse reactions (as the relevance of this interaction in vivo is currently unknown). In case of unexpected toxicities, participants should stop using all herbal medications. Use of all such medications (including frequency of administration) should be documented.

6.2.1.3 Use of bisphosphonates/RANK-ligand inhibitors

The use of bisphosphonates/Receptor activator of nuclear factor κ B (RANK)-ligand inhibitors (e.g. denosumab) regardless of indication is allowed provided participants have been on stable doses for at least 2 weeks prior to trial treatment initiation. Stable dose should be maintained during the treatment period.

Bisphosphonates may be given according to the local prescribing information and routine clinical practice, at the investigator's discretion.

Participants taking bisphosphonates prior to entering the trial should continue with the same bisphosphonate treatment, given as per local medical practice.

Participants requiring initiation of bisphosphonate/RANK-ligand inhibitors treatment during the course of the trial should be assessed by appropriate image modalities to exclude disease progression; if disease progression is documented, the participant should discontinue trial treatment. If bisphosphonate therapy/RANK-ligand inhibitors therapy is to be started after the first dose of trial treatment, the reason for its use must be clearly documented.

Osteonecrosis of the jaw (ONJ) is a known adverse reaction for bisphosphonates/RANK-ligand inhibitors. In SOLAR-1, ONJ was reported in 4.2% subjects (12/284) in the alpelisib plus fulvestrant arm compared to 1.4% subjects (4/287) in the placebo plus fulvestrant arm. All subjects experiencing ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid). Therefore, in participants receiving alpelisib and bisphosphonates, an increased risk of development of ONJ cannot be excluded. For prevention and clinical management of ONJ, prescribing information of bisphosphonates should be followed.

6.2.2 Prohibited medication

The following medications are prohibited during combined alpelisib plus fulvestrant treatment in this trial (see in Appendix 2 "Prohibited Medication", this list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions):

- **Strong inducers of CYP3A4**: Avoid co-administration of alpelisib with a strong CYP3A4 inducer as it could potentially reduce the effectiveness of alpelisib, refer to Table 16-2 "List of prohibited strong inducers of CYP3A".
- **Inhibitors of BCRP**: Avoid the use of BCRP inhibitors in participants treated with alpelisib. If unable to use alternative drugs, closely monitor for increased adverse reactions, refer to Table 16-3 "List of prohibited BCRP inhibitors".
- **Other investigational and antineoplastic therapies.**
- **Hormonal contraception**: hormonal contraception is contraindicated for patients with ER positive breast cancer, therefore it is not to be considered as contraception method for the trial.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the trial by a Participant Number (Participant No.) assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial.

The Participant No. consists of the Center Number (Center No.; assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the ICF, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this trial. Only one cohort of participants will be enrolled in this trial.

6.4 Treatment blinding

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

6.5 Dose escalation and dose modification

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. For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are either recommended or mandated in order to allow participants to continue the trial treatment. Dose modifications are summarized in Table 6-3"Criteria for dose reduction / interruption and re-initiation of alpelisib for adverse drug reactions". A maximum of 2 dose reductions will be allowed after which treatment must be discontinued as indicated in Table 6-4 "Dose Reduction Steps for Alpelisib". Deviations to stepwise dose reductions are not allowed.

These dose changes must be recorded on the appropriate eCRF

AEs for alpelisib are graded according to CTCAE v4.03 since this version is more objective with regard to hyperglycemia grading since it is based on laboratory values. Clinical judgment of the investigator, including confirmation of laboratory values if deemed necessary, should guide the management plan of each participant based on individual benefit/risk assessment.

After treatment is resumed at a lower dose:

- If the same toxicity reoccurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration, except if specified in Table 6-3 "Criteria for dose reduction/interruption and re-initiation of alpelisib for adverse drug reactions".
- Once the alpelisib dose has been reduced by the investigator, no re-escalation is allowed, even upon resolution of AE.

If a participant requires a withholding of alpelisib dose, the participant could continue fulvestrant, per investigator discretion. All scheduled assessments will continue to be performed as per protocol.

Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-3 "Criteria for dose reduction/interruption and re-initiation of alpelisib for adverse drug reactions" or listed in Section 9.1" Discontinuation and completion". These dose changes must be recorded on the appropriate eCRF.

Table 6-3 Criteria for dose reduction / interruption and re-initiation of alpelisib for adverse drug reactions

Dose Modifications for alpelisib as specified below. Combination drug may be continued while alpelisib dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib**
Investigations (Fasting Glucose)	
Hyperglycemia (see also Section 6.5.1.3 "Guidelines for the treatment of alpelisib induced hyperglycemia") Consultation with a diabetologist or HCP experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia. Always recommend/reinforce on lifestyle changes as per American Diabetes Association (ADA) and/or European Association for the study of Diabetes (EASD), i.e. exercise and dietary advice (e.g. controlled carbohydrate intake, high fiber, low process food intake. Three macronutrient-balanced meals and 2 optional small snacks rather than one large meal). Note: this table provides dose management recommendations. Dose modifications and management should only be based on fasting glucose (FG) values (fasting plasma glucose or fasting blood glucose). Fasting glucose values can be obtained using a glucometer (self-measured) or through laboratory investigation. Laboratory confirmation of self-measured high glucose values may be requested by the investigator if deemed necessary. The investigator will use clinical judgment to guide the management plan of each participant based on individual benefit/risk assessment. As metformin is widely available, it is an appropriate choice as initial therapy for alpelisib-induced hyperglycemia. However, SGLT2 inhibitors are acceptable as well and may be administered alone or in combination with metformin. Refer to Section 6.5.1.3 "Guidelines for the treatment of alpelisib induced hyperglycemia" for additional details regarding the use SGLT2 inhibitors. In case of intolerance to or unavailability of metformin, investigator's judgment should be exercised and other oral anti-diabetic agents such as thiazolidinediones or dipeptidyl peptidase-4 Inhibitors can be used. As SGLT2 inhibitors may increase the risk of euglycemic diabetic ketoacidosis, monitoring of serum ketones will be mandated in participants treated with SGLT2 inhibitors/	
Grade 1 (FG > 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 applies only for values > 140 mg/dL (7.7 mmol/L)	• Maintain dose level, and remind participant on lifestyle changes*. • Start/intensify metformin as per guidance below or in cooperation with a healthcare expert experienced in hyperglycemia management or a diabetologist. Metformin 500 mg orally 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. Titrate to the MTD over a period of 3 weeks. • Alternatively, consider starting an SGLT2 inhibitor alone or in combination with metformin, especially in participants at risk for developing severe hyperglycemia (See Section 6.5.1.3 "Guidelines for the treatment of alpelisib induced hyperglycemia"). Starting dose and titration should be in accordance with the local prescribing information and consistent with local practice. • Monitor fasting glucose levels as clinically indicated and at least twice weekly for 8 weeks, then continue checking at least weekly until FG is within baseline values.

Dose Modifications for alpelisib as specified below. Combination drug may be continued while alpelisib dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 2 (FG > 160 to 250 mg/dL) [> 8.9 to 13.9 mmol/L]	• Maintain dose level and remind subject on lifestyle changes*, exclude confounding factors like e.g. urinary tract infection, and consider consultation with a healthcare expert experienced in hyperglycemia management or a diabetologist. • Start/intensify oral anti-diabetic treatment with metformin or alternatively start an SGLT2 inhibitor alone or in combination with metformin. • Additional oral anti-diabetic agents may be initiated, if needed. If fasting glucose levels are still rising on maximum tolerated dose of metformin or persistently > 160 mg/dl (> 8.9 mmol/L), add an SGLT2 inhibitor if available, e.g. empagliflozin up to 25 mg (max. dose). Alternatively an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose) can be added. • Monitor fasting glucose levels as clinically indicated and at least weekly until FG resolves to ≤ Grade 1. • If FG 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 fasting glucose levels at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FG > 250 mg/dL.

Dose Modifications for alpelisib as specified below. Combination drug may be continued while alpelisib dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 3 (FG > 250 to 500 mg/dL) [> 13.9 to 27.8 mmol/L]	• Omit alpelisib and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Regardless of fasting status, consider IV fluids if symptoms of hyperglycemia or signs of volume depletion. Exclude confounding factors like e.g. urinary tract and consider consultation with a diabetologist. Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate. Insulin may be used for 1 to 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. Start or further intensify oral anti-diabetic treatment and titrate as outlined for Grade 2. Monitor fasting glucose levels as clinically indicated and at least twice weekly until FG resolves to ≤ Grade 1. • If FG resolves to ≤ 160 mg/dL within 3 to 5 days, while off alpelisib and on metformin, re-start alpelisib and reduce 1 dose level, continue with anti-diabetic treatment. A second and third oral hypoglycemic agent may be initiated concomitantly, if needed, in consultation with a diabetologist. Check FG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG > 250 mg/dL. • If FG does not resolve to ≤ 160 mg/dL within 3 to 5 days while off alpelisib and on metformin, consultation a diabetologist for management of diabetes is strongly recommended. • If FG does not resolve to ≤ 160 mg/dL 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 (FG > 500 mg/dL) [≥ 27.8 mmol/L]	• **Omit alpelisib** confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Regardless of fasting status, consider IV fluids. • Exclude confounding factors like e.g. urinary tract infection. • Consult 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 FG is confirmed as > 500 mg/dL and confounding factors could be excluded, permanently discontinue participant from alpelisib.
CTCAE v 4.03 is modified to allow fasting blood glucose values in addition to fasting plasma glucose values. * For specific recommendations please see Section 6.5.1.3 “Guidelines for the treatment of alpelisib induced hyperglycemia”	
Investigations (Hepatic). Note: this is for newly occurred or worsened from baseline	
Isolated total Bilirubin elevation	

Dose Modifications for alpelisib as specified below. Combination drug may be continued while alpelisib dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 1 (> ULN - 1.5 × ULN)	• No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 1.5 to 3.0 × ULN)	• Interrupt dose until recovery to Grade ≤ 1 and resume at the same dose if resolved in ≤ 14 days or resume at the next lower dose level if resolved in > 14 days.
Grade 3 (> 3.0 to 10.0 × ULN)	• Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (> 10.0 × ULN)	• Permanently discontinue.
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3.0 × ULN) **Grade 2** (> 3.0 to 5.0 × ULN)	• No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 (> 5.0 to 20.0 × ULN)	• Interrupt dose until recovery to Grade ≤ 1, then decrease dose level.
Grade 4 (> 20.0 × ULN)	• Permanently discontinue.
Combined ALT/AST and TBIL elevation	• Please see specific instructions in Section 6.5.1.5 “Follow up on potential drug-induced liver injury (DILI) cases”
Gastrointestinal	
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements.	
Grade 1 (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline)	• Maintain dose level but initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental Activities of Daily Living (ADL))	• 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 • Initiate or intensify appropriate medical therapy and monitor as clinically indicated.
Grade 3 (Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL)	• 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 antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.
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 antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.
Investigations (Pancreatic)	
Pancreatitis	
Grade 2 or Grade 3	Omit dose until resolved to Grade ≤ 1, then resume treatment at decreased dose level. If toxicity recurs, permanently discontinue participant from alpelisib
Skin and subcutaneous tissue disorders	

Dose Modifications for alpelisib as specified below. Combination drug may be continued while alpelisib dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib**
Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. (see also Section 6.5.1.2 "Guidelines for the treatment of trial drug 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, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).	
Rash	
Grade 1 (< 10% body surface area (BSA) with active skin toxicity*)	• Maintain dose level. • Initiate topical corticosteroids 3 to 4 times daily, preferred compounds to use are triamcinolone, betamethasone for up to 28 days, as long as skin toxicity is active. • If active rash is not resolved within 28 days of appropriate treatment, add low dose systemic corticosteroid (20 to 40 mg/d), such as prednisone 10 mg 3 times daily. For participants with symptoms like burning and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating antihistamine such as diphenhydramine once daily at night
Grade 2 (10 to 30% BSA with active skin toxicity*)	• Maintain dose level. • Initiate or intensify topical corticosteroids 3 to 4 times daily, preferred compounds to use are triamcinolone or betamethasone for up to 28 days, as long as skin toxicity is active. • Add systemic corticosteroids 20 to 40 mg/d. If rash improves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued. For participants with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night.

Dose Modifications for alpelisib as specified below. Combination drug may be continued while alpelisib dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 3 (> 30% BSA with active skin toxicity*)	• **Omit alpelisib** dose until rash /skin toxicity has improved to ≤ Grade 1 or resolved, recommend documentation by photography and consider performing a skin biopsy. • Initiate topical corticosteroids 3 to 4 times daily, preferred compounds to use are triamcinolone or betamethasone for at least 28 days. • Add systemic corticosteroids 20 to 40 mg/d. • If rash improves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued. • Re-start alpelisib dose once rash /skin toxicity is fading but no longer active (Grade 1): - at reduced dose in case of first 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, add a non-sedating antihistamine such as cetirizine once daily during daytime and a sedating antihistamine such as diphenhydramine once daily at night. 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 subject from alpelisib • Consult a dermatologist, ensure documentation by photography, and obtain a skin biopsy. • 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/ Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or other SJS/TEN/DRESS like severe skin reactions	• Permanently discontinue participant from alpelisib. • Consult a dermatologist, ensure documentation by photography and obtain skin biopsy. • Follow local treatment guidelines for SJS/TEN/DRESS.
* “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.	
Immune system disorders	
Hypersensitivity	
Please see specific instructions in Section 6.5.1.6 “Guidelines for hypersensitivity”	
Investigations (Pulmonary disorders)	
Pneumonitis	
Please see specific instructions in Section 6.5.1.1 “Management of Pneumonitis/Interstitial lung disease”	
Investigations (Metabolic)	

Dose Modifications for alpelisib as specified below. Combination drug may be continued while alpelisib dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib**
Asymptomatic amylase and/or lipase elevation (see also Section 6.5.1.4 “Follow-up on amylase or lipase elevation (≥ CTCAE Grade 3”)	
Grade 1 (> ULN - 1.5 × ULN)	• Maintain dose level.
Grade 2 (> 1.5 to 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 decrease 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 fractionated amylase) as specified in Section 6.5.1.4 “Follow-up on amylase or lipase elevation (≥ CTCAE Grade 3”
Note: Withhold trial 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 decrease dose level.
Grade 4	• Permanently discontinue participant 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).

Table 6-4 Dose reduction steps for alpelisib[1].

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

[1] Only one dose reduction is permitted for pancreatitis.

6.5.1 Follow-up for toxicities

Participants, whose treatment is interrupted or permanently discontinued due to an AE or a clinically significant laboratory value, must be followed until resolution or stabilization of the event (and/or up to EOT visit), whichever comes first. Further guidelines and recommendations for the management of specific trial treatment combination-induced toxicities are provided below.

6.5.1.1 Management of pneumonitis/interstitial lung disease

Alpelisib is associated with pneumonitis/interstitial lung disease. Closely monitor all participants for signs and symptoms of pneumonitis.

All participants will be routinely asked about and observed for the occurrence of AEs including new or changed pulmonary symptoms (consistent with lung abnormalities).

Participants who are suspected to have developed pneumonitis should interrupt (alpelisib and combination drug) immediately and undergo appropriate imaging (high resolution CT scan) and broncho-alveolar lavage; biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out. Investigators should follow institutional practice for management of pneumonitis which generally includes treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the trial treatment.

After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with alpelisib and promptly initiate appropriate treatment and supportive measures.

6.5.1.2 Guidelines for the treatment of trial drug-induced skin toxicity

Skin toxicity is a class-effect AE observed with PI3K inhibitors agents.

Close monitoring of potential skin reactions will be performed and will be reported as AE (see Section 4.5.3 “Risk Management Strategies”). The most frequent skin AEs reported are: maculopapular rash (only a minority present acneiform rash); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate co-medication and treatment interruption if needed. Skin reactions may improve over several weeks. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity at any grade, and mandated if severe cutaneous reaction like Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected.

Workup for skin toxicity events may include a complete blood count with differential, and a full chemistry panel.

Antihistamines administered prior to rash onset may decrease incidence and severity of rash based on Study CBYL719C2301; therefore, at the investigator’s discretion, non-sedating antihistamines (e.g. cetirizine (Zyrtec®), fexofenadine (Allegra®), loratadine (Claritin®)) may be used as prophylactic treatment starting at Cycle 1, Day 1 to reduce severity of rash in all participants and especially for participants with a history of atopy such as allergic rhinitis, asthma, atopic dermatitis, or drug allergies.

Recommended therapies for skin toxicity events of all grades and as clinically indicated include:

- Mid to high potency topical steroids: triamcinolone 0.01% or fluocinonide 0.05% twice daily for at least 28 days. Recommend spray, lotion, or cream preparation for ease of application on trunk. For scalp involvement, recommend a foam or solution preparation.

- Gamma-aminobutyric acid agonists: gabapentin 300 mg every 8 hours, pregabalin 50 to 75 mg every 8 hours (to adjust of renal impairment). Depending on participant's clinical condition, be aware of potential and common side effects observed with gamma-aminobutyric acid agonists such as: somnolence, dizziness (both drugs) and peripheral edema (gabapentin) among others AEs.

For grade 4 skin events or any grade of severe cutaneous reactions (including Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme, DRESS), alpelisib treatment must be permanently discontinued without any re-challenge.

If dry skin is reported, it is recommended that participants with dry skin use mild and fragrance-free soaps and detergents.

Although preclinical experiments demonstrated that alpelisib have no potential phototoxic effect, participants should avoid sun exposure during treatment with alpelisib, especially when they already have experienced rash or other skin toxicities as the increased blood flow of the skin may worsen skin symptoms. Participants should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts, and long pants when outdoors.

6.5.1.3 Guidelines for the treatment of alpelisib-induced hyperglycemia

Alpelisib, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy et al 2012). Alpelisib induced hyperglycemia is generally manageable with adequate anti-diabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Participants with pre-diabetes (i.e. FG 100 to 125 mg/dl; 5.6 to 6.9 mmol/L) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in fasting glucose while on alpelisib treatment. However all participants, even those with fasting glucose within normal limits at screening, may develop alpelisib-induced hyperglycemia which is an on-target effect seen with PI3K inhibitors. Participants should always be instructed to follow dietary guidelines provided by the ADA and/or the European Association for the study of Diabetes, e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal and exercise, as appropriate.

Detailed guidelines for management of alpelisib induced hyperglycemia is provided in Table 6-3 "Criteria for dose reduction/interruption and re-initiation of alpelisib treatment for adverse drug reactions" and detailed guidelines on use of oral anti-diabetics is provided in Section 6.2.1.1 "Permitted concomitant medications". In brief, this includes early administration of metformin or a SGLT2 inhibitor (alone or in combination with metformin). Metformin may be titrated to a daily dose of 1000 mg twice a day. Since SGLT2 inhibitors may increase the risk of euglycemic diabetic ketoacidosis, serum ketones levels will be assessed throughout the trial in participants treated with SGLT2 inhibitors at screening, Day 1 of each cycle, and at end of trial.

Local standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting glucose testing will be performed both locally (at home using a glucometer or at a local laboratory) and/or at the investigative site for rapid availability for safety evaluation and

management guidance. Laboratory confirmation of self-measured high glucose values may be requested if deemed necessary by the investigator. The investigator will use clinical judgment to guide the management plan of each participant based on individual benefit/risk assessment.

Special attention should be paid to the risk of hypoglycemia in participants interrupting alpelisib treatment and concomitantly receiving insulin and/or sulfonylureas. Due to the short half-life of alpelisib, all glucose lowering medications should be discontinued when alpelisib is stopped.

If metformin or an anti-diabetic agent is interrupted for radiologic assessments or another reason, then alternative hyperglycemia management should be considered for those days to ensure optimal hyperglycemia management.

Consultation with a diabetologist or HCP experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia.

6.5.1.4 Follow-up on amylase or lipase elevation (≥ CTCAE Grade 3)

Participants with amylase or lipase elevation ≥ CTCAE Grade 3 must be tested weekly (or more frequently if clinically indicated) until ≤ Grade 1 (or baseline). After resumption of dosing, continue to test weekly for one additional cycle. If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle.

An exception to these follow-up guidelines will be made for cases of isolated amylase elevations in which amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. In such cases, total amylase and fractionated amylase should be monitored weekly (or more frequently if clinically indicated) for 4 weeks. If pancreatic amylase remains ≤ Grade 1, subsequent monitoring must be performed at least every 4 weeks (or more frequently if clinically indicated).

Participants who discontinue trial treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ Grade 1 or stabilization occurs (no CTCAE v4.03 grade change over 4 weeks).

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold trial treatment, then perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.

See also dose modification guidelines described in Table 6-3 “Criteria for dose reduction/interruption and re-initiation of alpelisib for adverse drug reactions”.

6.5.1.5 Follow up on potential drug-induced liver injury cases

Participants with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential drug-induced liver injury (DILI), and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

In general, any increase of serum aminotransferases to > 3 × ULN should be followed by repeat testing within 48 to 72 hours.

If total bilirubin is elevated > 2 × ULN, fractionation into direct and indirect bilirubin is required.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and TBIL value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 × ULN combined with TBIL > 2.0 × ULN
- For participants with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 3.0 × baseline] OR [AST or ALT > 8.0 × ULN], whichever occurs first, combined with [TBIL > 2 × baseline AND > 2.0 × ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as medical review needs to ensure that liver test elevations of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), glutamate dehydrogenase, prothrombin time/INR, alkaline phosphatase, albumin, and creatine kinase.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion - e.g. using CT, magnetic resonance imaging (MRI), or duplex sonography.

Perform relevant examinations (ultrasound or MRI, Endoscopic Retrograde Cholangiopancreatography) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an ALP elevation > 2.0 × ULN with R value < 2 in participants without bone metastasis, or elevation of the-specific ALP isoenzyme 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 the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (livertox.nih.gov/rucam.html).

If DILI confirmed: permanently discontinue trial treatment.

If DILI is unlikely: interrupt treatment. Treat identified cause according to institutional guidelines. If resolved, reduce by one dose level. Re-administration of trial treatment should be considered only if the investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of trial drug/s and dose regimen should be discussed with the Novartis medical safety team.

Table 6-5 "Alternative causes of liver disease" provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed liver function test abnormalities.

Table 6-5 Alternative causes of liver disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Epstein-Barr virus (EBV) infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, gammaGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Following appropriate causality assessments, as outlined above, the causality of the drug is estimated as "probable" i.e. > 50% likely, if it appears greater than all other causes combined. The term "drug-induced" indicates probably caused by the drug, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

Following appropriate causality assessments, as outlined above, the causality of the drug is estimated as "probable" i.e. > 50% likely, if it appears greater than all other causes combined. The term "drug-induced" indicates probably caused by the drug, not by something else, and only such a case can be considered a DILI case and should be reported as a serious AE (SAE).

6.5.1.6 Guidelines for hypersensitivity

Alpelisib and combination drug are associated with hypersensitivity reactions, including anaphylaxis. These are manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever or tachycardia. Alpelisib and/or combination drug should be permanently discontinued and should not be re-introduced in participants with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

6.6 Additional treatment guidance

6.6.1 Trial treatment compliance

Participants or caregivers will complete a medication diary during the entire trial through the telemedicine application to report compliance.

6.6.2 Trial treatment accountability

The dispatch of trial treatment from the site to the participant's home remains under the responsibility of the investigator. The investigator or designee must maintain an accurate record

of the shipment and dispensing of trial treatment in a treatment accountability log. Participants will be asked to return all unused trial treatment and packaging at the end of the trial or at the time of trial treatment discontinuation either directly to the site during the EOT visit or by a courier company. In case a courier company is used, site personnel will organize the shipment.

At trial close-out, and when appropriate during the course of the trial, the investigator will ship all remaining trial treatment to the central pharmacy for destruction. Verification of the accountability should be performed by the clinical research associate prior to shipping to the central pharmacy. Processes will be described in details in the Monitoring Plan. A certificate of destructions will be provided by the central pharmacy to be filed in the investigator folder.

6.7 Preparation and dispensation

At Cycle 1, Visit 1, participants will receive their first dose of trial treatment on site, and will be provided with one cycle of supply of alpelisib for self-administration at home, including instructions for administration. After the Cycle 1, Visit 1, participants will receive trial treatment on an outpatient basis with trial treatment delivered at their home by a courier company. The investigator or responsible site personnel must instruct the participant or caregiver to take the trial treatment per protocol (promote compliance). Fulvestrant, and if applicable goserelin, will be injected by either a district nurse at the participants' homes, at the district nurse clinic, or by the local oncologist when a visit is planned at time of drug administration (i.e. on Day 1 of Cycle 4, Cycle 7, and Cycle 10). All dosages prescribed to the participant and all dose changes during the trial must be recorded on the Dosage Administration Record CRF.

6.7.1 Handling of trial treatment and additional treatment

6.7.1.1 Handling of trial treatment

Trial treatment will be labeled at a central pharmacy in Sweden. The dispatch of trial treatment from the site to the participant's home remains under the responsibility of the investigator. Site personnel will order trial treatment from the central pharmacy and organize the delivery of the treatment to individual participants by direct contact with the courier company. Such process will ensure that no personal data is disclosed to Novartis as the Sponsor of the clinical trial as only site personnel will have knowledge of participant's details and the courier will only have access to the minimum require information to provide the service (name and address). The chain of custody for trial treatment will be documented in the Investigator Folder and includes at a minimum pick-up times from the clinical trial site, time of receipt confirmed by the participant at home, and temperature control log. Participants will be informed about the planned delivery to ensure secure receipt of the trial treatment.

Processes set in place for handling of trial treatment are compliant with measures approved for COVID-19 pandemic procedures. Additional information will be included in the Site operational manual.

6.7.1.2 Handling of additional treatment

Goserelin, SGLT2 inhibitors, metformin and any other additional drugs, such as antihistamines, prescribed by the investigator will be reimbursed through standard reimbursement coverage.

6.7.2 Instruction for prescribing and taking trial treatment

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. Participants should be instructed to take the dose of alpelisib at approximately the same time each day immediately after food (preferably in the morning), except on the days blood collection is scheduled at the clinic. On those days, local oncologists will instruct participants to take alpelisib according to their current practice at their regional hospital.

Alpelisib tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Tablets that are broken, cracked, or otherwise not intact should not be ingested.

On the days of combination drug administration, alpelisib tablets should be taken 1 hour prior to the infusion of combination drug.

Should any participant enrolled on the trial miss a scheduled dose of alpelisib, the participant will be allowed to take immediately the missed scheduled dose up to a maximum of 9 hours after that scheduled dose time. If greater than 9 hours after the scheduled dose time, the missed dose should not be taken, and the participant should take their allotted dose at the next scheduled time.

If the participant vomits after taking the alpelisib dose, the participant should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.

On days when pre-dose fasting blood samples are collected, participants should be instructed to arrive at the laboratory in fasted state. The following additional guidelines should be followed:

- The participants must be fasting overnight for at least 8 to 12 hours prior to the blood collection for fasting glucose. Water, coffee/tea (unsweetened and without milk) is allowed during all fasting periods; however juice is not permitted during the fasting period.
- On days when participants have a fasting blood sample collected, participants must have their blood sample collected prior to taking their trial treatment
- The participants must take alpelisib immediately after having breakfast.

Fulvestrant 500 mg will be given at Cycle 1, Day 1 and 15 after randomization and then at Day 1 of each subsequent cycle during the randomized treatment phase (± 3 days).

Fulvestrant is administered intramuscularly into the buttocks slowly as two 5 mL injections, one in each buttock. No dose modification is allowed for fulvestrant. Please refer to the local approved prescribing information. Any planned variance from these guidelines in the view of the patient safety must be previously discussed with the Sponsor unless there is an urgent need for action.

7 Informed consent procedures

Eligible participants may only be included in the trial after providing (witnessed, where required by law or regulation) independent Ethics committee (IEC)-approved informed consent. If applicable, in cases where the participants' representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the trial to the extent possible given his/her understanding. If the participant 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 trial-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed ICF that complies with the ICH GCP guidelines, regulatory requirements, and applicable data privacy guidelines, and is considered appropriate for this trial. Any changes to the proposed ICF suggested by the investigator must be agreed by Novartis before submission to the IEC.

Information about common side effects already known about the trial treatment can be found in the SmPC (Piqray® SmPC, Novartis; Faslodex® SmPC, Astra Zeneca). This information will be included in the participant ICF and should be discussed with the participant during the trial as needed. Any new information regarding the safety profile of the trial treatment that is identified between SmPC 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 ICF and then must be discussed with the participant.

A main trial consent will be included in this trial, including a subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data collected during this trial.

A copy of the approved version of all consent forms must be provided to Novartis after IEC approval.

8 Visit schedule and assessments

On-site visits will occur during screening, at Cycle 1, Day 1, and at EOT. Any other assessments are planned to be performed remotely supported by a telemedicine platform, local oncologists and district nurses.

Local oncologists are defined in this protocol as oncologist working in a regional hospital. The support for the participant at home could include district nurses, or other qualified healthcare professionals such as home-nursing professionals from ASIH performing standard of care procedures.

Participants will be visited by district nurse on Cycle 1, Day 15 and Day 1 of each cycle from Cycle 3 onwards, except when meeting with the local oncologist.

This visit can occur at the participant’s home or, alternatively, patients can visit district nurse at the local health center, depending on patient preference.

Visits at the local oncologist practice will occur on Day 1 of Cycle 2, Cycle 4, Cycle 7, and Cycle 10. Depending on clinical practice and feasibility, participants may either:

- Go to the local oncologist and have their blood drawn, and imaging and medical evaluation assessment performed on the same day. In this case, the investigator will review results remotely to decide whether participant should continue treatment or not. If the decision is made for the participant to continue, then the district nurses will be informed by the investigator to inject fulvestrant.
- Have their blood drawn and imaging assessments performed in the week preceding the visit to the local oncologist. In that case, the investigator will review the results prior to the visit with the local oncologist and confirm whether or not the participant should continue with treatment. If the decision is made for the participant to continue, then the participant will attend the visit with the local oncologist per schedule and, if there are no medical concerns, they will receive fulvestrant injection at the end of the visit.

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

Participants will attend visits and perform assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. For visits a general ± 7 days window is allowed, except when specified otherwise. Laboratory evaluations and Fulvestrant injection should be performed in a ± 3 days window. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who no longer wish to participate remotely will be offered the possibility to attend on-site visits.

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. Additional contacts or visit performed by the Investigator through the telemedicine platform are not to be considered unscheduled visits.

Participants who wish to prematurely discontinue the trial for any reason should be scheduled for an on-site visit as soon as possible, at which time all of the assessments listed for the EOT visit will be performed. At this EOT visit, all dispensed trial treatment should be reconciled, and the AEs and concomitant medications recorded on the dedicated CRFs.

If the participants is not able to attend the visit on site, Investigators should make every effort to collect safety follow-up information and should ask the patient availability to return the study drug and the devices provided for the trial, through the courier.

Table 8-1 Assessment schedule

Period	Scr.	Treatment Period [9]													EOT
Cycle Day		C1 D1	C1 D15	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	End of C12
Assessment **Location**	**Site**	**Site**	**Remote**												**Site**
			DN	**LO**	**DN**	**LO**	**DN**	**DN**	**LO**	**DN**	**DN**	**LO**	**DN**	**DN**	
Participant informed consent	X														
Telemedicine platform (use, interaction and e-diary completion)	X[1]	X[1]	continuous												X
Patient History															
Demographic	X														
Height and Weight	X														
Medical History[2]	X														
Performance status (WHO/ECOG)	X														
Physical Examination[3]	X	X		X		X			X			X			X
Vital Signs[3]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X														
Imaging Assessment[4]															
Tumor assessment and response	X					X			X			X			X
Participant Reported Outcomes[5]															
EORTC QLQ-C30		X				X			X			X			X
EQ-5D-5L		X				X			X			X			X
BPI-SF		X				X			X			X			X
Participant Satisfaction		X[7]		X[6]	X[6]	X[7]	X[6]	X[6]	X[7]	X[6]	X[6]	X[7]	X[6]	X[6]	X[7]

Period	Scr.	Treatment Period [9]												EOT
Cycle Day		C1 D1	C1 D15	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	End of C12
Assessment **Location**	**Site**	**Site**	**Remote**												**Site**
			DN	**LO**	**DN**	**LO**	**DN**	**DN**	**LO**	**DN**	**DN**	**LO**	**DN**	**DN**	
Laboratory Assessments[8]															
Serum Pregnancy test (pre-menopausal women only)	X														
Hematology	X			X	X	X	X	X	X	X	X	X	X	X	X
Full Chemistry Profile	X			X	X	X	X	X	X	X	X	X	X	X	X
FPG[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SMBG		Daily in the first two weeks, starting from Cycle 1 Day 2, and then as clinically indicated													
HbA1c	X			X			X			X			X		X
Treatments															
Previous and concomitant medication	X	Continuous													X
Fulvestrant		X	X	X	X	X	X	X	X	X	X	X	X	X	
Alpelisib		Daily													
Goserelin (pre-menopausal women only)		X		X	X	X	X	X	X	X	X	X	X	X	
Treatment compliance		Continuous													
Safety review															
ECG	X	When clinically indicated, at the discretion of the investigator													
Adverse events	X	Continuous, up to the EOT Visit													

BPI-SF= Brief Pain Inventory Short Form; DN = District nurse; ECG = electrocardiogram; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire; FPG = fasting plasma glucose; HbA1c = Glycosylated hemoglobin; LO = Local oncologist; Scr. = Screening; SMBG = self-monitoring blood glucose; TFQ = Trial Feedback questionnaire; WBC = white blood count. X = assessment to be recorded in the clinical database or received electronically from a vendor

1. Participant training and registration in the telemedicine platform
2. ER/PR status, HER2 status, and PIK3CA status will be collected as part of medical history
3. Assessment can be performed as clinically indicated in addition to the scheduled assessments. At Cycle 1, Day 1 and Cycle 1, Day 15, if accepted by local approved SmPC and according to Investigator's opinion, FPG evaluation could be replaced by SMBG assessment, and this will not be considered protocol deviation.

4. Imaging assessments at baseline to be performed from −28 days to −1 day before Cycle 1, Day 1. Depending on clinical practice and feasibility, assessments scheduled at Day 1 of Cycle 4, Cycle 7, and Cycle 10 can be either performed on the day of the visit or in the week prior to the visit. Tumor assessment and response will be performed by RECIST v1.1 criteria
5. During treatment period, questionnaires to be performed in the week preceding Day 1 of Cycle 4, Cycle 7, and Cycle 10. The baseline completion, should occur between screening and Cycle 1, Day 1, before trial treatment administration
6. Through dedicated questions in the e-diary
7. Through Novartis standard Trial feedback Questionnaire (TFQ) administration
8. Laboratory assessments at baseline to be performed from -14 days to -1 day before Cycle 1, Day 1. Depending on clinical practice and feasibility, laboratory assessments are scheduled at Day 1 of Cycle 4, Cycle 7, and Cycle 10 can be either performed on the day of the visit or in a 3 day window prior to the visit.
9. During treatment period, the Day 1 of each cycle is considered as the day of fulvestrant injection.

8.1 Screening

8.1.1 Eligibility screening

Participant eligibility will be checked by investigators once all screening procedures are completed. The investigator site will then be allowed to initiate treatment for the participant. Please refer and comply with detailed guidelines in the eligibility check user guidelines for the manual process.

It is permissible to re-screen a participant once if s/he fails the initial screening on laboratory values.

8.1.2 Information to be collected on screening failures

Participants who sign an ICF and are subsequently found to be ineligible will be considered a screening failure. The following CRFs must be completed for a screen failure patient:

- Screening phase disposition page of CRF (including reason for not being started on treatment)
- Informed consent
- Inclusion/Exclusion criteria
- Demography
- AEs (only if the participant experienced a SAE during the screening period after signing the ICF (see Section 10 “Safety monitoring and reporting” for SAE reporting details)
- Withdrawal of consent, if applicable
- Death, if applicable

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

Participants who sign an ICF and are considered eligible but fail to initiate treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition CRF.

8.2 Participant demographics and other baseline characteristics

The following baseline characteristics will be collected and assessed on-site at screening or at the Cycle 1, Day 1 visit:

- Demographic data (age and gender)
- Height and weight
- 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, mutational status [ER, PR, HER2, and PIK3CA status]) and current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing ICF).
- Ongoing medical conditions, symptoms, and disease that are recorded on the Medical History CRF should include the toxicity grade.
- Patient-reported outcome questionnaires (EORTC QLQ-C30, EQ-5D-5L, Brief pain inventory-short form [BPI-SF], and TFQ Section A) (see Section 8.5.1 “Participant

Reported Outcomes") should be completed by the participant in the period between screening and Cycle 1, Day 1 before treatment administration. This will enable the participant to gain confidence with the telemedicine platform.

- Prior and concomitant medications:
  - All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of trial treatment.
  - 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.
- Laboratory evaluations (e.g. hemoglobin, white blood count with differential, platelets, full chemistry profile, fasting plasma glucose, glycosylated hemoglobin, and pregnancy)
- Imaging assessments (see Section 8.3.1 "Imaging tumor assessment")
- ECG (see Section 8.4.4.1 "Electrocardiogram"), and other cardiac assessment if clinically indicated, at the discretion of the treating physician
- Furthermore the following assessments will be performed:
  - Physical examination
  - Vital signs
  - Performance Status (World Health Organization [WHO]/Eastern Cooperative Oncology Group [ECOG])

8.3 Efficacy

8.3.1 Imaging tumor assessment

Imaging will be performed on-site at screening and at EOT. 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 per current practice as allowed per country regulation. Additional details on transfer of source documents will be detailed in a separate operational manual. Site radiologist will assess tumor response according to the Novartis guideline version 3.1 (Appendix 3) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 8-2.

Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days prior to start of trial treatment (Day −28 to Day −1 prior to Cycle 1, Day 1). The whole body scan can be performed within 42 days prior to start of trial treatment. Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatment (42 days for the whole body scan), including before signing the main trial ICF, can be considered as the baseline images for this trial. Any imaging assessments obtained after treatment initiation cannot be considered as baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain CT or MRI, if clinically indicated
- Whole body bone scan
- Localized bone CT, MRI or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- Color photography for any skin lesions present
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

If a participant is known to have a contraindication to CT i.v. contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

If brain metastases are suspected at baseline, brain MRI or CT should be completed. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

At baseline all participants will undergo, a whole body bone scan per institutional standard of care [e.g., Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET) or sodium fluoride (NaF) PET], thereafter whole body scan should be performed as clinically indicated. Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen and pelvis CT/MRI.

If clinically indicated, CT or MRI of other areas (e.g., neck) of disease as appropriate should be performed.

If skin lesions are present at screening, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Each lesion that is measured at baseline must be measured by the same method (either same radiologic/nuclear method or by physical exam) throughout the trial so that the comparison is consistent. Criteria required for determining partial or complete response should be present for at least 4 weeks.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments described in Table 8-2 should be performed using the same imaging modality used at baseline, irrespective of trial treatment interruption or actual dosing (see Table 8-1). Imaging assessments for response evaluation will be performed every 12 weeks

(± 7 days) after treatment initiation (Cycle 1, Day 1), and at the EOT visit. The 12-week interval should be respected regardless of whether trial treatment is temporarily withheld or unscheduled assessments are performed.

Additional imaging assessments may be performed at any time during the trial at the investigator's discretion to support the efficacy evaluations for a participant, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the trial so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined Positron Emission Tomography/Computed Tomography (PET/CT) may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1.

Table 8-2 Imaging assessment collection plan

Procedure	Screening Day -28 to Day -1	Treatment phase	End of Trial Visit
CT or MRI (Chest, Abdomen, Pelvis)	Mandated	Mandated every 12 weeks after	Mandated*
CT or MRI for any site of disease	Mandated if suspected lesion at screening	If lesion at screening: every 12 weeks after treatment initiation	Mandated if lesion at screening*
Brain CT or MRI (only if existing or suspected brain metastasis)	Mandated at screening only if existing or suspected brain metastasis	If brain lesion at screening: every 12 weeks after treatment initiation	Mandated only if brain lesion at screening*
Whole Body Bone scan**	Mandated, within 42 days (6 weeks) prior to randomization.	As clinically indicated	As clinically indicated
Bone X-ray, CT or MRI	Mandated at screening only if skeletal abnormalities identified by bone scan at screening	If bone lesion at screening: every 12 weeks after treatment initiation	Mandated only if bone lesion at screening*
Skin color photography	Mandated if skin lesions at screening	If skin lesions at screening every 12 weeks after treatment initiation	Mandated if skin lesions at screening*

* Mandated for participants who discontinue trial treatment before the first scheduled post-screening tumor assessment and for participants whose previous tumor assessment did not demonstrate PD and was done more than 21 days prior to end of trial visit. In addition, EOT tumor assessment should be done in patients who discontinue due to clinical progression (e.g. investigator decision) to confirm disease progression by RECIST.

** Type of whole body bone scan according to institutional guidelines

*** If CT or MRI scan available before signing of ICF but within 28 days of first dose, no need to repeat the procedures

Note: All scans will be acquired and analyzed for primary endpoint locally.

8.3.2 Performance status

Performance status scale will be assessed as described in Table 8-3.

Table 8-3 WHO/ECOG performance status

Grade	WHO/ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

8.3.3 Appropriateness of efficacy assessments

Imaging assessments are standards and were the ones performed during the SOLAR-1 clinical trial (Andre et al 2019).

8.4 Safety and tolerability

Safety will be monitored by assessing physical examination, vital signs, ECG (if available), laboratory evaluations for hematology and biochemistry including but not limited to glucose monitoring as well as collecting of the AEs at every visit. Whenever necessary, the trial team will be able to assess rash and diarrhea symptoms through the telemedicine platform. For details on AE collection and reporting, refer to Section 10 “Safety monitoring and reporting”.

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

8.4.1 Physical examination

A complete physical examination will be performed at:

- Screening (Day −28 to Day −1) and at Cycle 1, Day 1 by the investigator.
- Day 1 of Cycle 2, Cycle 4, Cycle 7 and Cycle 10 by the local oncologist,
- The EOT visit by the investigator.

Whenever clinically indicated, additional physical examination can be performed by investigators or local oncologists.

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 on-site 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.

8.4.2 Vital signs

Vital signs (temperature, blood pressure [supine position preferred when optional ECG is collected] and pulse) will be monitored at:

- Screening (Day −28 to Day −1) and Cycle 1, Day 1 by the investigator,
- Day 1 of Cycle 2, Cycle 4, Cycle 7 and Cycle 10 by the local oncologist,
- Day 1 of Cycle 3, Cycle 5, Cycle 6, Cycle 8, Cycle 9, Cycle 11, and Cycle 12 by a district nurse,
- EOT visit by the investigator.

Additional vital signs assessments can be performed as clinically indicated by the investigator, the local oncologist or the district nurse. Blood pressure (systolic and diastolic) and pulse should be measured after the participant has been sitting for five minutes.

8.4.3 Laboratory evaluations

Clinical laboratory analyses are to be performed on-site at Screening (Day −28 to Day −1), Cycle 1, Day 1, and at the EOT visit, and at a local laboratory during remote participation. SMBG will be performed by the participant. Novartis must be provided with a copy of all the laboratories' certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the CRF. Any changes regarding normal ranges and units for laboratory values assessed during the trial must be reported via an updated tabulation indicating the date of revalidation.

The laboratory evaluation collection plan is presented in Table 8-4. Visit windows of ± 3 days are allowed for laboratory evaluations.

The investigator is responsible for reviewing all laboratory reports for participants in the trial and evaluating any abnormalities for clinical significance. Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate. At any time during the trial, abnormal laboratory parameters which are clinically relevant and require an action to be taken with trial treatment (e.g., require dose modification and/or interruption of trial treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the CTCAE version 4.0.3.

Unscheduled assessments may be performed if medically indicated to assess a (potential) AE or when needed by the treating physician for decision making (e.g. dose modifications).

Table 8-4 Laboratory evaluation collection plan

Test Category	Test Name	Screening Day -14 to Day -1	Treatment phase	End of Trial Visit
Hematology	Hemoglobin, White blood cells, Differential (Leukocytes, Neutrophils, Thrombocytes), and Platelets.	Mandated	D1 of Cycle 2, and thereafter Day 1 of each cycle	Mandated
Chemistry	For all participants: C-Reactive Protein, Albumin, Alkaline Phosphatase, alanine aminotransferase, Aspartate aminotransferase, Bilirubin, Creatinine, Sodium, Potassium, Cancer Antigen 15-3, Lactate Dehydrogenase (LDH). For participants treated with SGLT2 inhibitors with or without metformin: ketones	Mandated	D1 of Cycle 2, and thereafter Day 1 of each cycle	Mandated
	Fasting Plasma Glucose	Mandated	Day 1, and Day 15 of Cycle 1, Day 1 of Cycle 2, and thereafter Day 1 of each cycle Day 1 and Day15 of Cycle 1, if accepted by local approved SmPC, FPG evaluation could be replaced by SMBG assessment, and this will not be considered protocol deviation.	Mandated.
	SMBG	-	Daily from Day 2 to Day 14 of Cycle 1, and thereafter as clinically indicated	
	Glycosylated hemoglobin (HbA1c)	Mandated	Day 1 of Cycle 2, Cycle 5, Cycle 8, and Cycle 11	Mandated
	Serum pregnancy test	Mandated	-	-

Note: All laboratory analyses will be performed locally.
SMBG=self-monitoring blood glucose

8.4.4 Cardiac assessments

Cardiac assessments will only be performed if clinically indicated by the investigator or the local oncologist.

8.4.4.1 Electrocardiogram

A standard 12-lead ECG will be performed on-site at screening and thereafter only if clinically indicated. ECG will be performed after the participant has been resting for 5 to 10 min. The interpretation of the tracing must be made by a qualified physician and documented in the ECG

section of the CRF. Each ECG tracing should be labeled with the Participant No, date, and kept in the source documents at the trial site. If an ECG is performed during the screening period, clinically significant abnormalities present when the participant signed ICF should be reported on the Medical History CRF page. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the participant in the trial. New or worsened clinically significant findings occurring after signing of ICF must be recorded on the AEs CRF page.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this participant population.

8.5 Additional assessments

No additional tests will be performed on participants entered into this trial, apart from collection of participant-reported outcomes (PROs).

8.5.1 Participant reported outcomes

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 Trial Feedback questionnaire (TFQ) will be used to assess participant satisfaction throughout the conduct of the trial. The ePRO assessment collection plan is presented in Table 8-5.

All ePRO data will be collected using the telemedicine platform: the baseline collection will be done between screening visit and Cycle 1, Day 1 visit, before trial treatment administration. The next ePROs will be collected at home during the week preceding the visits with the local oncologist, i.e. prior to Day 1 of Cycle 4, Cycle 7, and Cycle 10. ePROs will be administered in Swedish. All ePRO measures will be administered before any trial treatment administration at the time-point indicated. Participants should be given sufficient space and time to complete all trial questionnaires. During the remote participant monitoring period, participants will receive a reminder that ePROs are available to be completed through their device.

All administered questionnaires should be reviewed for completeness. When applicable, if missing responses are noted, participants should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all participants, including from those who discontinue prior to the trial evaluation completion visit, however, if participants refuse to complete questionnaires, this should be documented in trial source records.

Participant's refusal to complete trial questionnaires are not protocol deviations.

Completed questionnaires must be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs. This review should be documented in trial source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in Section 10 "Safety monitoring and reporting" of this protocol.

Investigators should not encourage the participants to change responses reported in questionnaires.

Table 8-5 Participant reported outcomes collection plan

Participant Questionnaires	Baseline collection (between Screening and C1D1)	Treatment phase In the week preceding	End of Trial
EORTC QLQ-C30	Mandated	Day 1 of Cycle 4, Cycle 7, and Cycle 10	Mandated
EQ-5D-5L	Mandated	Day 1 of Cycle 4, Cycle 7, and Cycle 10	Mandated
BPI-SF	Mandated	Day 1 of Cycle 4, Cycle 7, and Cycle 10	Mandated
TFQ	Mandated (Section A)	Day 1 of Cycle 4, Cycle 7, and Cycle 10 (Section B)	Mandated (Section C)

Note: If questionnaires are to be completed on the same day than other assessments, they should be completed prior to any clinical assessment, drug dosing or diagnostic testing.
BPI-SF = Brief Pain Inventory Short Form; C1D1 = Cycle 1, Day 1; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire; TFQ = Trial Feedback Questionnaire

8.5.1.1 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).

8.5.1.2 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 5-level EQ-5D version (EQ-5D-5L) was introduced by the EuroQol Group in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the EQ-5D-3L. 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.

8.5.1.3 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. The short version of the BPI is completed in 5 min.

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.

The BPI has been validated in a patient population with breast cancer (Castel et al 2007) and has been linguistically validated in Swedish.

8.5.1.4 Trial Feedback Questionnaire

The Trial Feedback Questionnaire (TFQ) is a brief, validated patient questionnaire designed to capture patient trial experience independent of disease and treatment. The face and content validity of the questionnaire was tested and confirmed by research conducted by Adelphi, PatientsLikeMe and HRM using established Patient Reported Outcome (PRO) methodology through cognitive debriefing with participants from phase I-III studies for various conditions (Brohan et al 2014). The questions have been further tested quantitatively and qualitatively through electronic administration and/or in depth interviews with >400 trial experienced patients (Manson et al 2015). Therefore, the questionnaire can be considered to have face and content validity in clinical trial participants.

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.

Individual participant level responses will not be reviewed by investigators.

8.6 DCT elements included in the Trial

8.6.1 The telemedicine platform

The Sponsor has qualified and contracted a third party vendor who provides the telemedicine platform technology for this hybrid DCT. Trial participants can interact with site personnel using online communication tools built into the platform. The telemedicine platform includes the following key capabilities:

- Secure videoconferencing, which allows the patient to directly connect with the investigator and site staff

- ePROs and e-Diaries (for capturing information such as compliance with study drug, self-reporting glucose level and events), to be completed by the trial participant
- Reminders, to be automatically sent to participants to ensure timely completion of ePROs and the e-Diary
- Electronic Data Capture for sites data entry from source clinical information
- Automated summary reports for the investigator and site staff, to support participant management and for maintaining study oversight

Additional details are available in the Site Operational Manual.

8.6.2 Conduct of study visits away from the investigator site

Participants in the study agree during enrollment to participate in visits supported by local oncologists, district nurses, local laboratory facilities and specialized radiology centers and to connect with the site staff using the telemedicine platform, based on the visit/assessment schedule summarized in Section 8. Roles and responsibilities of local oncologists and district nurses will be fully defined in a written agreement with the investigative site.

The main aspects of the remote visits and activities are:

- Investigative site: the investigator will maintain oversight and accountability for participant's treatment and safety as defined in the protocol, oversee local oncologist and district nurse activities, and maintain regular contact with the participant to ensure their safety and well-being. On an ongoing basis, the investigator will review the data reported by the participant (trial medication compliance, ePRO, e-diaries etc.) directly in the platform and will assess and report accordingly any AEs/SAEs as defined in Section 10.
- Local oncologist: the investigator is responsible to engage with qualified local oncologists who are willing to support remote study visits during the study participation. The local oncologist will support the investigator by performing clinical practice procedures and will make medical records pertaining to remote visits available to the investigator. Any changes to the participant's medical health will also be shared, in addition to any performed laboratory assessments, but any trial-related decisions will remain under the responsibility of the investigator.
- District nurse: as per local process, the investigator could request the assistance and support of a district nurse (or ASIH program) to conduct specific assessments. These delegated assessments may include vital signs collection, administration of fulvestrant (Faslodex® 500 mg i.m.), concomitant medication when prescribed by the investigator, and assisting participants on the use of the glucometer. After each assisted visit, the district nurse will document the visit as per local process, and make them available to the investigator.
- Participant: Participants will perform remote visits with the investigator via the telemedicine platform, and will attend in-person assessments (with the local oncologist or district nurses or at the local lab or radiologist centers) in accordance with the schedule defined in Section 8.

  Participants will also be requested to complete PRO assessments and electronic diaries using the telemedicine application (by providing the participant with a smartphone or by using their own device, at the participant's request). In addition, participants will receive

automated notifications within the telemedicine platform, to remind them to complete the required assessments in a timely manner.

- Other facilities: Laboratory and radiology center appointments may also be ordered by the investigator, as per local process, to conduct these standard assessments. The investigator should discuss and arrange for direct access to these reports.

Participants will be instructed to contact the site at any time if they have questions about the completion of activities, regarding functionality of the telemedicine application, and also if there are any changes to their health status.

The telemedicine platform can generate regular summary reports, to support the investigator's assessment and participant's safety management on an ongoing basis.

9 Trial discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Trial treatment discontinuation and trial discontinuation

Discontinuation of trial treatment for a participant occurs when trial treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator. Participants who discontinue trial treatment will be prematurely withdrawn from the trial.

The investigator must discontinue trial treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Trial treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which trial participation might result in a safety risk to the participant

If discontinuation of trial treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of trial treatment and record this information.

Whenever possible, participants discontinued early for any reason, should be requested to complete the assessments planned in EOT visit.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the trial for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the trial anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further trial related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information. All efforts should be made to complete the assessments prior to trial discontinuation. A final evaluation at the time of the participant's trial discontinuation should be made as detailed in the assessment table. Trial 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 participant are not allowed unless safety findings require communicating or follow-up.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Novartis will continue to retain and use all research results (data) that have already been collected for the trial evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for trial 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 participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Early trial termination by the sponsor

The trial can be terminated by Novartis at any time.

Reasons for early termination can be unexpected, significant, or unacceptable safety risk to participants enrolled in the trial.

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Considering that both alpelisib and fulvestrant are marketed drugs in Sweden and that participants will be able to pursue treatment as part of their standard of care, no specific procedures have been set up in case of early termination by the sponsor. The investigator or sponsor depending on local regulation will be responsible for informing IECs of the early termination of the trial.

9.2 Trial completion and post-trial treatment

The end of study is defined as the last visit of the last participant, i.e. the End of Trial (EOT) visit of the last ongoing patient (Cycle 1, Day 28 or final visit for a participant who dropped-out early).

Participants will be followed-up until they reach the EOT visit and any repeat assessment associated with this visit have been documented and followed-up appropriately by the investigator, or until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, whichever occurs first. Participants no longer willing to be follow-up remotely will be offered to attend only on-site visits and will not be considered to have prematurely discontinued the trial.

The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.4 "SAE Reporting". Documentation of attempts to contact the participant should be recorded in the source documentation.

Considering that both alpelisib and fulvestrant are marketed drugs in Sweden and that participants will be able to pursue treatment as part of their standard of care after trial completion, no specific procedures have been set up for continuing care.

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 clinical investigation participant after providing written informed consent for participation in the trial. 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 participant and identifying AEs.

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

Once the main trial ICF is signed, all AEs per the descriptions below will be captured as AEs. The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the trial. AEs also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, PROs or other assessments.

AEs 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 10.1.4 "SAE Reporting"):

1. The severity grade (CTCAE Grade 1-4)
2. Its relationship to the trial treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the trial indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial treatment, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
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 trial drugs.

   All AEs must be treated appropriately. Treatment may include one or more of the following:

   - Dose not changed
   - Dose reduced/increased
   - Drug interrupted/withdrawn

6. Its outcome

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For Grade 3 and 4 AEs only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant. AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

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 trial – EOT visit), 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.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a SAE, except if the investigator considers that progression of malignancy is related to trial treatment.

AEs separate from the progression of malignancy (i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the trial treatments can be found in their respective SmPCs.

Abnormal laboratory values or test results constitute AEs 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 which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any AE [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 participant 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, 2004).

- 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 trial and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant'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 participant 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 participant 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, 2004).

All new 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 trial indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered SAE irrespective if a clinical event has occurred.

10.1.3 Adverse events of interest

AESI are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, 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.

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 "Risk Management Strategies".

10.1.4 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until EOT visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours 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. 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 Package Insert (new occurrence) and is thought to be related to the trial treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any trial with the same trial treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the EOT visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to trial treatment.

10.1.5 Pregnancy

This trial is planned for men, post-menopausal women or pre-menopausal women with ovarian suppression. No pregnancies are expected for participants. However, in the rare cases when this occurs, to ensure participant safety, each pregnancy occurring while the participant is on trial treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Baby status should be followed up to one year after pregnancy due date.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis CMO&PS.

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the trial treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took trial treatment in this trial. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.6 Reporting of trial 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 HCP, participant 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.

Trial treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

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

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional trial treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a 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

Designated investigator staff will enter the data required by the protocol into the CRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, investigator or site personnel will not be given access to the electronic data capture (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 (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 participant 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 contract research organization) 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 or site personnel 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 World Health Organization (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 MedDRA terminology.

The telemedicine platform will be the source document for the ePROs.

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.

Additional information will be included in a separated operation manual.

11.3 Site monitoring

Before trial initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the trial, Novartis 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 participant records, the accuracy of data capture/data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that trial treatment is being stored, dispensed, and accounted for according to specifications. Key trial personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight. If applicable and approved by local law, remote monitoring including remote source data verification (where applicable) will be performed. Additional details will be included in the Monitoring Plan.

The investigator must maintain source documents for each participant in the trial, 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 participant's file. The investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant).

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 site 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 trial-specific site monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Data analysis will be carried out when all patients have completed the trial. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants that received any trial treatment.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data collected during the trial will be listed and summarized descriptively for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class (SOC) and preferred term (PT).

12.3 Treatments

Duration of trial treatment exposure, cumulative dose and dose intensity, the number of participants with dose changes/interruptions along with reasons for the dose change/interruption will be presented.

Number of participants treated with SGLT2 antagonist or metformin, dose, duration of treatment and reason for treatment administration (prophylaxis or hyperglycemia) will be summarized descriptively. Number of participants treated with goserelin will be described.

Concomitant medications taken concurrently with the trial treatment will be listed and summarized by Anatomical Therapeutic Chemical Classification System term, preferred term by means of frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries will include therapy starting on or after the start of trial treatment (defined as Cycle 1, Day 1) or therapy starting prior to the start of trial treatment and continuing after the start of trial treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of trial treatment will be listed.

12.4 Analysis of the primary endpoint

12.4.1 Definition of primary endpoint

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

Participant satisfaction will be assessed at the start of the trial, every 12 weeks, and at the end of the trial through the TFQ.

12.4.2 Statistical model, hypothesis, and method of analysis

The number of participants completing the TFQ and the number of missing or incomplete assessments will be summarized for each scheduled assessment time point. No formal statistical tests will be performed. No imputation procedures will be applied for missing items or missing assessments. Descriptive statistics will be used to summarize items of the questionnaire.

12.5 Analysis of secondary endpoints

Full details of the methods to be used for the analysis of these endpoints will be given in the statistical analysis plan (SAP), which will be finalized before any analysis takes place.

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.

12.5.1 Patient retention on DCT approach

Proportion of patients on remote monitoring at 3, 6, 12 months for participants still on treatment will be summarized descriptively.

12.5.2 Safe and suitable remote management of patients on DCT approach

Total number of unscheduled in-clinic visits because of safety reasons, total number of unscheduled in-clinic visits and the reason, and number of unscheduled in-clinic visits per participant in the study will be summarized descriptively. Discontinuation rate related to AEs will be summarized descriptively.

12.5.3 Compliance with treatment and adherence to procedures

Number of patients with missed doses, adjusted dose, interruptions and discontinuations and reason why will be summarized descriptively.

Overall compliance will be summarized descriptively overall and by categories ($\leq 80\%$, $80 <$ and $< 100\%$, and $\geq 100\%$). Overall compliance will assess the degree of correspondence of the actual dosing history with the prescribed drug regimen. Detail of overall compliance calculation will be provided in the SAP.

12.5.4 Safety endpoints

The safety endpoint will be type, frequency and severity (incidence proportion) of AESIs per CTCAE v4.03. In addition, a separate summary for death will be provided.

Adverse events

The number (and percentage) of participants with treatment emergent AEs (events started after the first dose of trial medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by primary SOC and PT
- by primary SOC, PT and maximum severity
- by PT

Separate summaries will be provided for trial medication related AEs, death, SAEs, other significant AEs leading to discontinuation.

A participant with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by SOC and or PT, severity (based on CTCAE grades), type of AE, and relationship to trial treatment.

SAEs, non-serious AEs and AESIs during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and SAEs will be listed.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by participant and visit/time, and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 4.03. The calculation of CTCAE 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 following listings/summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 4.03 grades if applicable and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE version 4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 4.03 grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by CTCAE version 4.03:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

12.5.5 Participant reported outcomes: Global Health Status, Quality of Life, and Pain

For each PRO (EORTC QLQ-C30, EQ-5D-5L, and BPI-SF), the number of participants completing each questionnaire and the number of missing or incomplete assessments will be summarized for each scheduled assessment time point. No formal statistical tests will be performed.

Scoring of PRO data and methods for handling of missing items or missing assessments will be performed according to the scoring manual and user guide for each respective participant questionnaire. No imputation procedures will be applied for missing items or missing assessments.

For each questionnaire, descriptive statistics will be used to summarize dimension values and overall score. Additionally change from baseline will be summarized. Participants with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

12.5.6 Treatment effectiveness

Analysis of PFS according to RECIST 1.1 will be described to assess effectiveness of treatment alpelisib plus fulvestrant. The median PFS along with 95% confidence intervals will be presented.

12.6 Analysis of exploratory endpoints

Not Applicable.

12.7 Interim analyses

Not Applicable.

12.8 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.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical trial was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and General Data Protection Regulation (EU) 2016/679 [GDPR]), with the guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IEC for the trial protocol, written ICF, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to trial start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the trial 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, 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.

Roles and responsibilities of local oncologists and district nurses will be defined in a contract with site.

Participants will be closely monitored by the investigator via the telemedicine platform and the investigator will also have oversight of the local oncologist and district nurse. Local oncologist and district nurse will be in charge of standard of care assessments, but they could also be involved in unscheduled visits for adverse events monitoring, if requested by Investigator.

Investigators will keep the responsibility and authority to make decision for all aspects related to the management of participants during the entire clinical trial duration.

13.3 Publication of trial protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after trial completion (defined as last participant last visit) and finalization of the trial report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

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.

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures 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, site 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 standard operative procedures, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the trial objectives, the trial procedures and the data to be collected on trial participants. Additional assessments required to ensure safety of participants 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 treatment under the protocol, other than the purpose of the trial. 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 trial, except for the appropriate monitoring on trial participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the 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 IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing 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 participant included in this trial, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IEC at the trial site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Permitted medication to be used with caution

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this trial, except as specifically prohibited below. Combination administration of trial drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or alpelisib. Please note that all lists in Section 6-2 are not comprehensive. Please refer to regular updated online sources and the label of a concomitant drug to decide whether a drug is permitted (with caution) or prohibited based on Section 6-2. In doubt, please contact the medical monitor with any questions.

16.1.1 Permitted medication to be used with caution

This list of CYP substrates and list of inhibitors / inducers were compiled from the University of Washington's Drug Interaction Database (Updated November 2020). This list is only meant to be used as a guide.

Table 16-1 List of CYP450 substrates to be used with caution

Category	Drug names
CYP2C9 substrates	
Narrow Therapeutic index substrates of CYP2C9	(S)-Warfarin
Sensitive substrates of CYP2C9	Benzbromarone, Celecoxib, Glimepiride, Glipizide, (R)/(S)-Ibuprofen, Lornoxicam, Meloxicam, Piroxicam, Tolbutamine, (S)-Warfarin
CYP2B6 substrates	
Narrow Therapeutic index substrates of CYP2B6	Not Applicable
Sensitive substrates of CYP2B6	Bupropion, Efavirenz
Selected CYP3A4 substrates	
CYP3A4 substrates which are known or potential auto-perpetrators	Clarithromycin, Conivaptan, Encorafenib, Erythromycin, Diltiazem, Mifepriston, Ribociclib, Telthromycin, Troleandomycin, Verapamil

Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsades de Pointes, QT prolongation).

CYP3A4 substrates which are auto-perpetrators: Based on Novartis internal assessment.

16.1.2 Prohibited Medication

Strong inducers of CYP3A4

This list of CYP inducers was compiled from the University of Washington's Drug Interaction Database (Updated November 2020). This list is only meant to be used as a guide.

Table 16-2 List of prohibited strong inducers of CYP3A

Category	Drug Name
Strong CYP3A Inducers	Apalutamide, Avasimibe[1], Carbamazepine, Enzalutamide, Ivosidenib, Lumacaftor, Mitotane, Phenobarbital, Phenytoin, Rifapentine, Rifampin (Rifampicin), St. John's wort (hypericum perforatum)[1]

[1] Herbal product

Inhibitors of BCRP

The table encompasses only drugs and molecular entities for which inhibition of BCRP has been investigated and/or formally shown in vivo in a clinical DDI study. Please note that this is not an exhaustive list and only meant to be used as a guide. When in doubt, refer to the prescribing information of the drug to assess whether a potential for BCRP inhibition is described.

Table 16-3 List of prohibited BCRP inhibitors

Category	Drug Name
BCRP inhibitors - Evidence for DDI potential shown in vivo	Atazanavir/ritonavir[1,2], Elvitegravir/cobicistat[1,2], Lopinavir/ritonavir[1,2], Tipranavir/ritonavir[1,2], Curcumin[1,2], Cyclosporine[1,2], Daclatasvir[1,2], Eltrombopag[1,2], Gefitinib[2], Lapatinib[1], Ledipasvir[2], Pantoprazole[1,2], Paritepravir[2], Tipranavir[2]

[1] Lee et al 2015

[2] Novartis PK Sciences DDI List (January, 2018)

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-4 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	· ALT or AST > 5 × ULN · ALP > 2 × ULN (in the absence of known bone pathology) · Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) · ALT or AST > 3 × ULN and INR > 1.5 · Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) · Any clinical event of jaundice (or equivalent term) · ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia · Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	· ALT or AST > 2 × baseline or > 300 U/L (whichever occurs first)

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal

Table 16-5 Follow up requirements for liver laboratory triggers with liver symptoms

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 × ULN **If elevated at baseline:** ALT > 2 × baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	· **No change to trial treatment** · Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. · Follow-up for symptoms.
If normal at baseline: ALT > 5 × ULN for more than two weeks **If elevated at baseline:** ALT > 3 × baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	· **Interrupt trial drug** · Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. · Follow-up for symptoms. · Initiate close monitoring and workup for competing etiologies. · Trial drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 × ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 × ULN **If elevated at baseline:** ALT > 2 × baseline or > 300 U/L (whichever occurs first)	TBL > 2 × ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT > 3 × ULN **If elevated at baseline:** ALT > 2 × baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-6 Follow up requirements for liver laboratory triggers

Criteria	*Actions required*	*Follow-up monitoring*
Total Bilirubin (isolated)		
> 1.5 to 3.0 ULN	· Maintain treatment · Repeat LFTs within 48 to 72 hours	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline
> 3 to 10 × ULN (in the absence of known Gilbert syndrome)	· Interrupt treatment · Repeat LFT within 48 to 72 hours · Hospitalize if clinically appropriate · Establish causality · Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 × ULN	· Discontinue the trial treatment immediately · Hospitalize the participant · Establish causality · Record the AE and contributing factors(e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	· Consider trial treatment interruption or discontinuation · Hospitalization if clinically appropriate · Establish causality · Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease