NOVARTIS

Novartis Research and Development

BYL719, Alpelisib

Oncology Clinical Protocol CBYL719X2402 / NCT03056755

BYLieve: A phase II, multicenter, open-label, three-cohort, non-comparative study to assess the efficacy and safety of alpelisib plus fulvestrant or letrozole in patients with PIK3CA mutant, hormone receptor (HR) positive, HER2-negative advanced breast cancer (aBC), who have progressed on or after prior treatments

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List of abbreviations

aBC	Advanced Breast Cancer
ADA	American Diabetes Association
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
AI	Aromatase Inhibitor
Akt	Protein Kinase B
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/GPT
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
ARA	Acid Reducing Agents
ASCO	American Society of Clinical Oncology
ASMA	Anti-smooth Muscle Antibody
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/GOT
ATM	Ataxia-telengiectasia mutation
AUC	Area Under the Curve
bid	bis in diem (twice a day)
BAL	Broncho-Alveolar Lavage
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BMA	Bone Modifying Agents
BMI	Body Mass Index
BOR	Best overall response
BSA	Body Surface Area
BSEP	Bile Salt Export Pump
BUN	Blood Urea Nitrogen
CAR	Constitutive Androstane Receptor
CBR	Clinical Benefit Rate
CDK4/6	Cyclin-Dependent Kinases 4 and 6
CDKi	Cyclin-Dependent Kinase inhibitor
CDS	Core Data Sheet
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
CL	Clearance
CLIA	Clinical Laboratory Improvement Amendments
Cmin	Minimum Concentration
Cmax	Maximum Concentration
CMV	Cytomegalovirus

[redacted]

CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTP	Clinical Trial Protocol
CV	Coefficient of Variation
CYP	Cytochrome P
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DKA	Diabetic Ketoacidosis
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Overall Response
DTI	Direct Thrombin Inhibitors
EASD	European Association for the Study of Diabetes
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form; the term CRF can be applied to either EDC or Paper
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EM	Erythema Multiforme
EMA	European Medicines Agency
EOT	End of Treatment
ER	Estrogen Receptor
ERCP	Endoscopic Retrograde Cholangio Pancreatography
ET	Endocrine Therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin-fixed paraffin-embedded
Fg	Intestinal Availability
FG	Fasting Glucose
FISH	Fluorescence In Situ Hybridization
FPFT	First Patient First Treatment
FPG	Fasting Plasma Glucose

[redacted]

FSH	Follicle-stimulating Hormone
G	Grade
GABA	Gamma-aminobutyric acid
GCS	Global Clinical Supply
GGT	Gamma-glutamyltranspeptidase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
GnRH	Gonadotropin Releasing Hormone
HAV	Hepatitis A Virus
HbA1c	Glycosylated Hemoglobin
HbsAg	Hepatitis Surface Antigen
HDL	High Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
HEV	Hepatitis E Virus
HHNKS	Hyperglycemic Hyperosmolar Non-Ketotic Syndrome
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor
HR+	Hormone Receptor Positive
HSV	Herpes Simplex Virus
i.v.	intravenous(ly)
IA	Interim Analysis
IB	Investigator Brochure
IC	Inhibitor Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Tests
LHRH	Luteinizing Hormone-Releasing Hormone
LLN	Lower limit of normal
LPFT	Last Patient First Treatment

[redacted]

LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
mBC	Metastatic Breast Cancer
MCF7	Michigan Cancer Foundation-7
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MRP2	Multidrug Resistance Protein 2
mTOR	Mammalian Target of Rapamycin
MUGA	Multiple Gated Acquisition
NCCN	National Comprehensive Cancer Network
NCDS	Novartis Clinical Data Standards
NCI-CTCAE	National Cancer Institute Common Terminology Criteria Adverse Event
NGS	Next Generation Sequencing
NSAI	Non-Steroidal Aromatase Inhibitors
ONJ	Osteonecrosis of the Jaw
ORR	Overall Response Rate
OS	Overall Survival
PBPK	Physiologically based Pharmokinetics
p.o.	per os (by mouth/orally)
PD	Progressive Disease
PET/CT	Positron Emission Tomography/Computed Tomography
PFS	Progression-Free Survival
PFS2	Progression-Free Survival in next-line treatment
P-gp	P-glycoprotein
PgR	Progesterone Receptor
PHI	Protected Health Information
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Gene which encodes the p110alpha catalytic subunit of PI3K
PIKKs	Phosphoinositol 3-kinase-related- kinases
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PROS	Patient Reported Outcomes
PSDS	Post-Study Drug Supply
PSL	Protocol Standard Language
PT	Prothrombin Time
PTEN	Phosphatase and Tensin Homolog
PTT	Partial Thromboplastin Time

q.d.	Quaque Die (every day)
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
R Value	ALT/ALP in x ULN
RANK	Receptor activator of nuclear factor - kB
RBC	Red Blood Cells
REB	Research Ethics Board
RBG	Random Blood Glucose
RP2D	Recommended Phase Two Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	Stable Disease
SERM	Selective Estrogen Receptor modulator
SGLT2	Sodium glucose cotransporter 2
SGLT2i	Sodium glucose transporter 2 inhibitor
SISH	Silver *in situ* Hybridization
SJS	Stevens-Johnson-Syndrome
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
t.i.d.	Three times a day
TBIL	Total Bilirubin
Tc-99	Technetium-99
TdP	Torsade de Pointes
TEN	Toxic Epidermal Necrolysis
T_{max}	Time to reach maximum plasma concentration
ULN	Upper Limit of Normal
USPI	United States Prescribing Information
V_{ps}	Vacuolar protein sorting
WBC	White Blood Cell
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No. NCDS)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples
Random Blood Glucose	Blood glucose levels measured from a blood sample taken at a random time, regardless of when the subject last ate
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

[redacted]

Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of study consent (WoC)/Opposition to use of data/biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

[redacted]

Amendment 6 (28-Mar-2023)

The first study patient was screened on 14-Aug-2017, and as of 14-Dec-2020, study enrollment is complete and a total of 380 patients have been enrolled in the study. As of 30-Jan-2022, 9 patients remain on treatment.

The primary purpose of this amendment is to increase the duration of the Extension Phase from up to 12 months to up to 36 months) to allow treatment access for patients who are continuing to benefit from study treatment following the previous defined end of treatment (18 months post LPFT, per protocol amendments 4 and 5) and where Post-Study Drug Supply (PSDS) is not allowed per local regulations. The study will continue to consist of two phases: the Core Phase (initial treatment phase, FPFT until 18 months post LPFT) and the Extension Phase (treatment phase starting at the end of Core Phase until 36 months).

Rationale for increasing the duration of the Extension Phase:

PSDS is not allowed per local regulations for some of the participating countries; the Study Extension Phase will be a mechanism to continue to provide study treatment. Patients who are benefiting from treatment and are eligible for PSDS or a rollover protocol becomes available, should be discontinued from the study and access treatment via PSDS or rollover trial (whichever occurs first). For patients continuing in the Extension Phase, study treatment will be provided for the respective assigned Cohort treatment that the patients were receiving during the Core Phase.

During the Extension Phase, patients will continue to be evaluated as per institution's standard of care to determine clinical benefit and safety will continue to be monitored as per the protocol requirements. The only efficacy assessment to be collected will be the physician's determination of whether or not the patient is continuing to clinically benefit from the study treatment. Since the purpose of the extension phase is to provide continued access to study treatment, study assessments (such as central labs, RECIST, etc.) collected during the Core Phase will no longer be required and are detailed in the protocol.

In addition, the protocol is revised to align with the alpelisib protocol standard language based on other studies in the BYL719 development program and the following updated documents since the last protocol amendment:

- Investigator Brochure (IB) Edition 17 (11-Jul-2022)
- Updated Core Data Sheet (CDS) version 2.3 (12Sep2022)
- One Clinical Trial Protocol (CTP) Oncology template version 5.0 (14-Jan-2022)

The changes are outlined as follows in order of appearance:

- Protocol Summary:
    - Study Design: Updated duration of the Extension Phase
- Section 1.2.4.2 : Updated Clinical experience per IB
- Section 2.2: Updated duration of the Extension Phase
- Section 4.1: Study Design – Updated duration of the Extension Phase

[redacted]

- Figure 4-2: Updated Study Design schematic increasing the duration of the Extension Phase
- Section 4.3: Updated the durations for the Extension Phase
- Section 6.1.5: Updated Treatment duration regarding the duration of the Extension Phase
- Table 6-3: Updated text regarding monitoring and management of hyperglycemia Grade 1, 2 and 4. Added definitions and updated management details for diarrhea and colitis, for grades 1, 2 and 3. Added additional antihistamine guidance for treatment of grade 2, 3 and 4 skin toxicity in addition to any grade of Stevens-Johnson-Syndrome.
- Section 6.3.2.1.2: Updated text for the guidelines for the treatment of study drug induced skin toxicity as per IB/PSL
- Section 6.3.2.1.3: Updated text for the guidelines for alpelisib induced hyperglycemia as per IB/PSL
- Section 6.3.2.1.4: Updated text to remove 'perform' from sentence
- Section 6.3.2.3: Updated text for the guidelines for hypersensitivity as per IB/PSL
- Section 6.4.1.1: Updated Oral anti-diabetes text as per IB/PSL
- Section 6.4.3: Updated text to 'bone modifying agents' as per CTP v5
- Section 7.1.4: Updated consent information for the increased Extension Phase
- Section 13.0 added Jabbour S., and Ziring B reference
- Section 14.2: Updated text for the guidelines for alpelisib induced diarrhea as per IB/PSL

IRB/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.

[redacted]

Amendment 5 (14-Jan-2022)

The first study patient was screened on 14-Aug-2017, and as of 14-Dec-2020, study enrollment is complete and a total of 380 patients have been enrolled in the study. As of 04-Jan-2022, 21 patients remain on treatment.

The primary purpose of this amendment is to add an extension phase (for up to 12 months) to provide treatment access to patients who are continuing to benefit from treatment following the previous defined end of treatment (18 months post LPFT, per protocol amendment 4) where Post-Study Drug Supply (PSDS) is not allowed per local regulations.The study will then consist of two phases: the Core Phase (initial treatment phase, FPFT until 18 months post LPFT) and the Extension Phase (treatment phase starting at the end of Core Phase until 12 months). An interim analysis will be done to evaluate the data from the Core Phase.

In addition, the protocol is revised to align with the alpelisib protocol standard language based on other studies in the BYL719 development program and the following updated documents since the last protocol amendment:

- Investigator Brochure (IB) Edition 15 (20-Aug-2020) and Edition 16 (07-Jul-2021)
- Updated Core Data Sheet (CDS) version 2.1 (10-May-2021)
- One Clinical Trial Protocol (CTP) Oncology template version 4.0 (15-Feb-2021)

Rationale for addition of an extension phase:

PSDS is not allowed per local regulations for some of the participating countries; the Study Extension Phase will be a mechanism to continue to provide treatment. Patients who are benefiting from treatment and are eligible for PSDS will exit the trial at the end of the main study Core Phase. For patients entering the Extension Phase, treatment will be provided for the respective assigned Cohort treatment that the patients were receiving during the Core Phase.

During the Extension Phase, patients will be evaluated as per institution's standard of care to determine clinical benefit and safety will continue to be monitored as per the protocol requirements. The only efficacy assessment to be collected will be the physician's determination of whether or not the patient is continuing to clinically benefit from the study treatment. Since the purpose of the extension phase is to provide continued access to treatment, study assessments (such as central labs, RECIST, etc.) collected during the Core Phase will no longer be required and are detailed in the protocol. As the Extension Phase will extend Last Patient Last Visit (LPLV) by up to 12 months, an interim analysis has been added to evaluate all data up to the end of the Core Phase.

Note: Efficacy assessments will continue to be collected as per protocol until approval of this amendment and participants have transitioned to the Extension Phase.

Rationale for protocol standard language/IB updates:

The protocol amendment is aimed to align with the most current alpelisib protocol standard language and IB with regard to safety management (particularly hyperglycemia and rash), alpelisib dose modifications, and Drug-Drug Interactions (DDI).

[redacted]

This amendment also addresses:

- Correction to the frequency of monitoring blood glucose for the management of hyperglycemia Grade 2 as it was inconsistent with the latest Core Data Sheet (CDS) version 2.1 (10-May-2021).
- Minor editorial changes and additional clarifications as described in the list of changes below are included

The changes are outlined as follows in order of appearance:

- Title Page: Removed list of authors per current One CTP template
- Updated List of abbreviations
- Updated Glossary of Terms for Withdrawal of Consent and added details for the opposition to the use of data/biological samples as per One CTP template
- Protocol Summary:
    - Added Protocol Number
    - Study Design: Added details of the Core and Extension Phases
    - Efficacy assessments: Added clarified assessments during Core and Extension Phases
    - Safety assessments: Added detail of Safety assessments during the Extension Phase
    - Other assessments: Clarified biopsy samples to be collected at the end of the Core Phase
    - Data analysis: Added third interim analysis to evaluate all data up to the end of the Core phase
- Section 1.2.4.1: Updated Non-clinical experience, Pharmacodynamics of alpelisib per IB
- Section 1.2.4.2 : Updated Clinical experience per IB
- Section 1.2.4.3: Updated Clinical pharmacokinetics and added Consideration of gender effect per IB
- Section 2.2: Added details of the Core and Extension Phases
- Section 2.6.2: Added “Trial” to the section title
- Section 2.6.3: Updated risk management in relation to women of childbearing potential and sexually active males.
- Section 2.6.4: Added new section per CTP template regarding public health emergency mitigation procedures
- Table 3-1: Added Ext Phase objectives/endpoint for evaluating clinical benefit
- Section 4.1: Study Design – Added details of the Core and Extension Phases
- Figure 4-2: Updated Study Design schematic to include the Extension Phase

[redacted]

- Section 4.2: Updated the timing of interim analysis to include Core Phase Interim Analysis 3 (IA3)
- Section 4.3: Updated the End of study in reference to Extension Phase and defined the durations for the Core and Extension Phases
- Section 6.1.1: Updated Novartis Drug Supply group to the current name: Global Clinical Supply (GCS); also clarified Treatment Phases to include Core and Extension Phase
- Section 6.1.1.1: Updated alpelisib dosing per IB/PSL
- Section 6.1.1.1.1: Updated additional dosing guidelines per IB/PSL
- Section 6.1.5: Updated Treatment duration in regards to the duration of the Core and Extension Phases
- Section 6.3.1.4: Updated clarification of CTCAE version for alpelisib AEs as per IB/PSL and added text regarding withholding alpelisib dosing.
- Table 6-3: Updated text regarding interruption and re-initiation of alpelisib treatment; corrected frequency of monitoring blood glucose for the management of hyperglycemia Grade 2, 3, and 4. Added description for the grading of diarrhea, updated dose modifications for diarrhea grade 2. Added additional antihistamine guidance for treatment of grade 3 skin toxicity.
- Section 6.3.2: Updated text regarding the follow-up until resolution for treatment that is interrupted or permanently discontinued as per IB/PSL; clarified the post-treatment follow-up for toxicities are safety follow-ups.
- Section 6.3.2.1.2: Updated text for the guidelines for the treatment of study drug induced skin toxicity as per IB/PSL
- Section 6.3.2.1.3: Updated text for the guidelines for alpelisib induced hyperglycemia as per IB/PSL
- Section 6.3.2.2: Added details for follow-up on potential drug-induced liver injury cases as per IB/PSL
- Section 6.3.2.3: New Section added for guideline for hypersensitivity as per IB/PSL
- Section 6.4.1: Updated text for permitted concomitant therapy as per IB/PSL as per CTP template; clarified Concomitant Medications or the Surgical and Medical Procedures eCRF completed during Core Phase only.
- Section 6.4.1.1: Updated Oral anti-diabetes text as per IB/PSL
- Section 6.4.1.4: Updated Palliative radiotherapy as per IB/PSL
- Section 6.4.2: Updated permitted concomitant therapy requiring caution and/or action as per IB/PSL
- Section 6.4.3: Updated Use of bisphosphonates as per IB/PSL
- Section 6.4.4: Updated Prohibited concomitant therapy per IB/PSL
- Section 6.5.2: Treatment assignment clarified it occurs at the start of the Core Phase
- Section 6.6: Clarified text for study drug preparation and dispensation; added text for mitigations for delivery of IMP to patient's home during a public health emergency as per CTP template

[redacted]

- Section 6.6.1: Updated Novartis Drug Supply management group to the current name: Global Clinical Supply (GCS)
- Section 6.6.4: Updated Disposal and destruction per CTP template
- Section 7.1: Updated text in regards to the Core and Extension Phase for the study flow and visit schedule and added updated text for this section related to Public Health emergency as per CTP template
- Table 7-1: Updated table to include Core Phase
- Table 7-2: New VES for Extension Phase added; the subsequent tables of Section 7 are renumbered accordingly and their respective cross-references have also been updated
- Section 7.1.3: Clarified Core and Extension Phase treatment periods
- Section 7.1.4: Added new section for Extension Phase procedures
- Section 7.1.5: Updated discontinuation of study treatment in regards to the Core and Extension phases
- Section 7.1.6: Updated Withdrawal of Consent text and added detail for Opposition to the use of data/biological samples as per CTP template
- Section 7.1.7: Clarified follow-up for safety evaluations in the Core and Extension Phases
- Section 7.1.8: Clarified text for efficacy followup for the Core Phase only
- Section 7.1.9: Clarified text for survival followup for the Core Phase only
- Section 7.1.11: Clarified text regarding end of study disposition phase eCRF for the Core and Extension Phases
- Section 7.2.1.1: Clarified imaging tumor assessments are required in Core Phase only and no per protocol efficacy assessments other than physician's determination as per standard of care of whether or not the patient is continuing to derive clinical benefit from the study treatment.
- Section 7.2.2: Clarified Safety and tolerability assessments during the Core and Extension Phases
- Section 7.2.2.1: Clarified physical examination during the Core Phase only
- Section 7.2.2.3: Clarified Weight done during the Core Phase only
- Section 7.2.2.4: Clarified ECOG performance status during the Core Phase only
- Section 7.2.2.5 and Table 7-5: Clarified Laboratory evaluations are required during the Core Phase only and if needed during the Extension Phase per standard of care labs will go for local testing (instead of central lab)
- Section 7.2.2.5.1: Clarified Hematology required during Core Phase only
- Section 7.2.2.5.2: Clarified Clinical chemistry required during Core Phase only
- Section 7.2.2.5.3: Clarified monitoring of RBG and fasting c-peptide, lipid panel, amylase, lipase and HbA1c during the Core Phase
- Section 7.2.2.5.4: Clarified Coagulation assessment during the Core Phase
- Section 7.2.2.5.5: Clarified Urinalysis during the Core Phase
- Section 7.2.2.5.6: Clarified Urine test required in the Core and Extension Phase
- Section 7.2.2.6: Clarified Radiological examinations required in Core Phase

[redacted]

- Section 7.2.2.7: Clarified Cardiac Assessments to be performed in the Core Phase
- Table 7-6: Clarified Local ECG collection at EoT is during the Core Phase
- Section 7.2.2.7.2: Clarified Cardiac imaging during the Core Phase
- [redacted]
- Section 8.2.2: updated SAE report requirement as required by BfArM (Federal Institute for Drugs and Medical Devices in Germany)
- Section 8.4: Updated Pregnancy reporting and follow-up text per CTP template
- Section 10.5.1.7: New section added for analysis of extension phase clinical benefit.
- Section 10.7: Added details of the Core Phase interim analysis (IA3)
- Section 10.8: Clarified the first two interim analysis under sample size calculation
- Section 11.3: Updated the text for Informed Consent procedures based on CTP template
- Section 14.1.2: Updated date for list of CYP inducers per IB/PSL
- Table 14-3: Updated Prohibited Medication per IB/PSL
- Table 14-5: Updated Liver Event and laboratory trigger definitions per IB/PSL
- Table 14-6: Updated Follow-up requirements for liver laboratory triggers with liver symptoms per IB/PSL
- Table 14-7: Updated Follow-up requirements for liver laboratory triggers

IRB/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.

[redacted]

Amendment 4 (31-Oct- 2019)

The first study patient was screened on 14-Aug-2017 and as of 08 Oct 2019, 254 patients have been enrolled in the study CBYL719X2402.

The primary purpose of this amendment is to revise protocol language, in order to allow analyses of the primary endpoint for each cohort independent of the other cohorts. The primary analysis for each cohort will be performed 6 months after the last patient enrolled in that specific cohort has started treatment.

The purpose of this amendment is also to provide a protocol update on the following based on the recently released IB Edition 13:

- New clinical pharmacology data and Drug-Drug Interactions (DDI)
- Update of the Inclusion /Exclusion criteria
- Update on permitted concomitant medications to be used with caution, prohibited medications and the use of bisphosphonates/denosumab
- Update on guidance of dose interruption/modifications, management of AEs associated with the use of alpelisib, and guidance for follow-up on toxicities.
- Other editorial changes, to align with BYL new protocols in other indications

Rationale

Re: Cohort Primary Analysis: Based on the difference in timing between cohorts in enrollment and completion of the minimum 6 months follow up required for the primary analyses, the protocol language is being revised to allow analyses of the primary endpoint for each cohort independent of the other cohorts. This will allow for earlier availability of the primary analyses by cohort

Re: IB update: On 24-May-2019, based on the results of the pivotal Phase III study CBYL719C2301, the United States Food and Drug Administration (FDA) granted approval of alpelisib in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. Other global submissions are currently under review by other Health Authorities worldwide. The Investigator's Brochure (IB) Edition 13, dated 15-Oct-2019, included comprehensive assessments of SOLAR-1 safety data (with cutoff date: 20 Oct 2018) and all other available safety data which led to further defining alpelisib safety profile and risks associated with alpelisib. Additionally, the IB was updated with new DDI data which warrants an update of the concomitant medications to be used with caution and the prohibited medications. Accordingly, this amendment covers these updates along with updates for the existing guidelines for the management of adverse events associated with the use of alpelisib and follow-up on toxicities.

[redacted]

This amendment also addresses:

- Clarification on Cohort C patient population regarding prior endocrine therapy. Prior endocrine therapy can include monotherapy or in combination (except Cyclin-Dependent Kinases 4 and 6 inhibitors (CDK 4/6i+ AI); combination with CDK4/6i plus fulvestrant may be included after enrollment completion of Cohort B. The purpose is to evaluate the clinical benefit of alpelisib + fulvestrant in patients who received CDK4/6i plus fulvestrant as immediate prior therapy; this will assess alpelisib activity in overcoming endocrine resistance while maintaining the same endocrine partner, fulvestrant. Note: CDK 4/6i + AI is not included in Cohort C as this is studied under Cohort A.
- Minor editorial changes and additional clarifications as described in the list of changes below are included

Changes to the protocol:

The changes are outlined in order of appearance:

- Updated current authors
- Updated List of abbreviations
- Protocol Summary:
    - Investigational and reference therapy – clarified Cohort C prior therapy
    - Efficacy assessments – deleted 18 months after LPFV
    - Data Analysis – deleted at the final analysis
- Section 1.2.4.2: Updated Clinical experience and approval information of Alpelisib (Piqray®)
- Section 1.2.4.3: Added SOLAR1 pharmacokinetic analyses and data on food effect
- Section 2.2: Clarified patient population in Cohort C: Includes patients who received prior ET as monotherapy or combination (excluding CDK 4/6i + AI); after completion of enrollment of Cohort B, patients who receive prior CDK4/6 inhibitors plus fulvestrant are eligible, This change was also updated in the protocol summary, Sections 4.1, 5.2, 6.1.1 and 6.5.2
- Section 4.1, Figure 4-2: corrected LPLV to LPFT and under Cohort C corrected and deleted “monotherapy”, which was a note to file from previous protocol amendment (PA3)
- Section 4.3:
    - Removed redundant text already stated in Section 10 regarding analysis timings
    - Clarified and corrected end of study definition

Since end of study is defined in Section 4.3, revised redundant text throughout document when referring to “end of study” without repeating the 18 months follow up text, etc.

- Section 5.2 Inclusion criteria:

[redacted]

- #7: clarified Cohort C prior therapy
- #10: updated total serum bilirubin to <2 x ULN (from ≤ULN) and added any elevated bilirubin should be asymptomatic at enrollment

- Section 5.3 Exclusion criteria:
  - #9 added [testing not mandatory unless required by local regulations or requirements]
  - #10 corrected CYP3A4 (from CYP3A) and added inhibitors of BCRP
  - #13 added based on investigator discretion
  - #14 added interstitial lung disease
  - #19 added Erythema Multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  - #20 C is updated with text prior to initiating study treatment
  - #21 (new) 'subjects with unresolved osteonecrosis of the jaw' based on observations within SOLAR-1 data
- Section 6.1.1.1 Alpelisib dosing: Additional guidance on missed dose instructions indicating, if greater than 9 hours, skip the dose
- Table 6-3: Updates to Criteria for interruption and re-initiation of alpelisib treatment made per IB:
  - Updates made to Hyperglycemia, Diarrhea and Skin and subcutaneous tissue disorders
  - Updated criteria for Isolated AST or ALT Elevation, Combined elevations of AST or ALT and total Bilirubin, and Cardiac investigations
  - Updated criteria for skin and subcutaneous tissue disorders
- Section 6.3.2.1.1: added Alpelisib association with pneumonitis/interstitial lung disease and to closely monitor subjects for signs and symptoms of pneumonitis
- Section 6.3.2.1.2: Guidelines for the treatment of study drug induced skin toxicity:
  - Clarification for Grade 3 events recommend photography and skin biopsies, for Grade 4 they must be taken
  - Inclusion of anti-histamine administration prior to onset of rash may decrease the incidence and severity based on data from SOLAR-1 study
- Section 6.3.2.1.3 updated with low processed food intake and with due to the short half-life of alpelisib all glucose lowering medications should be discontinued when alpelisib is stopped
- Section 6.3.2.2: Follow up on potential drug-induced liver injury (DILI) cases. Additional language included specifying other causes of abnormal liver tests should be

considered and clarified before diagnosis of DILI is confirmed. Table 6-4 (new) included highlighting alternative causes of liver disease

- Section 6.4.1.1 updated with hyperglycemia and CYP2C9
- Section 6.4.1.2 updated with gastric protection agents
- Section 6.4.2: Updated text for medications to be used with caution for CYP2C9, CYP2B6, CYP3A4 and Herbal Medication
- Section 6.4.3 (new): Additional information and guidance on the use of bisphosphonates based on SOLAR-1 study data and the incidence of osteonecrosis of the jaw with alpelisib in combination with fulvestrant.
- Section 6.4.4 (previously 6.4.3): Prohibited Concomitant Therapy
    - Inclusion of strong CYP3A4 inducers based on additional data (as listed in Table 14-2)
    - Inclusion of BCRP efflux transporters
    - Removed risk of Torsades de pointes and drugs associated with QT prolongation and/or TdP
- Table 7-1: VES – added Skin Photographs for skin toxicity/SJS/TEN
- Table 7-6 updated with visit details for skin samples
- Section 7.2.3.1.1 Clarified bone samples cannot be accepted for central confirmation mutation testing
- Section 10: Revised text with respect to timing of primary analyses for each cohort (refer to protocol amendment purpose and rationale above for details). Clarified final analysis will be at the end of the study as defined in Section 4.3
- Section 13.0 added Lee CA et al reference
- Section 14.1 Appendix 1:
    - Added Table 14-1 (new) List of CYP450 substrates to be used with caution and text under Section 14.1.1 (new) Permitted medication to be used with caution
    - Added Table 14-2 (new) List of prohibited strong inducers of CYP3A4 and added text under Section 14.1.2 (new) Strong inducers of CYP3A4
    - Deleted previous Table 14-1 List of CYP450 substrates to be used with caution , Table 14-2 List of prohibited QT prolonging drugs, Table 14-3 List of QT prolonging drugs to be used with caution and Section 14.1.2 Drugs that prolong the QT interval and/or induce Torsades de Pointes
    - Section 14.1.3 BCRP inhibitors: Updated text and replaced Table 14-4 list of BCRP inhibitors to be used with caution with Table 14-3 (new) List of prohibited BCRP inhibitors

[redacted]

- Section14.4 Appendix 4 Liver event and laboratory trigger definitions and follow-up requirements (new) : added text and Table 14-5 (new) Liver event and laboratory trigger definitions

IRB/IECs

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[redacted]

Amendment 3 (30-Jan-2019)

Amendment rationale

The first study patient was screened on 14-Aug-2017 and as of 22-Jan-2019, 127 patients have been enrolled in the study CBYL719X2402.

The purpose of this amendment is to:

- Add a new cohort (C) to enroll patients who have failed prior aromatase inhibitor (AI) treatment (either in the adjuvant or metastatic setting) and received systemic chemotherapy or endocrine treatment (ET) as immediate prior treatment.
- Increase the total number of patients to approximately 340 for this study; this includes increasing the sample size for the existent cohorts (A & B) from 80 patients to 112 patients and the addition of the third cohort (C) consisting of 112 patients.
- Revise assessments to include only those assessments that are clinically necessary to reduce patient inconvenience. Please refer to Table 7-1 for all revisions.
- Allow monitoring of fasting or random blood glucose (RBG) levels instead of the current mandatory fasting glucose (FG) tests. Please refer to Section 7.2.2.5.3.
- Add one additional interim analysis to be performed when approximately [redacted] patients (50% of enrolled patients) have been treated in the study (regardless of cohort) and have at least 6 months of follow up on study.

Rationale to add Cohort C

The primary analysis from the phase III [CBYL719C2301 (SOLAR-1)] study confirms statistically significant and clinically relevant benefit with alpelisib in combination with fulvestrant in PIK3CA mutant, HR+ HER2- advanced breast cancer patients who have progressed on AI treatment. The BYLieve study was originally designed to investigate the benefit risk ratio of PIK3CA inhibitor treatment following prior use of CDK4/6 inhibitor treatments but was restricted to patients who received CDK4/6 inhibitors as their last treatment prior to study entry. Since then, the approval of CDK4/6 inhibitors for use in first line metastatic breast cancer has led to increasing number of patients receiving the treatment in an earlier line, followed by systemic chemotherapy or ET. Based on these developments in the current treatment landscape for aBC and the results from SOLAR -1 study, the enrollment into BYLieve study is being extended to patients who may have received systemic chemotherapy or an ET as immediate prior treatment and have previously failed AI treatment (either in adjuvant or metastatic setting).

The sample size from cohorts A and B was revised to allow for a more robust assessment of benefits vs. risk in the investigated patient populations.

Rationale to allow assessment of random blood glucose levels (non- fasted):

The primary analysis of SOLAR-1 [CBYL719C2301] confirms previously established safety and tolerability for alpelisib from early phase studies. The class effect of hyperglycemia can be monitored through regular blood tests and upon occurrence, is readily manageable through existing guidelines recommended in the protocol. Based on this information, the study is being amended to allow for monitoring of either fasting or random blood glucose (RBG) levels (non-

[redacted]

fasted). Patients who experience rise in fasting or RBG levels will be subjected to previous management guidelines: plasma glucose levels can be monitored via peripheral blood tests at the discretion of the investigator.

Rationale to add the interim analysis

A second interim analysis will be performed when approximately [redacted] patients (50% of enrolled patients) have been treated in the study (regardless of cohort) a have at least 6 months of follow up. This interim analysis will be performed to report preliminary efficacy (ORR, CBR) as well as key safety data in a descriptive fashion to provide additional information in this patient population.

Changes to the protocol

The changes are outlined as follows in order of appearance:

- Title of protocol revised to include three cohorts and patients that have progressed on or after prior treatments
- Updated current authors
- Revised protocol summary sections for title, brief title, purpose and rationale, primary objective, secondary objective, study design, population, key inclusion, investigational and reference therapy, efficacy assessments, safety assessment and data analysis
- Section 2.1: Revised to include cohort C patient population and updated key purpose of the study
- Section 2.2: Revised to include cohort C patient population
- Section 2.3: Revised to include cohort C patient population
- Section 2.5: Deleted reference to CDK4/6 inhibitors
- Section 2.6.1: Revised to include cohort C patient population
- Table 3-1: Revised to update primary objective to include cohort C patient population, add secondary objective of overall survival [redacted]
- Section 4.1: Revised to include cohort C patient population, approximate number of patients to prescreen and enroll and revision to allow tumor assessments to be collected every 12 weeks
- Figures 4-1 and 4-2: Revised to include cohort C patient population
- Section 4.2: Add additional interim analysis
- Section 4.3: Revised to update primary and final analysis
- Section: 4.4: Revised to new template language for early termination reasons
- Section 5.1: Revised to include cohort C patient population
- Section 5.2: Revised to include cohort C patient population
- Section 6.1.1: Revised to include cohort C patient population
- Section 6.1.1.2: Revised to remove no dose modification for letrozole
- Section 6.1.1.3: Revised to remove no dose medication for fulvestrant
- Section 6.3.1.1: Revised to remove no dose medication for fulvestrant
- Section 6.3.1.2: Revised to remove no dose modification for letrozole

[redacted]

- Section 6.3.1.4: Revised to remove no dose modification letrozole, fulvestrant, goserelin and leuprolide
- Table 6-3: Revised dose modifications to allow for RBG testing, updated management of skin toxicity
- Section 6.3.2.1.2: Revised management of skin toxicity
- Section 6.3.2.1.3: Revised dose modifications to allow RBG testing
- Section 6.5.2: Revised to include cohort C patient population
- Table 7-1: Revised to update molecular prescreening in source only, allow tumor assessments to be collected every 12 weeks, other assessments to be conducted as clinically indicated, adding FBG or RBG collection, capture local PIK3CA mutation in database, add cohort C dosing
- Section 7.1.2.2: Revised to remove capture of prescreening patients in database
- Section 7.1.2.3: Revised demographics collected based on CRF availability
- Section 7.1.4: Revised tumor assessments to be collected every 12 weeks
- Section 7.1.7: Revised tumor assessments to be collected every 12 weeks and revised eCRF page
- Section 7.1.8: Paragraph was deleted since it was duplicated from section 7.2.1.2
- Section 7.1.10: Revised eCRF page
- Section 7.2.1.1: Removed whole body scan and revised tumor assessments to be collected every 12 weeks
- Table 7-2: Removed whole body scan and revised tumor assessments to be collected every 12 weeks
- Section 7.2.2.5: Added RBG testing
- Table 7-4: Removed fasting criteria for partial chemistry labs
- Section 7.2.2.5.3: Added random glucose testing
- Section 7.2.3.1.3: Revised to add information regarding optional testing
- Table 7-5: Deleted ECG at every 3 cycles
- Section 10: Clarified primary and final analyses
- Section 10.4: Revised to include cohort C patient population
- Section 10.4.2: Revised to include cohort C patient population
- Table 10-1: Revised confidence intervals
- Section 10.5: Revised secondary objectives confidence intervals
- Section 10.5.1.6: Added overall survival
- [redacted]
- Section 10.7: Revised to include additional interim analysis
- Section 10.8: Revised confidence intervals and updated sample size
- Table 10-2: Updated Operating Characteristics
- Section 11.3: Revised fetotoxic potential
- Section 13: Added reference for SOLAR-1

[redacted]

IRBs/IECs

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Amendment 2 (02-May-2018)

Amendment rationale

The first study patient was screened on 14-Aug-2017 and as of 02-May-2018, 30 patients have been enrolled in the study CBYL719X2402.

The current amendment is intended to clarify the use of goserelin or leuprolide (LHRH agonists) as study treatment for pre-menopausal women (as applicable) and men (cohort B).

Changes to the protocol

The changes are outlined as follows in order of appearance:

- Updated glossary of terms due to EEA General Data Protection Regulation (GDPR)
- Section 1.1.2: Revised LHRH agonist to goserelin and leuprolide
- Section 1.2.3: Clarified that goserelin or leuprolide (LHRH agonists) allowed for use in this study
- Section 2.3: Clarified the usage of goserelin or leuprolide in men and premenopausal women in this study
- Section 2.6 and 2.6.3: Added goserelin or leuprolide
- Table 3-1: Aligned the endpoint correctly with objective
- Section 4.1: Clarified that goserelin or leuprolide will be used for gonadal suppression
- Figure 4-1: Updated to include the end of study information
- Section 4.3: Clarified paragraph to align with protocol
- Section 5.2: Inclusion criterion #6: clarified the requirement for menopausal status of goserelin or leuprolide to be used concomitantly with alpelisib in combination with fulvestrant or letrozole
- Section 5.2; Inclusion criterion #7: clarified lines of treatment
- Section 5.3: Exclusion criterion #1: added goserelin or leuprolide to the known hypersensitivity
- Section 5.3: Exclusion criterion #20b: added to women that highly effective contraception during dosing and for at least 8 months after stopping study medication. Provides consistency between both males and females.
- Section 6.1: Defined the use of goserelin or leuprolide for men and premenopausal women as study treatment
- Section 6.1.1.1: Deleted paragraph and moved to Section 6.1 for clarity
- Table 6-1: Renamed table and added goserelin and leuprolide dose and treatment scheduled
- Section 6.1.1.4 and Section 6.1.1.5: Added section for dosing for goserelin and leuporolide
- Section 6.3.1.3: Added section for goserelin and leuprolide dose modifications

[redacted]

- Section 6.3.1.4: Deleted sentence under Table 6-2 as it was a duplicate from above paragraph
- Section 6.3.1.4: Deleted last sentence in paragraph and moved to Section 6.3.2
- Section 6.3.2: Clarified patient follow up information
- Section 6.4.1: Corrected name of eCRF page
- Section 6.4.1.3: Deleted paragraph as it was a duplicate from Section 6.4.1
- Section 6.4.3: Clarified the use of probiotics
- Section 6.6: Added goserelin and leuprolide study drug preparation
- Table 6-5 and Table 6-6: Added goserelin and leuprolide supply and storage treatments
- Table 7-1: Added goserelin and leuprolide under study administration
- Section 7.1.5: Updated due to EEA General Data Protection Regulation (GDPR)
- Section: 7.1.6: Clarified patient follow up information and updated eCRF to be collected
- Section 7.2.2.7.1: Deleted last paragraph as it was a duplicate from above paragraph
- Table 14-1: Removed footnotes as not required

IRB/IECs

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Amendment 02 also includes minor editorial changes and additional clarifications to address investigators' questions as described in the list of changes below.

[redacted]

Amendment 1 (30-Jan-2018)

Amendment rationale

The first study patient was screened on 14 Aug 2017 and as of 23 January 2018, 9 patients have been enrolled in the study CBYL719X2402.

The purpose of this amendment is to:

- Provide updated guidance on the management of skin and subcutaneous reactions
- Allow for premenopausal women to be included in the study as long as they are receiving concomitant ovarian suppression with LHRH agonist (examples for use in this study include but are not limited to goserelin, leuprolide or locally available treatment) based on current treatment guidelines as standard of care in this population throughout the duration of the study (ASCO Guidelines 2016) as requested from Steering committee.
- Plan an Interim Analysis (IA) after at least [redacted] patients receiving alpelisib plus fulvestrant (cohort A) have at least 6 months of follow up. At the time of the IA, preliminary efficacy (ORR, CBR) as well as key safety data will be analyzed descriptively
- Revise section 8.1.1 regarding the length of time needed for the safety follow up visit. Patient will be monitored for safety for 30 days after study treatment (alpelisib) discontinuation (this is longer than 5 half-lives for alpelisib). Since fulvestrant and letrozole are marketed products, and locally approved labeling is being followed, the safety follow-up period for these agents will also be 30 days.
- Update alpelisib information based on the data available on the current IB version (v10, release date: 12 July 2017; safety cut-off date: 13 May 2017)
- Update additional background information regarding preclinical data for alpelisib in PI3K mutant patients post CDK inhibitors and information to include rapidly changing advanced breast cancer (aBC) landscape

Rational to update skin toxicity management guidance

Skin toxicity is a known class effect of PI3K/mTOR pathway inhibition. In addition to the previously reported case of Stevens-Johnson Syndrome (SJS) from study CMEK162X2109, a new suspected case of SJS related to alpelisib treatment was reported from study [CBYL719C2301 (SOLAR-1)] (see IB Ed 10 for details on both cases). An overall assessment of the risk of alpelisib for severe cutaneous reactions such as SJS but also Erythema Multiforme (EM) has been conducted in April 2017 across the development program. In the Novartis safety database for severe adverse events, there were overall 2 cases of SJS and 2 cases EM reported for 1710 patients exposed to alpelisib across all studies (cut-off May 2017). This assessment indicated that a causal role of alpelisib in development of SJS and EM cannot be excluded. Therefore, in the current protocol and across the alpelisib development program, the existing guidance for the management of skin and subcutaneous reaction have been updated to include further detailed dose modification and follow-up management guidelines in case of severe cutaneous reactions.

[redacted]

Rationale to modify the inclusion of Premenopausal patients

Premenopausal patients (receiving concomitant ovarian suppression with LHRH agonists as standard of care) are assessed to be allowed in the study, based on current treatment guidelines suggesting similar treatment strategies in premenopausal patients with ovarian suppression as post-menopausal patients. Standard language around contraception was added to the inclusion/exclusion criteria as of result of this change. Additional clinical data from a smaller study was also included.

Note: throughout this document perimenopausal and premenopausal status is grouped together and referred to as "premenopausal'.

Rationale to add the interim analysis

Due to lack of data availability in this patient population of post CDK 4/6 combination therapy, an interim analysis will be performed to report preliminary efficacy (ORR, CBR) as well as key safety data in a descriptive fashion.

Changes to the protocol

The changes are outlined as follows in order of appearance:

- Protocol "acronym" BYLieve added to this protocol
- List of abbreviations updated
- Summary section of the protocol has been updated to maintain consistency with the main body of the protocol
- Throughout the document: Typographical and grammatical corrections
- Section 1.1.1: Updated breast cancer information
- Section 1.1.2: Updated section to include epidemiology to include pre-menopausal women-
- Section 1.1.4; Updated information regarding mechanism of action with PI3K/mTOR pathway
- Section 1.2.2.1: Updated fulvestrant pharmacokinetic data
- Section 1.2.3: Added information regarding LHRH agonist for pre-menopausal patients
- Section 1.2.4.1: Added pharmacodynamics information for alpelisib
- Section 1.2.4.1.2: Updated nonclinical PK and metabolism information for alpelisib
- Section 1.2.4.1.3: Updated safety pharmacology and toxicology information for alpelisib
- Section 1.2.4.2: Updated clinical information based on alpelisib investigator brochure version 10
- Section 1.2.5.1: Updated clinical experience with alpelisib and aromatase inhibitors
- Section 1.2.5.2: Updated alpelisib and fulvestrant information
- Section 1.2.6.3: Added section to include low potential for drug-drug interactions with letrozole to be consistent within the protocol

[redacted]

- Section 2.1: Updated study rationale and purpose with phase Ib [CBYL719XIC01] information
- Section 2.2: Updated information for rationale for the study design to include recent preclinical data
- Section 2.3: Updated rationale for dose and regimen to include premenopausal women
- Section 2.6.3: Added information for risk management strategies
- Section 4.1: Added information in description of study design to include premenopausal women.
- Figure 4-1: Revised figure to update molecular prescreening window (can occur by Day -21).
- Figure 4-2: Revised figure to add cohort A and B in the schematic
- Section 4.2: Added interim analysis
- Section 4.3: Revised information regarding the definition of end of study
- Section 5.2: Inclusion criteria have been numerically rearranged for clarity and flow of criteria. These changes have not been tracked since no content was modified (only the numerical order)
- Section 5.2 Inclusion criteria #2 added for consistency in the metastatic breast cancer population
- Section 5.2 Inclusion criteria # 5 – revised to remove minimum slides requirements from a biopsy. Please note this requirement has not changed; it was only removed from inclusion criteria. [redacted]
- Section 5.2 Inclusion criteria # 5 – added blood for a known pathology report confirming PIK3CA status
- Section 5.2 Inclusion criteria #6 added to include pre-menopausal women population
- Section 5.2: Inclusion criteria #7, 9. 10, 11 and 13 were revised for clarity
- Section 5.3 Exclusion criteria #1 added to exclude patients with known hypersensitivities to study treatment medications
- Section 5.3: Exclusion criteria bilateral diffuse lymphangitic carcinomatosis was removed
- Section 5.3 Exclusion criteria # 4 revised to clarify diabetes mellitus
- Section 5.3: Exclusion criteria #8 now revised for HIV patients regarding local HA regulations
- Section 5.3: Exclusion criteria 7, 9, 14 and 17 were revised for clarity
- A section 5.3: Exclusion criterion 19 was deleted due to the patient population of advanced metastatic breast cancer. It would be unethical for patients to wait 30 days or 5 half-lives (especially if coming from Fulvestrant trial) from a previous trial to start another therapy due to the advanced condition
- Section 5.3: Exclusion criteria #21 added to exclude patients who may be at higher risk of skin and subcutaneous reactions
- Section 5.3 Exclusion criteria # 22 revised to add language due to premenopausal patients and contraception requirements

[redacted]

- Section 6.1.1.1.1: Added to include additional information for fasting guidelines
- Section 6.3.1.3: Revised to clarify recommendations for dose reduction for alpelisib
- Table 6-3: Table revised for consistency to standard language for alpelisib compound
- Section 6.3.2 and 6.3.2.1: Revised for clarity and consistency to standard language for alpelisib compound
- Section 6.3.2.1.2: Revised to include Stevens-Johnson Syndrome
- Table 6-6: Revised to include both central supplies for fulvestrant
- Section 7.1: Revised to clarify molecular pre-screening ICF can occur by Day -21
- Table 7-1 Added serum and urine pregnancy to allow for premenopausal patients; added estradiol for screening in patients < 60 years of age; revised molecular prescreening window (by Day -21), added cohort assignment page, local PIK3CA mutation assessment page and End of study treatment window to within 21 days of last dose
- Section 7.1.1: Revised to clarify molecular pre-screening consent to complete by Day -21 and clarified certified laboratory requirements
- Section 7.1.2: Revised to clarify certified laboratory requirements
- Section 7.1.4: deleted as duplicate information to section 7.1.5
- Section 7.2.3.1: Revised to clarify that decalcified samples are not acceptable for PIK3CA mutation analysis
- Section 7.2.3.1: Revision to clarify optional tumor tissue requirements
- Section 7.2.2.5.6: Added pregnancy and hormone levels
- Table 7-4: Revised to include pregnancy serum and urine tests due to adding pre-menopausal population and estradiol testing
- Table 7-6: Removed restriction on the age of archival tissue
- Section 8.1.1: Revised to clarify when adverse events are collected and removed 5 half lives
- Section 8.4: Added additional information regarding patient population
- Section 9.1: last paragraph deleted as subject initials and date of birth are not collected for the study
- Section 10.7 and 10.8: Added interim analysis plan
- Section 13: Added new references
- Appendices: Tables revised to be consistent with alpelisib standard language

[redacted]

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[redacted]

Protocol summary:

Protocol Number	CBYL719X2402
Title	BYLieve: A phase II, multicenter, open-label, three-cohort, non-comparative study to assess the efficacy and safety of alpelisib plus fulvestrant or letrozole in patients with PIK3CA mutant, hormone receptor (HR) positive, HER2-negative advanced breast cancer (aBC), who have progressed on or after prior treatments
Brief title	Study assessing the efficacy and safety of alpelisib plus fulvestrant or letrozole, based on prior endocrine therapy, in patients with PIK3CA mutation with advanced breast cancer who have progressed on or after prior treatments
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the efficacy and safety of treatment with alpelisib (BYL719) plus endocrine therapy (either fulvestrant or letrozole) in patients with HR+, HER2-negative aBC, harboring PIK3CA mutations, who have progressed on or after prior treatments. Pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy, in particular fulvestrant or letrozole. Promising clinical activity has been observed with single agent alpelisib, in heavily pre-treated Estrogen Receptor (ER)+ Metastatic Breast Cancer (MBC) patients, and when alpelisib was given in combination with fulvestrant or AI to HR+ HER2-negative metastatic breast cancer patients.
Primary Objective(s)	The primary objective is to assess the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment per RECIST v1.1 separately in Cohorts A and C (alpelisib in combination with fulvestrant) and Cohort B (alpelisib in combination with letrozole) among patients with HR+, HER2-negative aBC harboring a PIK3CA mutation whose disease had progressed on or after prior treatments.
Secondary Objectives	• To assess Progression-Free Survival (PFS) based on local investigator assessment for each cohort • To assess PFS on next-line treatment (PFS2) for each cohort • To assess overall response rate (ORR) and clinical benefit rate (CBR) based on local investigator assessment for each cohort • To assess duration of response (DOR) in patients with confirmed complete response (CR) or partial response (PR) for each cohort • To evaluate the safety and tolerability of the combination for each cohort • To assess Overall Survival (OS) for each cohort

[redacted]

	• To evaluate the safety and tolerability of the combination for each cohort • Evaluate clinical benefit as assessed by the Investigator during the Extension Phases
Study design	This is a phase II, multicenter, open-label, three-cohort, non-comparative study of alpelisib plus endocrine therapy (either fulvestrant or letrozole) in patients with HR+, HER2-negative aBC harboring PIK3CA mutation(s) in the tumor whose disease has progressed on or after prior treatments. The study includes two phases: **Core Phase:** Includes treatment phase for all patients from First Patient First Treatment (FPFT) until 18 months post Last Patient First Treatment (LPFT) + 1 month Safety follow-up (total 19 months post LPFT) **Extension Phase:** includes treatment phase starting at the end of the treatment Core Phase until Last Patient Last Visit (LPLV) (up to 36 months); The extension treatment phase is only for patients who are continuing to benefit from study treatment at the end of the Core Phase who are not eligible for PSDS (Post-Study Drug Supply) in their country based on local regulations. Patients will continue on their existing study treatment assigned in the Core Phase until discontinuation or Last Patient Last Treatment (LPLT) of the Extension Phase. Note: If PSDS becomes available for a patient or a rollover protocol becomes available, the patient should be discontinued from the study and access treatment via PSDS or rollover trial (whichever occurs first). Patients who are benefiting from the study treatment and are eligible for PSDS will exit the trial at the end of the Core Phase.
Population	The study will include a total of approximately 340 men and women (pre- and post-menopausal) with HR+, HER2-negative aBC harboring a PIK3CA mutation in the tumor, who progressed on or after prior treatments. The investigator or designee must ensure that only patients who meet all of the inclusion and none of the exclusion criteria are offered treatment in the study.
Key Inclusion criteria	• Patient is an adult male or female ≥ 18 years old. • Patient has adequate tumor tissue for the analysis of PIK3CA mutational status by a Novartis designated laboratory. It is recommended to provide a tumor sample collected after the most recent progression or recurrence. • Advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy • Patient has been confirmed as PIK3CA mutant as determined by a certified designated laboratory • Patient has histologically and/or cytologically confirmed ER+ and/ or PgR+ BC • Patient has confirmed, HER2-negative aBC. HER2-negative defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+ or 2+. • Patients must be diagnosed with aBC, with documented evidence of tumor progression on or after prior treatments. No

[redacted]

	more than one prior regimen of chemotherapy for the treatment of metastatic disease is permitted. The maximum number of prior therapies for aBC or mBC is limited to two (maintenance therapies, where applicable, must be regarded as part of the main therapy). Patients must have recovered to grade 1 or better from any adverse events (except alopecia) related to previous therapy prior to study entry. • Patient has either measurable disease, i.e. at least one measurable lesion as per RECIST v1.1 criteria or if no measurable disease is present than at least one predominantly lytic bone lesion must be present • Patient has ECOG performance status of ≤ 2 • Patient has adequate bone marrow function
Key Exclusion criteria	• Patient has received prior treatment with any PI3K inhibitors • Patients with an established diagnosis of diabetes mellitus type I or uncontrolled type II (based on FG and HbA1c in inclusion criterion 11) • Patient has a concurrent malignancy or malignancy within 3 years of study screening period, with the exception of adequately treated basal or squamous cell carcinoma, non-melanoma skin cancer or curatively resected cervical cancer • Patient has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to enrollment, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia) • Patients receiving systemic corticosteroids ≤ 2 weeks prior to treatment with alpelisib • History of acute pancreatitis within 1 year of screening or past medical history of pancreatitis • Patient has impaired GI function or GI disease that may affect the absorption of study drugs • Patient has documented pneumonitis • Patients being concurrently treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme Cytochrome P (CYP)3A within the last 5 days prior to study entry
Investigational and reference therapy	Male and pre and postmenopausal female patients with HR+, HER2-negative aBC patients harboring PIK3CA mutation(s) in the tumor who progressed on or after prior treatments will receive alpelisib combination therapy: Cohort A: Patients who received any CDK 4/6 inhibitor plus AI as immediate prior treatment will receive alpelisib + fulvestrant Cohort B: Patients who received any CDK 4/6 inhibitor plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole Cohort C: Patients who have received systemic chemotherapy, or ET (including monotherapy or in combination except CDK 4/6i + AI) as immediate prior treatment, will receive alpelisib + fulvestrant

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<table>
<tr><td></td><td>
<table>
<tr><th>Study treatment</th><th>Pharmaceutical form and route of administration</th><th>Frequency and/or Regimen</th></tr>
<tr><td>Fulvestrant</td><td>Two 5 ml injections for IM administration</td><td>Dosed every 28 days (Day 1) and Day 15 of Cycle 1 and Day 1 for all subsequent Cycles</td></tr>
<tr><td>Alpelisib</td><td>Film coated tablet for oral use</td><td>Once daily</td></tr>
<tr><td>Letrozole</td><td>Film coated tablet for oral use</td><td>Once daily</td></tr>
<tr><td>Goserelin</td><td>Injectable subcutaneous implant</td><td>Every 28 days (only for men in cohort B and premenopausal women)</td></tr>
<tr><td>Leuprolide</td><td>Injectable intramuscular depot</td><td>Every 28 days (only for men in cohort B and premenopausal women)</td></tr>
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</td></tr>
<tr><td>Efficacy assessments</td><td>
• Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) every 12 weeks until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, or until the end of the Core Phase
• Brain CT or MRI as clinically indicated if brain lesion at screening
• Bone X-ray, CT or MRI (if bone lesion at screening) every 12 weeks until end of the Core Phase
• Skin color photography (if skin lesions at screening) every 12 weeks until end of the Core Phase
• CT/ MRI for any disease outside of the chest, abdomen, pelvis (if lesion identified at screening) every 12 weeks until end of the Core Phase
• Survival status every 12 weeks (or earlier if required) regardless of treatment discontinuation reason (except if consent is withdrawn, death or patient is lost to follow-up) or until the end of the Core Phase
• During the Extension Phase, clinical benefit assessments will follow the local standard of care per the physician’s determination if the patient is continuing to clinically benefit from the study treatment.
</td></tr>
<tr><td>Safety assessments</td><td>
• Core Phase:
o Physical examination
o ECOG performance status
o Height, weight, and vital signs
o 12 lead ECGs
o ECHO, MUGA scan as clinically indicated
o Laboratory assessments including hematology, biochemistry, fasting glucose (FG), random blood glucose (RBG), HbA1c, fasting lipase, fasting amylase, coagulation and urinalysis
• In the Extension Phase, safety assessments will consist of monitoring and recording all Adverse Events (AEs), including Serious Adverse Events (SAEs).
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Data analysis	The primary efficacy endpoint is the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment using RECIST v1.1 in each cohort. A proportion of [redacted] of patients alive without progression after 6 months is considered as a clinically meaningful threshold in all the cohorts for this study. Therefore, evidence of treatment effect in each cohort will be tested using the following hypothesis: H_0: p ≤0.30 vs. H_1: p >0.30 Where p is the proportion of patients who are alive without progression at 6 months. Three Interim Analyses (IA) are planned for this study. The first IA will be performed after at least [redacted] patients receiving alpelisib plus fulvestrant (cohort A) have at l[redacted]t 6 months of follow-up. A second IA will be performed when approximately [redacted] patients have been treated in the study (regardless of cohort) and have at least 6 months of follow-up on study. A third IA will be performed after the Core Phase has ended. The first two interim analyses will be performed to report preliminary efficacy (ORR, CBR) as well as key safety data in a descriptive fashion to provide additional information in this patient population. The third interim analysis will be performed to report all efficacy and safety data up to the end of the Core Phase. The final analysis will be performed after LPLV of the study which include cumulative data (eg safety and clinical benefit) since the Core Phase analysis. The primary efficacy analysis will be performed using modified full analysis set (mFAS). The modified Full Analysis Set (mFAS) comprises all patients of the FAS population who have PIK3CA mutation confirmed by a Novartis designated laboratory. The assessment of safety will be based mainly on the frequency of adverse events and laboratory values that fall outside of pre-determined ranges.
Key words	HR+, Human Epidermal Growth Factor Receptor 2 (HER2)-negative, advanced breast cancer, alpelisib, fulvestrant, letrozole, Phosphoinositol 3-kinase-related-kinases (PI3K), Gene encoding p110alpha catalytic subunit of PI3K (PIK3CA) mutant, Phase II, CDK 4/6 inhibitor, men, pre and postmenopausal, aromatase inhibitor, endocrine therapy

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Hormone receptor-positive breast cancer

Breast cancer (BC) is the most common cancer in women. It is estimated that more than 1.7 million new cases of breast cancer occurred among women worldwide in 2012 (GLOBOCAN 2012). It is estimated that worldwide over 508,000 women died in 2011 due to breast cancer (Global Health Estimates, WHO 2012). In 2014, an estimated 232,670 new cases were diagnosed in women in the United States; of those, 133,310 were in women < 65 years old. Fewer than 5% of breast cancers occur in women < 40 years old (American Cancer Society 2014), but it is still the leading cause of cancer death among women 20 to 59 years old (Siegel 2014). Breast cancer in men is a more rare disease and makes up < 1% of all cases of breast cancers, but its treatment is based on the guidelines for female breast cancer (Foerster 2014, Agrawal 2007, Patten 2013, Giordano 2002). Subtypes of invasive breast cancer are distinguished by expression of estrogen receptors (ER), progesterone receptors (PgR) and human epidermal growth factor receptor-2 (HER2), as well as by distinct gene expression profiles (Perou 2000; Sotiriou and Pusztai 2009). Within these subtypes, 60-70% of breast tumors are HR+, HER2-negative. Expression of the ER and/or PgR is one of the most important prognostic factors in invasive breast cancer. Estrogen deprivation therapy is the core treatment modality in patients with HR+ advanced breast cancer. Endocrine therapy options for postmenopausal women with ER+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer (mBC)) including selective ER modulators (SERM; tamoxifen), ER antagonists (fulvestrant), selective nonsteroidal AIs (NSAI; anastrozole and letrozole) and steroidal aromatase inhibitors (AIs; exemestane). Blocking estrogen signaling with tamoxifen has been the main approach in treatment for ER+ breast cancer for over 35 years, especially in pre-menopausal women. In postmenopausal women, AIs reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens in non-ovarian tissues; synthesis in these tissues is the primary source of estrogens in postmenopausal women. AIs are generally used as the first line of therapy for women with HR+ breast cancer (Beslija 2009; NCCN 2017). In those patients that progress the combination of targeted agent and endocrine therapies have also been evaluated in the Bolero-2 trial: everolimus, a (Mammalian Target of Rapamycin (mTOR) inhibitor, combined with exemestane showed synergistic inhibition of the tumor proliferation and is approved for postmenopausal women with advanced HR+, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole demonstrating progression survival improvement (Baselga 2012; Yardley 2014).

Recent data have noted that cell cycle related genes and proteins are frequently dysregulated in breast cancer. Cyclin D kinases inhibitors have been introduced with palbociclib, a Cyclin-Dependent Kinase 4 and 6 inhibitor (CDK4/6i) now approved in United States in combination with letrozole for the treatment of postmenopausal women with ER+, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease based on the results of a phase II Paloma-1 study (Finn 2015). Recently, palbociclib in combination with an AI was approved in EU in the similar population based on the phase 3 Paloma- 2 study (Finn 2016) in which the addition of palbociclib to letrozole resulted in a median PFS of 24.8 months vs 14.5

[redacted]

months in letrozole alone. Furthermore, a Phase III study of palbociclib in combination with fulvestrant in second line HR+ mBC patients (Paloma-3) demonstrated significant improvement in PFS versus fulvestrant alone (9.5 months vs 4.6 months) (Cristofanilli 2016). Ribociclib is another CDK 4/6 inhibitor, recently approved in both United States and Europe in HR+, HER2-negative post-menopausal patients with advanced breast cancer. MONALEESA-2, a Phase III study of ribociclib in combination with letrozole in the first line aBC setting met its primary endpoint early at a pre-defined interim efficacy analysis, demonstrating a statistical and clinically meaningful benefit in PFS with the combination compared with letrozole alone (Hazard Ratio=0.556; 95% CI, 0.429, 0.720; p=0.00000329x 10^6) (Hortobagyi 2016). Recent updates demonstrated continued benefit for patients with combination with PFS at 25.3 months compared with 16.0 months in letrozole alone group (Hazard Ratio=0.568; 95% CI,0.457-0.704; p=9.63x10-8) (Hortobagyi 2017).

Another CDK4/6 inhibitor, abemaciclib, also demonstrated clinical efficacy in same population in MONARCH-3 study, results showed a statistical and clinical meaningful improvement in PFS with combination arm with anastrozole or letrozole compared with letrozole alone (Hazard Ratio= 0.54, 95% CI, 0.41-0.72, p=0.000021) (Goetz 2017). Abemaciclib with Monarch -2 results also received FDA approval in post progression population on neoadjuvant/adjuvant or while post first line metastatic setting on endocrine therapy in combination on continuous daily dosing with fulvestrant 500 mg showing extended PFS benefit versus fulvestrant alone (median, 16.4 vs. 9.3 months; Hazard Ratio 0. 553; 95% CI, 0.449 to 0.681; p <0.001) (Sledge 2017).

1.1.2 Treatment options for HR+, HER2- negative premenopausal aBC

In premenopausal patients without previous exposure to an antiestrogen, initial treatment of advanced/metastatic disease involves the use of a selective ER modulator alone or ovarian suppression/ablation plus endocrine therapy as for postmenopausal women. Tamoxifen is approved for the treatment of metastatic breast cancer in this population, which works by blocking the ER in the breast cancer cells, thereby preventing estrogen from binding. In women < 40 years of age with HR+ breast cancer, 5 years of adjuvant tamoxifen, with or without ovarian suppression, is considered the standard endocrine treatment and remains the first choice for endocrine therapy in the metastatic setting as well (Christinat 2013). Tamoxifen may be given either alone or in combination with an ovarian function suppression (OFS) agent, such as goserelin or leuprolide, as approved agents for the palliative treatment of pre- and perimenopausal advanced breast cancer [Zoladex® or Lupron® Prescribing Information]. These agents may function through different pathways (those of estrogen withdrawal and estrogen receptor blockade, respectively), which might target different cell populations and suppress the tamoxifen-induced stimulation of the pituitary-ovarian function and act in a similar way to an oophorectomy (Davidson 2000).

In premenopausal women who received a prior endocrine therapy within 12 months, the preferred therapy involves ovarian ablation or suppression + endocrine therapy - such as aromatase inhibitors (AIs) as for post-menopausal patients (NCCN 2017). Based on the clinical benefit shown in postmenopausal patients, AIs in combination with ovarian function suppression (OFS) have been investigated in premenopausal patients with breast cancer in neoadjuvant, adjuvant and advanced settings. Although data are limited (Montagna 2013), clinical benefit of the combination of AIs and OFS agents in premenopausal women with

[redacted]

advanced ER+ breast cancer has been shown in small phase II studies with letrozole and anastrozole. Clinical guidelines have been updated to include treatment of pre-menopausal women as in parallel or similar with postmenopausal women with AI in combination with OFS agents as standard of care.

1.1.3 PI3K pathway

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

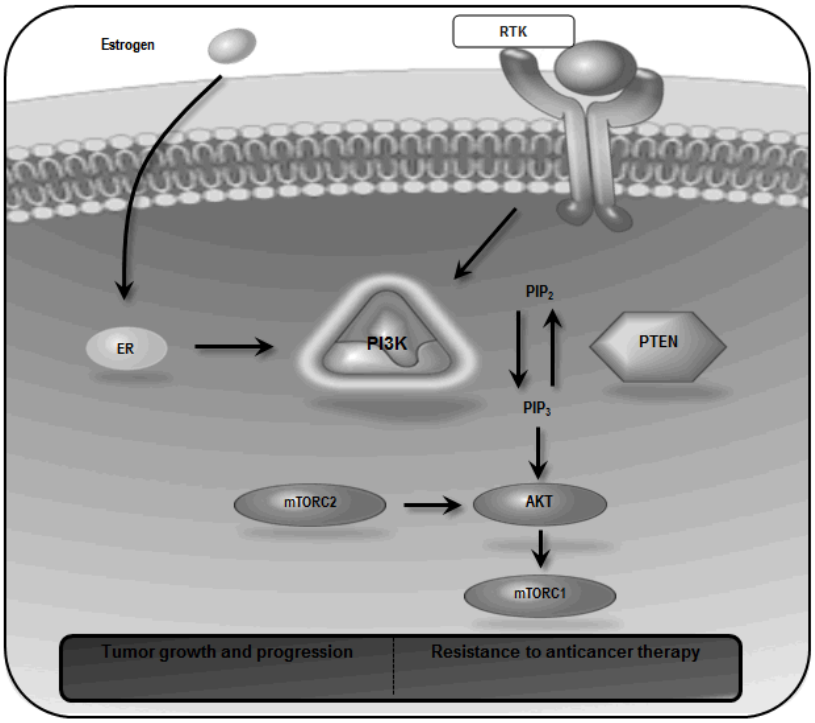
Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to:

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

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

[redacted]

Figure 1-1 Schematic representation of the PI3K pathway



Somatic missense mutations of PIK3CA that increase the kinase activity of PIK3α protein have been identified in tumor tissues and have been linked to cellular transformation in many different human cancers (Samuels 2004). The majority of somatic mutations were identified in mutational hotspots affecting the helical (exon 9) and kinase (exon 20) domains of the protein (Karakas 2006). However, some mutations were also identified in other domains of PI3K, such as the C2 domain (Bader 2005; Samuels 2004). Mutations affecting the helical or kinase domains were shown to enhance PI3K lipid kinase activity, to up-regulate the pathway downstream (increasing intracellular levels of phospho-Akt (Protein Kinase B) and phospho-S6), to drive cellular transformation *in vitro* and *in vivo*, and to enhance cell survival (Zhao 2008, Mankoo 2009). Mutations in the C2 domain were shown to induce or facilitate conformational changes leading to an increased activity of PI3Kα (Burke 2012, Hon 2012). Overall, the majority of gain-of function mutations identified in the PIK3CA gene were reported to occur in the mutational hotspots from exons 7, 9 and 20 which affect the C2, helical and kinase domains of PI3Kα respectively (Mankoo 2009).

1.1.4 PI3K pathway in HR+ breast cancer

The PI3K pathway is frequently altered in HR+ breast cancer. Gain-of-function mutations in PIK3CA have been observed in about up to 45% of HR+ breast cancer patients using next generation sequencing (NGS) approach (Table 1-1).

[redacted]

Table 1-1 PI3K signaling pathway mutations and alterations in breast cancer

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

Pre-clinical data suggest that the ER pathway interacts with the PI3K pathway with extensive crosstalk between ER and growth factor pathway (Miller 2011; Osborne and Schiff 2011).

For example, estrogen deprivation leads to hyperactivation of the PI3K/mTOR pathway, which induces in turn an increase in cell proliferation and survival (Bjornsti 2004; Crespo 2002; Huang 2004; Mita 2003; Wullschleger 2006). This mechanism is linked to de novo or acquired resistance to endocrine therapy (Campbell 2001), including AI resistance (Shoman 2005; Crowder 2009; Miller 2011). Treatment with PI3K inhibitors in absence of estrogen can inhibit proliferation of long term estrogen deprived cell lines supporting the concept of using combination of a PI3K inhibitor with an endocrine therapy in breast cancer.

More specifically, inhibition of the PI3K pathway has been shown to induce a unique synthetic lethality in the context of estrogen deprivation (Crowder 2009).

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of letrozole

Letrozole (Femara®) is a nonsteroidal competitive inhibitor of the aromatase enzyme system with demonstrated efficacy in the treatment of postmenopausal patients with HR+ breast cancer. Letrozole acts by inhibiting in a highly selective fashion the conversion of adrenal androgens to estrogens, which is the primary source of estrogens in postmenopausal women. Letrozole is a highly selective inhibitor of aromatase that induces a 75% to 95% decrease of estrogen levels after two weeks of treatment using daily doses of 0.1 to 5 mg, with no significant clinical and laboratory toxicities nor changes in levels of other hormones of the endocrine system as shown in early phase I (Lipton 1995; Trunet 1996). Letrozole was compared with tamoxifen in a phase III trial in the first line setting in ER+/HER2+ breast cancer. Letrozole was superior to tamoxifen for time to progression (median, 9.4 vs 6.0 months) and median OS was longer for letrozole (median, 34 vs 30 months) but this difference was not statistically significant (Mouridsen 2001). Letrozole is indicated for the treatment of advanced HR+ breast cancer, both in the first -line setting as well as in patients who have disease progression following anti-estrogen therapy. It is also indicated for the adjuvant treatment of women with HR+ early breast cancer as well as the extended adjuvant treatment of patients who have received 5 years of tamoxifen therapy.

The most frequently reported adverse events that were significantly different from placebo for letrozole in the adjuvant and extended adjuvant setting include hot flashes, arthralgia/arthritis and myalgia. In the first line setting, the most frequently reported adverse events include musculoskeletal pain (bone/back pain and arthralgia), hot flashes, nausea and dyspnea and

[redacted]

incidences of adverse events were similar for tamoxifen in this setting. In general, the observed adverse reactions are mild to moderate in nature [Femara® Prescribing Information, Novartis].

1.2.1.1 Clinical pharmacokinetics of letrozole

Letrozole is administered orally once daily at a dose of 2.5 mg and is rapidly and completely absorbed from the gastrointestinal tract. Concomitant intake of food has no effect on the extent of letrozole absorption and only a minor effect on the rate of absorption, which is considered to be of no clinical relevance. The terminal elimination half -life of letrozole is 2 days and steady-state plasma concentration with daily dosing at the standard dose is reached in 2-3 weeks. Letrozole is metabolized via CYP3A4 to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance.

For further details, please refer to the latest [Femara® Prescribing Information, Novartis].

1.2.2 Overview of fulvestrant

Fulvestrant (Faslodex®) is the first-in-class unique ER down regulator with no known agonist effects (Addo 2002). In fact, the fulvestrant mechanism of action is distinct from other endocrine agents (Wakeling 2000); it binds, blocks and, unlike tamoxifen or other SERMs, degrades the ER and completely inhibits ER signaling. As a result, there is less chance of the ER being activated by alternative pathways that are believed to cause resistance (e.g. growth factor–mediated mechanisms) (Nicholson 2005).

Fulvestrant is approved for the treatment of HR+ mBC in postmenopausal women with disease progression following anti-estrogen therapy (USA, Europe). However, current clinical practice and treatment guidelines also include fulvestrant as treatment option for postmenopausal women without symptomatic visceral disease after recurrence or progression to an AI (NCCN 2017).

The most common clinically significant adverse reactions occurring in ≥5% of patients receiving fulvestrant 500 mg were: injection site reactions, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation. Pooled safety analysis (SmPC) identified Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) or alkaline phosphatase increases in approximately 15% of the treatment population with grade 3 increases seen in 1-2%. There was no difference in rates of AST, ALT and AP elevations between groups treated with 250 mg and 500 mg doses. For further details please refer to the latest [Faslodex® Prescribing Information].

The phase III FALCON trial demonstrated superior median PFS for fulvestrant 500 mg q.d. compared to anastrozole 1 mg in the 1st line treatment of postmenopausal women with locally-advanced or metastatic breast cancer, who have not had prior hormonal treatment for hormone receptor positive (HR+) breast cancer. The results show that the median PFS was 2.8 months longer with fulvestrant than anastrozole (Hazard ratio 0.797; 95% Confidence Interval (CI): 0.637-0.999; p=0.0486). The median PFS was 16.6 months in the fulvestrant arm, compared with 13.8 months in the anastrozole arm. The most commonly reported adverse events in the fulvestrant and anastrozole arms were arthralgia (16.7% vs 10.3%), hot flashes (11.4% vs

[redacted]

10.3%), and nausea (10.5% vs 10.3%), respectively (Robertson 2016). Fulvestrant has since (2017) received approval for first line indication in the US and Europe.

1.2.2.1 Clinical pharmacokinetics of fulvestrant

The recommended dose (intramuscular injection) is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose. Fulvestrant is slowly absorbed reaching maximum plasma concentrations after about 5 days. Steady-state is achieved within the first month of dosing. The terminal half-life after intramuscular administration is governed by the absorption rate and was estimated to be 40-50 days. An *in vitro* inhibition study showed no relevant inhibition of CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. CYP3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant; however, non-P450 routes appear to be more predominant *in vivo* as interaction studies with rifampicin (CYP3A4 inducer) and ketoconazole (CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics. The relative contribution of P-450 and non-P-450 routes *in vivo* is unknown [Faslodex® Prescribing Information]. The potential for interaction with fulvestrant therefore appears to be low.

Increased exposure to fulvestrant was observed in patients with moderate hepatic impairment (Child-Pugh class B); therefore a dose of 250 mg is recommended in these cases. Fulvestrant has not been administered to patients with severe hepatic impairment (Child-Pugh class C). For further details on clinical pharmacokinetics of fulvestrant, please refer to the latest [Faslodex® Prescribing Information].

1.2.3 Overview of LHRH agonists

Luteinizing Hormone-Releasing Hormone (LHRH) or Gonadotropin Releasing Hormone (GnRH) agonists are synthetic analogues of gonadotropin-releasing hormone that by continuous stimulation of the GnRH receptor achieve desensitization of the pituitary gland to LHRH. LHRH agonists differ from the naturally-occurring LHRH by modification(-s) in the decapeptide structure (usually by amino acid substitution in position 6, but also in positions 9 and 10) to decrease degradation of the molecule. LHRH agonists allowed for use in this study are goserelin or leuprolide. However, one-month depot formulation of LHRH agonists must be used to suppress ovarian function in premenopausal women throughout this study as the 3-month depot formulations do not reliably suppress estrogen levels in all patients (Gradishar 2016).

The most common AEs occurring in women treated with LHRH agonists included hot flashes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea and peripheral edema.

The most common AE occurring in men treated with LHRH agonists include a transitory elevation in testosterone levels can occur in men after the first few doses, followed by the expected decrease of these hormonal levels; as a result, the most commonly observed adverse reactions, which occurred in at least 1 out of 10 men (10%) who participated in clinical trials, are hot flashes, sexual dysfunction, decreased erections and lower urinary tract symptoms (for example, urinary urgency, cystitis, blood in your urine). Some patients may experience a temporary increase in bone pain.

[redacted]

Refer to the most recent regional prescribing information and/or clinical guidelines for more information on [Zoladex® and Lupron® prescribing information].

1.2.4 Overview of alpelisib

Alpelisib is an oral class I α-specific PI3K inhibitor belonging to the 2-aminothiazole class of compounds. Alpelisib strongly inhibits the PI3Kα isoform (both p110α wild-type and p110α mutation+) and much less strongly the β, δ and γ isoforms. It is inactive against the majority of other kinases (Fritsch 2014).

Alpelisib has demonstrated anti-tumor activity in preclinical *in vitro* and *in vivo* tumor models. *In vitro*, alpelisib has been shown to preferentially inhibit the proliferation of cell lines harboring PIK3CA mutations (Fritsch 2014). *In vivo*, alpelisib has demonstrated dose-dependent tumor growth inhibition in various subcutaneous tumor transplant models.

For further details on clinical and non-clinical experience, please refer to the latest version of [Alpelisib Investigators Brochure].

1.2.4.1 Non-clinical experience

1.2.4.1.1 Pharmacodynamics of alpelisib

Alpelisib shows significant preclinical antitumor activity. In biochemical assays, alpelisib inhibits p110α (inhibitor concentration causing half maximal inhibition [IC50]=4.6 nM) much more potently than the p110δ and γ isoforms and PIK4β and has weak or no activity against p110β, Vps34 and mTOR. Alpelisib is equipotent against the most common somatic mutations of p110α (H1047R, E545K) compared to wild type p110α, and is selective against a wide range of protein kinases with at least a 50-fold selectivity window compared to p110α. The potency and selectivity of alpelisib is confirmed at the cellular level in mechanistic and relevant tumor cell lines. Alpelisib potently inhibits p110α cellular activity (IC50=74 nM) and shows significant selectivity against the p110β and p110δ isoforms (above 15-fold). Alpelisib is not interfering with phosphoinositol 3-kinase-related- kinases (PIKKs) involved in DNA-damage repair processes (IC50> 30μM on S15P-p53 and IC50> 10μM on S1981P-ataxia-telangiectasia mutation [ATM]). In vitro, alpelisib inhibits the phosphorylation of PI3K downstream targets and the proliferation of various cancer cell lines, and showed increased activity in cell lines harboring gene alterations in PIK3CA. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in *in vitro* and *in vivo* models.

In multiple cancer indications, including breast cancer, alpelisib inhibited the phosphorylation of PI3K downstream targets, including Akt and showed activity in cell lines harboring a PIK3CA mutation. In vivo, alpelisib inhibited the PI3K/Akt signaling pathway and reduced tumor growth in xenograft models, including models of multiple cancer indications, including breast cancer. More detailed information on the pharmacology of alpelisib, single and multiple dose pharmacokinetic (PK) studies conducted in multiple species and nonclinical safety evaluations, is provided in the [Alpelisib (BYL719) Investigator's Brochure].

[redacted]

1.2.4.1.2 Nonclinical PK and metabolism of alpelisib

Alpelisib demonstrates low plasma clearance, a moderate volume of distribution (Vss) at steady state and a good absolute oral bioavailability in all preclinical species tested. The compound is moderately bound to plasma proteins with no major species difference and this binding is independent of the concentration (free fraction in human plasma ~ 10.8%). Alpelisib showed a rapid distribution to almost all rat tissues, except the brain (rat Absorption Distribution Metabolism and Excretion (ADME) study). Results from 4-week Good Laboratory Practice (GLP) toxicology studies in dogs showed a roughly dose-proportional increase in exposure, while in rats the exposure increased up to a dose of 30 mg/kg beyond which no further increase was noted following single dose administration. The toxicology studies provided no clear evidence of increase in exposure following multiple dosing. No gender differences in exposure were observed in rats or dogs.

In vitro metabolism and transport

The overall metabolic turnover of alpelisib was very low in dog and human hepatocytes (as well as microsomes) and slightly higher in the rat. CYP3A4 was found to be the major P450 enzyme involved in hepatic oxidative metabolism *in vitro* with small contribution by other enzymes. While UGT phenotyping showed that UGT1A9 could be involved in the glucuronidation of alpelisib in human liver microsomes, the turnover rate of phase II metabolism in vitro was very low. No covalent drug protein adduct formation was noted in human microsomes or hepatocytes. The main biotransformation pathway that was observed consistently *in vitro* and *in vivo* (see below) across species was amide hydrolysis to BZG791, a pharmacologically inactive product which – based *on vitro* experiments – can be produced both chemically and enzymatically by ubiquitously expressed, high-capacity enzymes (esterases, amidases, choline esterase) unlikely to become fully inhibited by drug interactions.

Alpelisib was found to be a time-dependent inhibitor of CYP3A4 (Ki 5.6 µM, Kinact 0.011 min-1). Reversible inhibition of CYP2C8 (Ki 32 µM = 14 µg/ml), CYP2C9 (Ki 22 µM = ~10 µg/ml) and CYP2C19 (IC50 75 µM) was also observed. Alpelisib may inhibit metabolic clearance of co-medications metabolized by CYP3A4, CYP2C8, CYP2C9 and CYP2C19, if sufficiently high concentrations are achieved in vivo. A risk assessment based on the mechanistic static model (or a "net effect model") (Fahmi 2008), assuming a very sensitive substrate (fm =1) and no gut metabolism (Fg = 1), predicted an AUCR to be <1.1 with the lowest measured Ki for CYP2C9 at the calculated unbound hepatic inlet concentration (1.2 µM) at MTD level dose. Hence it is unlikely that inhibition of CYP2C9 or other CYP2C-family enzymes, which showed an even less inhibitory potential, translates into a clinical relevant interaction.

While clinically significant pregnant X receptor-(PXR)-mediated induction of CYP3A4 or aromatic hydrocarbon receptor-mediated induction of CYP1A2 by alpelisib has not been expected based on the negative result from in vitro nuclear activation assays, there has been recent growing evidence from a hepatocyte induction assay that alpelisib can induce CYP3A4 (EC50 = 1.7 µM, Emax = 0.83 relative to RIF control), likely via activation and crosstalk with the constitutive androstane receptor (CAR) receptor. Based on preliminary clinical data from the study investigating the combination of alpelisib with the CYP3A4 sensitive substrate everolimus [CBYL719Z2102] which showed no increase of everolimus exposure after

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concomitant administration with alpelisib at steady state, as well as physiologically-based pharmacokinetic (PBPK) modelling of alpelisib using SimCyp, time-dependent inhibition and induction of CYP3A4 by alpelisib seem to result in a neutral net effect *in vivo* at clinically relevant exposures.

Alpelisib is a substrate of Breast Cancer Resistance protein (BCRP) and has low affinity for P-glycoprotein (P-gp/MDR1). Alpelisib does not inhibit BCRP or Multi-drug resistance protein-2 (MRP2), but showed very weak inhibition of P-gp (IC50 = 97 µM). As the maximal inhibition of P-gp was only about 32% with respect to positive control, the overall interaction potential is expected to be low. Uptake of alpelisib in human hepatocytes was not influenced by inhibitors of the transporter families organic cation transporter (OCT), organic anion transporter (OAT), organic anion-transporting polypeptide (OATP) and sodium taurocholate co-transporting polypeptide (NTCP). Assessment of the hepatobiliary disposition mechanisms of alpelisib in sandwich cultured rat and human hepatocytes showed that it is actively transported into bile pockets.

Disposition of alpelisib

Elimination of alpelisib *in vivo* - at the current stage of knowledge - appears to be a three-parted pathway consisting of CYP450-mediated oxidative metabolism, hydrolysis to BZG791 (enzymatic or chemical, currently unknown) and biliary elimination. Recent results from human ADME trial [CBYL719X2107] have shown that the contribution of oxidative metabolism to the overall clearance of alpelisib can be considered minor, in line with *in vitro* metabolism results. The main circulating metabolite in human plasma was BZG791 which represented on average 21.4% of the Area Under the Curve 0-6h (AUC0-6h) (proportionately higher than in rat and dog). Other circulating metabolites (oxidative metabolite M3 and N-glucoronide M12) were considered minor, as they represented only 0.03% and 1.89% of total radioactivity in the plasma of one out of four subjects but were below the limit of quantification in the other subjects. Alpelisib and identified metabolites represented on average 94% of the plasma AUC0-6h. In terms of excretion the bulk of the dose was excreted in feces (78.8% of the dose) and urine (13.1 % of the dose) with only ~2% of unchanged alpelisib in urine indicating the renal clearance is negligible. In excreta (urine and feces combined), alpelisib represented 37.8% of the administered dose, BZG791 represented 39.1%. Biliary excretion has been also previously been demonstrated in a rat excretion study showing that 25% of the dose of [14C]-alpelisib was excreted in feces with 40% of the dose being found unchanged in bile. As alpelisib is a substrate for human BCRP *in vitro* there is strong evidence for a hepatobiliary excretion, which is also supported by rat and human sandwich-cultured hepatocyte experiments.

For further details on nonclinical PK and metabolism experience, please refer to the latest version of [Alpelisib Investigators Brochure].

1.2.4.1.3 Safety pharmacology and toxicology of alpelisib

PI3 kinase is involved in various cellular processes such as proliferation, metastasis, or energy metabolism. Therefore, it is not unexpected to observe toxic effects when cellular test systems or animals are exposed to an inhibitor of this pathway. In accordance with current guidance, repeated-dose toxicity studies were conducted up to 13 weeks of duration, using a daily oral treatment. In the 4- and 13-week studies, reversibility of toxicity findings was assessed for a 4-

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week treatment-free recovery period (8 weeks in the 13-week rat study). This package was complemented by *in vitro* and *in vivo* safety pharmacology studies to investigate effects on respiratory, neuronal and cardiovascular functions, an ICH-compliant genotoxicity battery and the evaluation of a phototoxic potential *in vitro*.

Alpelisib was relatively well tolerated in the 4- and 13-week repeated-dose toxicity studies at exposure levels at which tumor growth control was achieved in mouse or rat tumor models. Alpelisib affected rapidly dividing tissues which only resulted in pharmacologically relevant observations in the animals exposed to an alpelisib dose close to or at MTD. The most frequently affected organs were the bone marrow and lymphoid tissue (spleen, thymus), the epithelia of the alimentary tract, while other tissues like the vagina and uterus in rats, or prostate in dogs were also affected at higher doses.

Abnormal clinical chemistry and histopathology (pancreatic islets) findings indicated an altered glucose metabolism, correlating with a clear effect towards insulin insensitivity. In both rats and dogs, histopathology and clinical pathology findings were generally observed at higher doses that were also associated with reduced body weight development (in the growing animals) and reduced food intake. All toxic events were reversible or showed a tendency to reversibility after a 4-week or 8-week treatment-free recovery period.

Cardiac safety studies, conducted *in vitro* and *in vivo*, did not indicate an electrophysiological risk. Furthermore, alpelisib in the rat safety pharmacology studies showed no effect on neuronal or pulmonary function, and no evidence of a phototoxic potential was found in a 3T3 neutral red uptake test *in vitro*.

The majority of the observed toxicological effects of alpelisib were related to the pharmacological activity of alpelisib as a p110α specific inhibitor of PI3K pathway, such as an influence on insulin (and potentially glucose) homeostasis and the risk of increased blood pressure. The pharmacologically relevant toxicity was mainly observed at dosages close to or at MTD with the bone marrow and lymphoid tissue, pancreas, and some reproductive organs of both genders being the main target organs of the toxic effects.

For further details on safety pharmacology and toxicology experience, please refer to the latest version of [Alpelisib Investigators Brochure].

1.2.4.1.4 Genotoxicity status of alpelisib and metabolites

There is no evidence of a potential to induce reverse gene mutations or numerical or structural chromosome aberrations was seen for alpelisib.

For further details on genotoxicity data, please refer to the latest version of [Alpelisib Investigators Brochure].

1.2.4.2 Clinical experience

As of the cut-off date of 23-May-2022, a total of 2566 patients (including cancer patients, hepatic impaired subjects, healthy volunteers, and Patient Reported Outcomes (PROS)) had been exposed to alpelisib across 42 Novartis sponsored studies with alpelisib as a single agent or in combination (everolimus, everolimus + exemestane, MEK162, LGX818, LJM716, ribociclib, imatinib, trastuzumab emtansine (T-DM1), pertuzumab, olaparib), endocrine

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therapy (e.g. fulvestrant, letrozole) or chemotherapy (e.g. sb-paclitaxel, nab-paclitaxel, AUY922, AMG479, cetuximab, INC280, LDK378, LSZ102, BGJ398, tamoxifen-goserelin).

Alpelisib (Piqray®) was first approved on 24-May -2019 in the United States and is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative PIK3CA mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. On 27-Jul-2020, the European Medicines Agency (EMA) approved alpelisib in combination with fulvestrant for the treatment of 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 as monotherapy.

These approvals were based on the primary efficacy results of CBYL719C2301 (SOLAR-1) a Phase III, randomized, multicenter, double-blind, placebo-controlled, study that met its primary endpoint in patients with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation with a statistically significant and clinically meaningful improvement in PFS in favor of the alpelisib plus fulvestrant arm (Hazard Ratio=0.65, 95% CI: 0.50, 0.85, p=0.00065, one-sided) (cut-off date of 12-Jun-2018). Median PFS was prolonged by 5.3 months, from 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm to 11.0 months (95% CI: 7.5, 14.5) in the alpelisib plus fulvestrant arm. No clinically meaningful PFS benefit was observed in patients whose tumors did not have a PIK3CA tissue mutation (Hazard Ratio = 0.85; 95% CI: 0.58, 1.25).

The OS analysis for SOLAR-1 study was conducted, with cut-off date of 23-Apr-2020, based on 181 deaths. While the OS results did not cross the prespecified efficacy boundary, there was a clinically relevant improvement in OS of 7.9 months for patients with a PIK3CA mutation taking alpelisib plus fulvestrant compared to placebo plus fulvestrant (median OS 39.3 months vs. 31.4 months; this result did not reach the pre-specified threshold of statistical significance (one-sided $p \leq 0.0161$); Hazard Ratio=0.86; 95% CI: 0.64-1.15; p=0.15).

With a median follow-up of 42.4 months, the safety profile remains consistent with that previously reported based on the latest safety analysis for SOLAR-1 study (cut-off date of 23-Apr-2020). All grade AEs were reported in ≥ 20% of participants in the alpelisib plus fulvestrant treatment arm were hyperglycemia (65.8%), diarrhea (59.5%), nausea (46.8%), decreased appetite (36.3%), rash (51.8%), vomiting (28.5%), weight decreased (27.8%), fatigue (43.7%) (also includes asthenia), stomatitis (30.3%), and alopecia (20.4%). Grade ≥ 3 AEs in≥5% of patients were hyperglycemia (37%), rash (9.9%), maculo-papular (8.8%), diarrhea (7%), and weight decreased (5.3%). No Grade 4 diarrhea or rash was reported in the study. Less commonly reported, but clinically important, adverse reactions were pneumonitis, severe hypersensitivity and severe cutaneous reactions. More detailed information regarding alpelisib is available in the [Alpelisib (BYL719) Investigator's Brochure], Piqray® USPI and SmPC.

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Alpelisib has been investigated both as a single agent and as combination therapy in 42 Novartis sponsored clinical studies and as of 23-May-2022; 25 studies have been completed and 17 studies are ongoing. The safety profile of alpelisib is well characterized and manageable with generally reversible AEs. More detailed preclinical and clinical information is provided in the [Alpelisib (BYL719) Investigator's Brochure].

1.2.4.3 Clinical pharmacokinetics

The pharmacokinetics of alpelisib has been studied in healthy volunteers and adult patients with solid tumors. Steady-state alpelisib maximum plasma concentration (Cmax) and AUC increased proportionally over the dose range of 30 mg to 450 mg (0.1 to 1.5 times the approved recommended dosage) under fed conditions. The mean accumulation of alpelisib is 1.3 to 1.5 fold and steady-state plasma concentrations are reached within 3 days following daily dosage. In adult subjects who received alpelisib 300 mg once daily in the SOLAR-1 trial, mean steady-state alpelisib [coefficient of variation (CV%)] Cmax was 2480 (23%) ng/mL and AUC0-24hr was 33224 (21%) ng*h/mL based on a population PK approach. The median time to reach peak plasma concentration (Tmax) ranged between 2.0 to 4.0 hours. The half-life of alpelisib is predicted to be 8 to 9 hours. The mean (%CV) clearance of alpelisib is predicted to be 9.2 L/hr (21%) under fed conditions.

A high-fat high-calorie meal (985 calories with 58.1 g of fat) increased alpelisib AUC by 73% and Cmax by 84%, and a low-fat low-calorie meal (334 calories with 8.7 g of fat) increased alpelisib AUC by 77% and Cmax by 145% following a single dose of alpelisib. No clinically significant differences in alpelisib AUC were observed between low-fat low-calorie and high-fat high-calorie meals. Alpelisib can be co-administered with acid reducing agents, as long as it is taken after food, since food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH.

Alpelisib is primarily metabolized by chemical and enzymatic hydrolysis to form its metabolite BZG791 and to a lesser extent by CYP3A4 in vitro. Following a single oral dose of 400 mg radiolabeled alpelisib under fasted condition, 81% of the administered dose was recovered in feces (36% unchanged, 32% BZG791) and 14% (2% unchanged, 7.1% BZG791) in urine. CYP3A4-mediated metabolites (12%) and glucuronides amounted to approximately 15% of the dose. Excretion of unchanged alpelisib occurs primarily via hepatobiliary export and/or intestinal secretion of alpelisib. As alpelisib is a substrate of BCRP, its elimination may be affected when co-administered with BCRP inhibitors.

Alpelisib inhibits CYP3A4 in a time-dependent manner and induces CYP2B6, CYP2C9 and CYP3A4 *in vitro*. Alpelisib is an inhibitor of P-gp. No clinically significant differences in pharmacokinetics of everolimus (a substrate of CYP3A4 and P-gp), however, were observed when coadministered with alpelisib. Alpelisib has a low potential to inhibit BCRP (Breast Cancer Resistance Protein), MRP2, BSEP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1, and MATE2K at clinically relevant concentrations.

For further details on clinical pharmacokinetics, please refer to the latest version of [Alpelisib Investigators Brochure].

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Consideration of gender effect

The impact of gender on the pharmacokinetics of alpelisib was evaluated with a population PK approach. Due to the SOLAR-1 study enrolling primarily females (one male was randomized), this assessment was based on the Phase I population PK model. The analysis included 52 (21.2%) males and 193 (78.8%) females from Phase I studies CBYL719X1101 (in patients from Japan with advanced solid tumors) and CBYL719X2101 (as a first-in-human dose escalation and expansion study) single agent and fulvestrant combination data. In the final model, males had a 35% higher clearance (CL) compared to females, leading to a reduction in AUC by ~25% compared to a female with the same covariates. While exposure-response analysis in PIK3CA-mutant, ER-positive, HER2-negative metastatic breast cancer indicated relationships between exposure (PK exposure and dose intensity) and safety (hyperglycemia, rash) and efficacy (PFS), the clinical impact of the difference in males is difficult to assess at present, given the magnitude of the change and the observed intra-subject (intra-CV% ~30%) and inter-subject variability (~20%) in cancer patients as well as limited data in the male population.

1.2.5 Overview of the combination of alpelisib and endocrine treatments

Pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy. *In vitro* combination of letrozole or fulvestrant with alpelisib in a PIK3CA mutant cell line of ER+ breast cancer (MCF7) displays synergy (O'Brien 2014) in line with the concept of synthetic lethality seen previously when PI3K was inhibited in an estrogen deprived cell line (Crowder 2009). For further details on preclinical experience, please refer to the latest version of [Alpelisib Investigators Brochure].

1.2.5.1 Clinical experience with alpelisib and aromatase inhibitors in mBC

A completed investigator initiated trial (IIT), phase Ib (n=26) assessed the combination of alpelisib + letrozole in previously treated HR+ HER2-negative metastatic breast cancer patients. All the patients were pretreated with AI, 18 patients received endocrine therapy and 8 of them received chemotherapy in the metastatic setting, respectively. The RP2D of alpelisib in combination with letrozole was established as 300 mg/d q.d. Most common Grade 3 AEs at this dose were hyperglycemia, diarrhea (12% each), and transaminitis (6%). Overall, 5 PRs (19%) were reported, with SD in 12 (46%) patients. Six out 9 patients on treatment for ≥ 6 months had a PIK3CA mutant breast cancer, though clinical activity was not restricted to patients with PIK3CA mutant tumors alone (Mayer 2016).

Another IIT phase Ib trial of alpelisib plus letrozole or exemestane in HR+ HER2-negative metastatic breast cancer patients has been recently presented. Starting dose for alpelisib was selected at 300 mg q.d. Maximum Tolerated Dose (MTD) has not been determined for continuous dosing schedule (2/7 Dose Limiting Toxicities (DLTs) grade 3 rash observed). Common Grade 1 or 2 AEs included rash, hyperglycemia, mucositis, diarrhea, anorexia and abdominal pain. Grade 3 or 4 AEs included rash and hyperglycemia. With 10 patients evaluable for response (7 PIK3CA mutant and 3 wild-type), 1 confirmed PR (in a mutant patient) and 7 SD were observed (5 mutant and 2 wild-type) (Shah 2014).

[CLEE011X2107] is a phase Ib/II study investigating in three arms the combination of LEE011 (CDK4/6 inhibitor) and letrozole, alpelisib and letrozole, and LEE011 plus alpelisib and

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letrozole in adult patients with advanced HR+ HER2-negative MBC. Data from 17 patients have been reported, 7 of whom received alpelisib 300 mg q.d. (starting dose) + letrozole 2.5 mg. In alpelisib plus letrozole arm 2 DLTs (Grade 2 hyperglycemia) were observed and the most common of all grade AEs were hyperglycemia (57%), nausea (43%), decreased appetite (43%) and diarrhea (43%) (Munster 2014).

1.2.5.2 Experience with alpelisib and fulvestrant in mBC

The combination of alpelisib with fulvestrant was investigated as part of study [CBYL719X2101] in 87 patients with heavily pre-treated HR+ mBC in two groups: patients with mutated PIK3CA (52 patients, 59.8%) and patients with wild-type PIK3CA (33 patients, 37.9%). For two patients (2.3%), PIK3CA mutational status was unknown. The MTD was declared at alpelisib 400 mg QD and fulvestrant 500mg q28 days, with DLTs in 4 patients (diarrhea, vomiting, decreased appetite, abdominal, distension and fatigue). Also alpelisib doses of 350 mg and 300 mg QD were investigated and mainly 300 mg QD emerged as the best tolerated dose in this combination. Overall, the most frequent AEs (>20%), regardless of grade, causality and alpelisib dose, suspected of being drug related were diarrhea (56.3%), nausea (42.5%), hyperglycemia (48.3%), decreased appetite (37.9%), fatigue (29.9%), vomiting (25.3%), stomatitis (27.6%) and fatigue (29.9%). Preliminary clinical efficacy of alpelisib + fulvestrant was demonstrated across all dose levels. Best overall response (BOR) achieved was confirmed PR for 13 (26.5%) patients and SD for 26 (53.1%) patients with PIK3CA mutant tumors versus PR for 0 (0%) patient and SD for 15 (46.9%) patients with PIK3CA non-mutant tumors. Disease control rate was 79.6% (95% CI: 65.7–89.8) and 46.9% (95% CI: 29.1–65.3) in the PIK3CA mutant and PIK3CA non-mutant groups, respectively. Estimated median PFS was longer in the PIK3CA mutant group vs PIK3CA non-mutant group (9.1 months vs 4.7 months). Overall, 7 patients are still on treatment in this study (2 on alpelisib as single agent, 5 receiving alpelisib with fulvestrant (Juric 2016). This data led to a design of phase III randomized, double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor (AI) treatment [SOLAR-1, [CBYL719C2301].

For further details on clinical experience, please refer to the latest version of [Alpelisib Investigators Brochure].

1.2.6 Potential for drug interactions

1.2.6.1 Potential overlapping toxicities

Based on the fulvestrant prescribing information and current compound and class related risks identified for alpelisib, the following overlapping toxicities might occur:

- Nausea, vomiting, diarrhea
- Skin alterations/rash.

For further details on clinical safety, please refer to the latest version of [Alpelisib Investigators Brochure].

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1.2.6.2 Low Potential for drug-drug interactions with fulvestrant

The potential for a DDI between fulvestrant and co-administered drugs is considered to be low. There are no known drug interactions with fulvestrant. *In vitro* studies showed no relevant inhibition of the major CYP enzymes, including CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. The lack of inhibition of CYP3A4 was confirmed in an *in vivo* interaction study with midazolam. In addition, interaction studies with rifampicin (strong CYP3A4 inducer) and ketoconazole (strong CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics. Therefore, a DDI involving fulvestrant and alpelisib are unlikely to occur [Faslodex® Prescribing Information].

1.2.6.3 Low Potential for drug-drug interactions with letrozole

The potential for a drug-drug interaction between letrozole and co-administered drugs is considered low. There are no known drug interactions with letrozole.

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to assess the efficacy and safety of treatment with alpelisib plus endocrine therapy (either fulvestrant or letrozole) in patients with HR+, HER2-negative aBC, harboring PIK3CA mutations, whose disease has progressed on or after prior treatments.

As described above, promising pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with endocrine therapy, in particular fulvestrant (O'Brien 2014). Clinical activity has been observed when single agent alpelisib was given in heavily pre-treated ER+ (mBC) patients and also when alpelisib was given in combination with fulvestrant or AI to HR+, HER2-negative mBC patients (Janku 2014; Mayer 2016).

In HR+ BC, alpelisib has shown synergistic antitumor effects when used with endocrine therapy (e.g. letrozole). Clinical activity was observed independently of PIK3CA mutation status although clinical benefit was seen in a higher proportion of patients with PIK3CA mutated tumors. Therefore, the results from this phase Ib investigator initiated trial (IIT), investigating the combination of alpelisib + letrozole in previously treated HR+, HER2-negative metastatic breast cancer (mBC) patients study provides evidence that alpelisib plus letrozole is safe, tolerable and active in post-menopausal patients with ER+/HER2-negative metastatic breast cancer refractory to endocrine therapy (Mayer 2016).

Additionally in the phase Ib B-YOND study [CBYL791XIC01], premenopausal women with advanced HR+ breast cancer were treated with alpelisib and buparlisib. Interim data from the study, in a small group of 16 patients alpelisib in combination with tamoxifen and goserelin achieved 44% clinical benefit rate with 7 (44%) achieving partial response per RECIST v1.1, as best overall response, and a generally manageable safety profile. This led to conclusion that these pathways should also be further explored in this pre-menopausal population (Lu 2017).

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Rationale for enrolling PIK3CA mutant patients

Up to 45% of HR+ BC present with a mutation in the PIK3CA gene, and thus these tumors may be particularly suited to treatment with the alpha specific PI3K inhibitor alpelisib. More specifically, about 30% of patients' tumors display a PIK3CA mutation identified as one of the most frequently reported hotspots. While PIK3CA mutant cell lines display an increased sensitivity to alpelisib treatment (Fritsch 2014), sensitivity to alpelisib in combination with fulvestrant was observed in PIK3CA mutant patients (see Figure 1-1, Section 1.2.4.1). Indeed, HR+ BC particularly if previously treated with endocrine agents - may display a dependency on the PI3K pathway that is independent of a PIK3CA mutation and hence confer a level of sensitivity to alpelisib in non-PIK3CA mutant BC tumors as well (Fritsch 2014).

Clinical data confirms a better outcome (i.e. response rate, clinical benefit rate, PFS) in PIK3CA mutant breast tumors when treated with alpelisib (either in monotherapy or combination with an endocrine agent) (Mayer 2014; Shah 2014; Janku 2014; Andre 2018). Overall, the current pre-clinical and clinical findings show an increased efficacy of the combination of alpelisib and fulvestrant in PIK3CA mutant HR+ BC patients.

The key purpose of this study is to evaluate the efficacy and safety of alpelisib in combination with an endocrine partner for patients with tumors harboring PIK3CA mutations, who have progressed on or after prior treatments.

Preclinical breast cancer cell lines with acquired resistance to palbociclib data indicate that acquired resistance to CDK4/6 inhibition occurs through a loss of independence to Rb signaling; therefore targeting PI3K/mTOR as an alternative pathway might be a viable strategy requiring further clinical investigation (O'Brien 2017).Therefore, this study will include assessment of the efficacy and safety of alpelisib combination in PIK3CA mutant HR+, HER2-negative aBC patients following progression on CDKi based regimen. The choice of hormonal combination partner with alpelisib (fulvestrant or letrozole) will be determined based on the CDKi combination partner drug used prior to study entry in these patients.

2.2 Rationale for the study design

This is a phase II, multicenter, open-label, three-cohort, non-comparative study of alpelisib plus endocrine therapy (either fulvestrant or letrozole) in patients with HR+, HER2-negative aBC harboring PIK3CA mutation(s) in the tumor who have progressed on or after prior treatments. Patients will be assigned to cohort A, B or C based on the most recent prior therapy; patients whose prior treatment is CDK 4/6 inhibitor plus fulvestrant will be enrolled in Cohort B until Cohort B enrollment is closed and then enrolled into Cohort C until it is closed for enrollment. Eligible patients include male and female (pre and post-menopausal) patients with HR+, HER2-negative aBC harboring PIK3CA mutation(s) whose disease has progressed on or after prior treatments.

PIK3CA mutations will be identified by analyzing the PIK3CA gene for hotspots known to impact the PI3K function in exons 7, 9 and 20 (see Section 7.2.3.1.1). These hotspots are anticipated to include the majority of the PIK3CA mutations identified in HR+ breast cancer patients so far and have shown sensitivity to alpelisib in vitro (Novartis Internal Data).Based on Novartis Internal Data obtained on a similar population, frequency of PIK3CA mutation status in HR+ breast cancer is anticipated to be approximately 40% based on data from Novartis

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sponsored trials [CBKM120F2302 and CBKM120F2303]. Patients will be assigned to each cohort as follows:

Cohort A: Patients who received any CDK 4/6 inhibitor plus any AI as immediate prior treatment, will receive alpelisib + fulvestrant

Cohort B: Patients who received any CDK 4/6 inhibitor plus fulvestrant as immediate prior treatment, will receive alpelisib + letrozole

Cohort C: Patients who received systemic chemotherapy or ET (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant

Note: In Cohort C, ET includes letrozole, fulvestrant and CDK 4/6 inhibitor plus fulvestrant. It is hypothesized that patients with tumors harboring a PIK3CA mutation could derive clinically relevant benefits with a PI3K inhibitor containing treatment. This study will provide preliminary evidence of efficacy for the combination of alpelisib with letrozole or fulvestrant in this patient population of advanced HR+ breast cancer.

The study includes two phases:

Core Phase: Includes treatment phase for all patients from FPFT until 18 months post LPFT + 1 month Safety follow-up (total 19 months post LPFT)

Extension Phase: includes treatment phase starting at the end of the treatment Core Phase until LPLV (up to 36 months); The extension treatment phase is only for patients who are continuing to benefit from study treatment at the end of the Core Phase who are not eligible for PSDS in their country based on local regulations. Patients will continue on their existing study treatment assigned in the Core Phase until discontinuation (refer to Section 7.1.5) or LPLT of the Extension Phase. Note: If PSDS becomes available for a patient or a rollover protocol becomes available, the patient should be discontinued from the study and access treatment via PSDS or rollover trial (whichever occurs first).

Patients who are benefiting from treatment and are eligible for PSDS will exit the trial at the end of the Core Phase.

2.3 Rationale for dose and regimen selection

As described in Section 1.2.4.3, the recommended dose for alpelisib in combination with fulvestrant was 300 mg q.d. Alpelisib 300 mg q.d. has also emerged to be the best tolerated dose in combination with AIs (Mayer 2014; Shah 2014; Munster 2014; [CBYL719A2201] study) (see Section 1.2.4.2 and Section 1.2.4.3).

Therefore, in this clinical trial alpelisib will be given at the dose of 300 mg q.d. together with fulvestrant (in cohorts A and C) administered as per the product labeling (Faslodex® EU Summary of Product Characteristics (SmPC) and US PI): 500 mg given intra-muscularly (i.m.) at Day 1, 15 of Cycle (month) 1 and Day 1 of every cycle (month) thereafter. In cohort B alpelisib will be given at the same dose of 300 mg q.d. together with letrozole administered per the product labeling (Femara® Prescribing Information, Novartis): 2.5 mg q.d., orally. In this study, a cycle is defined as 28 ± 3 days.

[redacted]

Premenopausal women, in addition to the study medications, will also receive goserelin or leuprolide (as necessary) to achieve adequate hormonal suppression.

Men in cohorts A and C (alpelisib in combination with fulvestrant) are not required to receive LHRH agonist. For men in cohort B (alpelisib in combination with letrozole) goserelin or leuprolide will be added for hormonal suppression.

The standard dose of goserelin (3.6 mg subcutaneously every 28 days) and leuprolide (7.5 mg i.m. every 28 days) will be used in this study. Goserelin or leuprolide are not expected to affect the metabolism of nor be affected by co-administration of other drugs. Refer to the most recent regional prescribing information and/or clinical guidelines for more information on LHRH agonists.

2.4 Rationale for choice of combination drugs

The rationale to combine alpelisib with fulvestrant is discussed in Section 1.2.5.2.

The rationale to combine alpelisib with letrozole is discussed in Section 1.2.5.1.

2.5 Rationale for choice of comparators drugs

There are no comparator drugs due to the fact there is no data to suggest how prior treatment may impact the outcome of any subsequent treatment with AI or fulvestrant and/or PI3K inhibitors. This is a non-comparative study which will provide early data for both combinations.

2.6 Risks and benefits

Appropriate eligibility criteria as well as specific dose modification and stopping rules, are included in this protocol as guidance for the investigators. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as, close clinical monitoring pre-identifying risk factors and outlining dose stopping rules. There may be unforeseen risks with alpelisib, fulvestrant, letrozole or their combination which could be serious.

The addition of goserelin or leuprolide to premenopausal women and male patients is not expected to affect the metabolism of nor be affected by co-administration of the other drugs (alpelisib in combination with fulvestrant or letrozole), so no additional safety risks are expected with this combination.

For further details on clinical safety, please refer to the latest version of [Alpelisib Investigators Brochure], [Faslodex® prescribing information], [Femara® Prescribing Information, Novartis], [Zoladex® prescribing information] and [Lupron® prescribing information].

2.6.1 Potential benefit for participants

Treatment with alpelisib in combination with fulvestrant or letrozole may result in an improved clinical benefit in men and women (pre and post-menopausal) with HR+, HER2-negative aBC, who progressed on or after prior treatments and harbor the PIK3CA mutation. All patients enrolled in this trial will receive an active endocrine therapy in combination with alpelisib for their disease (see Section 2.5). Based on preclinical and preliminary clinical data (see Section

[redacted]

1.2.4), treatment with alpelisib in combination with fulvestrant or letrozole is expected to have an acceptable safety profile and it is hypothesized that it will result in delayed disease progression.

For further details on clinical safety, please refer to Section 1.2.2 and the latest version of [Alpelisib Investigators Brochure].

2.6.2 Potential risks to clinical trial participants

See Section 2.6.3.

2.6.3 Risk management strategies

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, recommendations for concomitant medications, guidance for prohibited medications and dose adjustments or interruptions or discontinuations as outlined in Section 6.3. There may be unforeseen risks with alpelisib in combination with fulvestrant or letrozole.

Patients in this study will be carefully monitored for key toxicities that have been observed with alpelisib (see Section 1.2.4) with combination of fulvestrant or letrozole (see Section 1.2.1) with the following assessments (see Section 7): periodic laboratory, renal and liver function, urinalysis and ECG.

Risk will be further minimized by adherence to inclusion/exclusion selection criteria (see Section 5), avoidance of prohibited medication (see Section 6.4.4), close safety monitoring (see Section 8.1) and dose adjustment guidelines (see Section 6.3) for alpelisib and fulvestrant [Faslodex® prescribing information], letrozole prescribing information [Femara® Prescribing Information, Novartis] goserelin and leuprolide [Zoladex® prescribing information] and [Lupron® prescribing information].

A Steering Committee (SC) (see Section 8.7) will be established comprising investigators and Novartis personnel participating in the trial to ensure transparent management of the trial according to the protocol. A Novartis Safety Management Team (SMT) periodically reviews and evaluates all emerging safety data across the alpelisib program for early detection of potential safety signal assessment in a timely manner.

Women of childbearing potential and sexually active males must be informed that taking this study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and up to the period required after the last dose of study 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 (postimplantation loss), reduced fetal weights, and increased incidences of fetal malformations at maternal exposures based on area under the curve (AUC) that were $\geq$ 0.8 times the exposure in humans at the recommended dose of 300 mg/day. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

[redacted]

Patients 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 study.

Study related risks include, but are not limited to, collection of fresh tumor samples, blood collections, the different imaging methods including Echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan, bone scans and electrocardiograms (ECGs). Please refer to the Consent Form for more information.

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

2.6.4 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. 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.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To assess the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment per RECIST v1.1 separately in cohorts A and C (alpelisib in combination with fulvestrant) and cohort B (alpelisib in combination with letrozole) among patients with HR+, HER2-negative aBC harboring a PIK3CA mutation who have progressed on or after prior treatments.	The primary endpoint of this study is the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment using RECIST v1.1 in each cohort	
Secondary		Refer to Section 10.5
To assess PFS based on local investigator assessment for each cohort.	PFS based on local investigator assessment using RECIST v1.1 in each cohort	
To assess PFS on next-line treatment (PFS2) for each cohort.	PFS2 based on local investigator assessment in each cohort	
To assess overall response rate (ORR) and clinical benefit rate (CBR) based on local investigator assessment for each cohort.	ORR based on local investigator's assessment according to RECIST v1.1 in each cohort Clinical Benefit Rate (CBR) based on local investigator's assessment according to RECIST v1.1 in each cohort	
To assess duration of response (DOR) in patients with confirmed complete response (CR) or PR for each cohort.	Duration of Response is the time from the date of first documented response (confirmed CR or PR) to the date of first documented progression or death	
To assess Overall Survival (OS) for each cohort	Overall Survival is defined as the time of start of treatment to date of death or lost to follow-up.	
To evaluate the safety and tolerability of the combination for each cohort.	Type, frequency and severity of adverse events per CTCAE v4.03 Type, frequency and severity of laboratory toxicities per CTCAE v4.03	

[redacted]

Objective	Endpoint	Analysis
Evaluate clinical benefit as assessed by the Investigator during the Extension Phase	Proportion of patients with clinical benefit as assessed by the Investigator at scheduled visits	

[redacted]

[redacted]

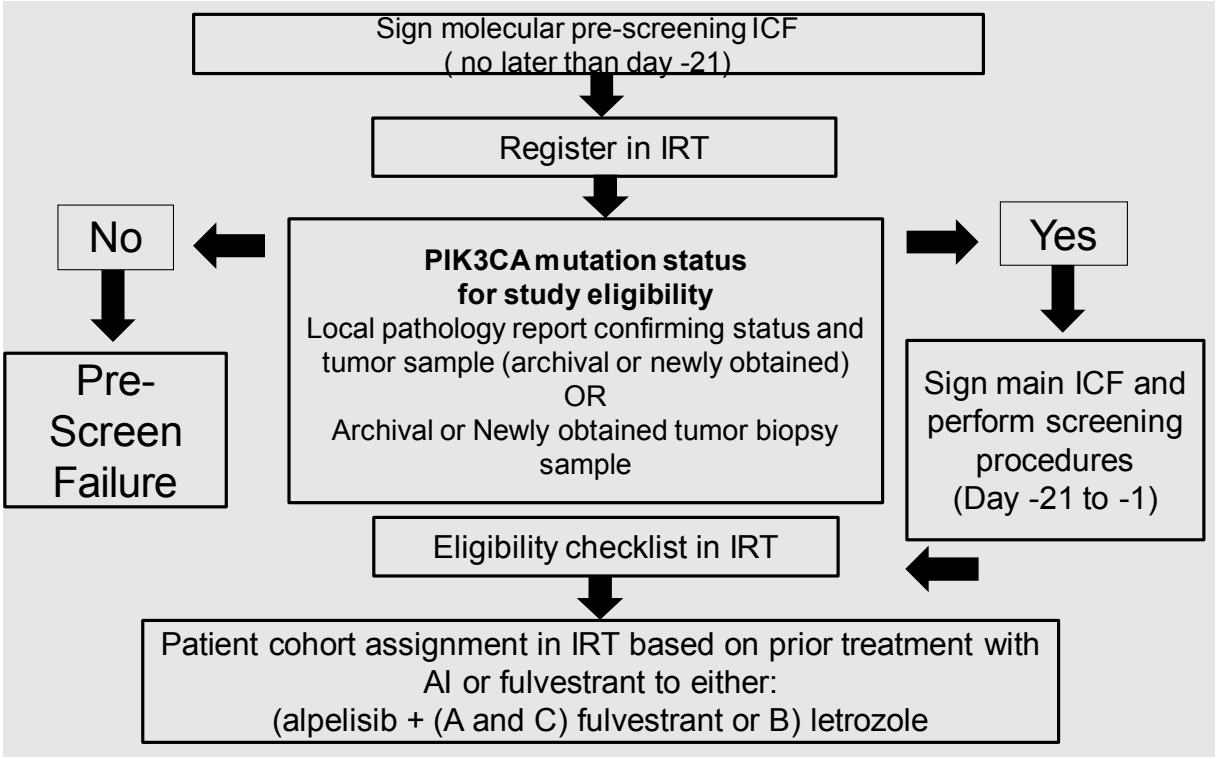
4 Study design

4.1 Description of study design

This is a phase II, multicenter, open-label, three-cohort, non-comparative study of alpelisib plus endocrine therapy (either fulvestrant or letrozole) in patients (pre and post-menopausal women and men) with HR+, HER2-negative aBC harboring PIK3CA mutation(s) in the tumor, whose disease has progressed on or after prior treatments. Gonadal suppression must be achieved with either goserelin or leuprolide in men and premenopausal women patients.

Patients must have the PIK3CA mutation to be eligible for the trial as detailed in inclusion criteria. Patients will be required to sign a molecular pre-screening consent to have their mutational status either analyzed by providing adequate tumor tissue or if PIK3CA status is known, providing tumor tissue to confirm PIK3CA mutational status using a Novartis designated central laboratory. This will be conducted during a pre-screening phase prior to enrolling into the trial by Day -21. Approximately 1300 patients are expected to be pre-screened to identify PIK3CA mutational status. Those patients that harbor the PIK3CA mutation are eligible for the study and will then have the opportunity to sign the main ICF to begin screening procedures to determine eligibility.

Figure 4-1 Pre-Screening to Screening



Approximately 340 patients (approximately 112 in each cohort), with HR+, HER2-negative

[redacted]

aBC harboring a PIK3CA mutation in tumor tissue, that have progressed on or after prior treatments are expected to be enrolled. Patients will be assigned to Cohort A, B or C based on the most recent prior therapy; patients whose prior treatment is CDK 4/6 inhibitor plus fulvestrant will be enrolled in Cohort B until Cohort B enrollment is closed and then in Cohort C until it is closed for enrollment.

At the start of the Core Phase, patients will be assigned to a cohort based on previous therapy (AI or fulvestrant) as indicated below:

Cohort A: Patients who received any CDK 4/6 inhibitor plus any AI as immediate prior treatment will receive alpelisib + fulvestrant

Cohort B: Patients who received any CDK 4/6 inhibitor plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole

Cohort C: Patients who received systemic chemotherapy or ET (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.

Note: In Cohort C, ET includes letrozole, fulvestrant and CDK 4/6 inhibitor plus fulvestrant.

The study includes two phases:

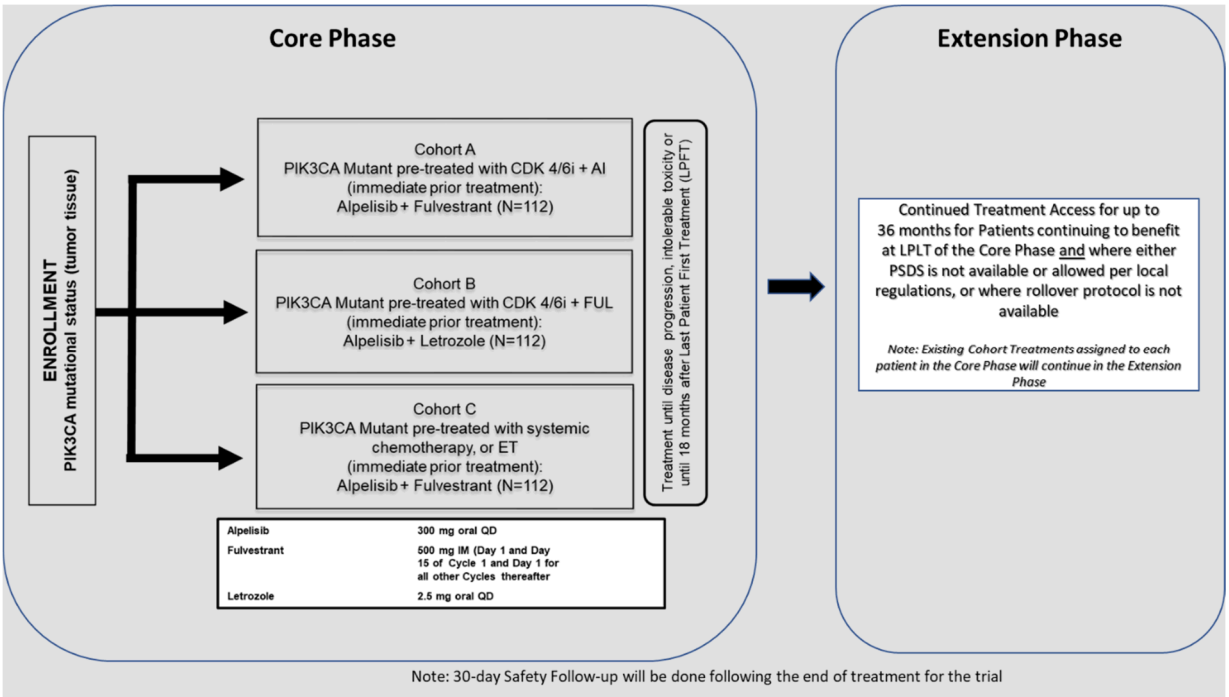
Core Phase: includes treatment phase for all patients from FPFT until 18 months post LPFT + 1 month Safety follow-up (total 19 months post LPFT)

Extension Phase: includes treatment phase starting at the end of the treatment Core Phase until LPLV (up to 36 months). The extension treatment phase is only for patients who are continuing to benefit from study treatment at the end of the Core Phase who are not eligible for PSDS in their country based on local regulations. Patients will continue on their existing study treatment assigned in the Core Phase until discontinuation (refer to Section 7.1.5) or LPLT of the Extension Phase. Note: If PSDS becomes available for a patient or a rollover protocol becomes available, the patient should be discontinued from the study and access treatment via PSDS or rollover trial (whichever occurs first).

Patients who are benefiting from the study treatment and are eligible for PSDS will exit the trial at the end of the Core Phase.

[redacted]

Figure 4-2 Study Design



A Steering Committee (SC) will be established comprising investigators and Novartis representatives participating in the trial to ensure transparent management of the study according to the protocol through recommending and approving modifications as outlined in Section 8.7.

Treatment crossover between cohorts will not be permitted in this study.

This study will use an Interactive Response Technology (IRT) system for patient molecular screening, screening, enrollment, discontinuation, and study medication management.

Safety data collected will include (S)AE reporting, grade 3/4 AEs, events of special interest, AEs leading to discontinuation and deaths, vital signs, physical examination, variation of the ECOG performance status, and hematology and clinical chemistry laboratory parameters at study visits while the patient remains on study and for 30 days after discontinuation.

After discontinuation of study treatment, all patients will be followed for safety for at least 30 days except in case of death, loss to follow-up or withdrawal of consent. For details please refer to Section 7.1.5.

All patients will be assessed for efficacy by the investigator; progression free survival (PFS) and best overall tumor response, using the Response Evaluation Criteria in Solid Tumor (RECIST v1.1), based on investigator assessment will be collected during the Core Phase.

[redacted]

Tumor assessments should be performed according to the current standard of care (every 12 weeks, until disease progression regardless of treatment discontinuation reason (except if consent is withdrawn, death or patient is lost to follow-up) until the end of the Core Phase. It is strongly recommended that a tumor assessment is performed before patient is switched to a new antineoplastic therapy and collected to determine PFS2.

4.2 Timing of interim analyses and design adaptations

Three Interim Analyses (IA), descriptive in nature, are planned for this study. The first IA will be performed after at least [redacted] patients receiving alpelisib plus fulvestrant (cohort A) have at least 6 months of follow-up on study. The second IA after at least [redacted] patients have been treated (regardless of cohort) and have at least 6 months of follow-up on study. The third IA will be performed after the Core Phase ends.

The primary endpoint will not be analyzed and no statistical hypothesis will be tested during any of the IAs and therefore multiplicity adjustments are not required.

4.3 Definition of end of study

Core Phase: The end of the Core Phase is defined as 19 months after last patient first treatment (LPFT); which includes 18 month follow-up plus 1 month safety follow-up.

Extension Phase: The extension starts after the last treatment for the Core Phase (LPLT of Core Phase) and will continue until the end of study; the end of study is defined as 37 months from extension start, which includes 36 months treatment extension plus 1 month safety follow-up.

The start of the Extension Phase will overlap with the safety follow-up phase of the Core Phase.

Note: if all patients in the study discontinue treatment prior to the of the Core Phase or Extension Phases end, the end of study will be sooner.

In the Core Phase, patients will receive treatment until disease progression, unacceptable toxicity, death, until 18 months after LPFT or discontinuation from the study treatment for any other reason. Following discontinuation of study treatment for any reason other than disease progression, withdrawal of consent, lost to follow-up or death, patients will continue to be followed for efficacy (only for Core Phase). Patients will be followed for disease progression and survival regardless of treatment discontinuation reason (except if consent is withdrawn, death or patient is lost to follow-up) until the end of the Core Phase.

If alpelisib is not commercially available and reimbursed in a participating country by the time the Core Phase is completed, patients continuing to derive clinical benefit from study treatment will be able to continue receiving trial therapy through alternative sources within local regulations (e.g. Managed Access Program (MAP)). If no local alternative program is available, patients continuing to benefit at the end of treatment will be able to continue treatment on the Extension Phase.

[redacted]

4.4 Early study termination

The study can be terminated by Novartis at any time. Reasons for early termination:

- Unexpected, significant or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) of the early termination of the trial.

5 Population

5.1 Patient population

This study will include men and women (pre and post-menopausal) with HR+, HER2-negative aBC harboring a PIK3CA mutation in tumor tissue and have progressed on or after prior treatments.

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 study.

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

Rescreening will be allowed for patients to repeat safety procedures and all eligibility must be reconfirmed prior to start of study treatment. Patients can only be rescreened once and will retain the same screening number.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

Written informed consent must be obtained prior to any screening procedures.

1. Patient is an adult male or female ≥ 18 years old at the time of consent and has signed informed consent (ICF) before any trial related activities and according to local guidelines.
2. Males or females with advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy.
3. Patient has a histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ breast cancer by local laboratory.
4. Patient has a confirmed, HER2-negative aBC. HER2-negative defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+ or 2+. If IHC is 2+, a

[redacted]

negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing.

5. Patient has PIK3CA mutation confirmed by a Novartis designated laboratory, in which adequate formalin-fixed paraffin-embedded tissue sections with >10% tumor tissue must be provided. It is recommended to provide a tumor sample collected after the most recent progression or recurrence,

   Or

   Patient has a pathology report confirming PIK3CA mutant status by a certified laboratory using a validated PIK3CA mutation assay (either from tissue or blood). It is also mandatory to provide a tumor sample (either archival or newly obtained) for PIK3CA mutation confirmation by a Novartis designated laboratory. It is recommended the tumor sample is collected after the most recent progression or recurrence.
6. In case of women, both premenopausal and postmenopausal patients are allowed to be included in this study; menopausal status is relevant for the requirement of goserelin or leuprolide to be used concomitantly with alpelisib in combination with fulvestrant or letrozole.
   a. Patient is postmenopausal woman defined as either:
      1. Prior bilateral oophorectomy or
      2. Age ≥60 or
      3. Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and/or estradiol in the postmenopausal 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, goserelin or leuprolide, serial measurements (per local guidelines) of FSH and/or estradiol are needed to ensure menopausal status.
   b. Patient is premenopausal defined as either:
      - Patient had last menstrual period within the last 12 months OR
      - If on tamoxifen or toremifene with in 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

        Note: Throughout this document, peri-menopausal and pre-menopausal status is grouped together and referred as “Premenopausal”
7. Patients must have documented evidence of tumor progression on or after
   - CDK 4/6 inhibitor treatment as last treatment regimen in cohorts A and B
   - AI treatment (either in adjuvant or metastatic setting) and received systemic chemotherapy or ET (monotherapy or combination except CDK 4/6i + AI) as last treatment regimen in cohort C: Note, upon completion of enrollment of Cohort B,

[redacted]

patients whose receive CDK4/6i+ Fulvestrant as immediate prior therapy are eligible for Cohort C .

- No more than two (2) prior anti-cancer therapies for aBC. Each unique regimen or 'line' is defined as a single or combination of medications given for a new relapse/ recurrence. Maintenance therapies, where applicable, must be regarded as part of the main treatment.
- Received no more than one prior regimen of chemotherapy for the treatment of advanced/metastatic disease is permitted,

  Note: Patients who received chemotherapy in (neo) adjuvant therapy for breast cancer are eligible.
- Recovered to grade 1 or better from any adverse events (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion) related to previous anti-cancer therapy prior to study entry,

8. Patients must have either:
   Measurable disease, i.e. at least one measurable lesion as per RECIST v1.1 criteria. (Tumor lesions previously irradiated or subjected to other locoregional therapy will only be considered measurable if disease progression at the treated site after completion of therapy is clearly documented),
   or
   If no measurable disease is present, then at least one predominantly lytic bone lesion must be present (Patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation).
9. Patient has adequate bone marrow and coagulation function as shown by the following laboratory values:
   - Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9$/L
   - Platelets $\geq 100 \times 10^9$/L (For patients with lesions involving the bone marrow, platelet count $\geq 75 \times 10^9$/L may be acceptable)
   - Hemoglobin ≥ 9.0 g/dL
   - INR ≤ 1.5 (INR ≤ 2.0 will be allowed for those patients treated with vitamin K antagonist)
10. Patient has adequate liver function as shown by:
    - In absence of liver metastases, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN or ≤ 5 x upper limit of normal (ULN) if hepatic metastases are present,
    - Total serum bilirubin <2 x ULN (any elevated bilirubin should be asymptomatic at enrollment) except for patients with Gilbert's syndrome who may only be included if the total bilirubin is $\leq 3.0 \times$ ULN or direct bilirubin $\leq 1.5 \times$ ULN
11. Patient has adequate renal function:
    - Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 35 ml/min using Cockcroft-Fault formula

[redacted]

12. Patient has fasting plasma glucose (FPG) ≤140 mg/dL (7.7 mmol/L) and glycosylated hemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met)
    *For patients with FPG ≥ 100 mg/dL and/or HbA1c ≥5.7% (i.e. threshold for pre-diabetes) at screening, recommend lifestyle changes according to ADA guidelines, i.e. dietary advice (e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrate intake over the course of the day, three small meals and 2 small snacks rather than one large meal) and exercise. A consultation with a diabetologist is highly recommended.
13. Patient has potassium, magnesium and calcium (corrected for albumin), within normal limits (either by central or local lab), or ≤ Grade 1 severity according to NCI-CTCAE v4.03 if judged clinically not significant by the investigator, or correctable with supplements before entry of study; re-screen is allowed.
14. Fasting serum amylase ≤ 2 × ULN.
15. Fasting serum lipase ≤ ULN.
16. Patient has ECOG (Eastern Cooperative Oncology Group) Performance Status ≤ 2.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient has a known hypersensitivity to alpelisib, fulvestrant, letrozole, goserelin or leuprolide or to any of the excipients of alpelisib, fulvestrant, letrozole, goserelin or leuprolide.
2. Patient has received prior treatment with any PI3K inhibitors.
3. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
   - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment.
   - Clinically stable CNS tumor at the time of screening untreated or without evidence of progressions for at least 4 weeks after treatment as determined by clinical examination and brain imaging (MRI or CT) during screening period and stable low dose of steroids for 2 weeks prior to initiating study treatment.
4. Patients with an established diagnosis of diabetes mellitus type I or uncontrolled type II (based on FPG and HbA1c, see inclusion criterion 12).
5. Patient has a concurrent malignancy or malignancy within 3 years of study screening period, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanoma skin cancer or curatively resected cervical cancer.
6. Patient has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to enrollment, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia).
7. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting treatment with alpelisib or has not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical

[redacted]

applications (e.g., for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops or local injections (e.g., intra-articular), stable CNS tumor on consistent low dose of steroids.

8. Patients with a known history of HIV seropositivity. Screening for HIV infection at baseline is not mandatory (unless required by local HA regulations).
9. Any concurrent severe and/ or uncontrolled medical conditions that would, in the investigator's judgment, contraindicate patient participation in the clinical study (e.g. chronic active hepatitis [testing not mandatory unless required by local regulations or requirements], severe hepatic impairment, etc.).
10. Patients being concurrently treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A4 or inhibitors of BCRP; switching to different medications prior to entry of treatment phase is allowed within the last 5 days prior to study treatment (see Appendix 1 for complete list).
11. Patient has a history of noncompliance to medical regimens.
12. Patient with severe liver impairment (Child Pugh score B/C).
13. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) based on investigator discretion.
14. Patient has documented pneumonitis / interstitial lung disease which is active and requiring treatment (chest CT scan performed at baseline for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).
15. Patient is concurrently using other anti-cancer therapy. All anti-cancer therapy must be discontinued prior to day one of study treatment. Drugs with overlapping toxicities must be discontinued within 7 days and AE resolved to NCI CTCAE v4.03 Grade ≤1 prior to study treatment. Exception to this criterion: patients with any grade of alopecia are allowed to enter the study.
16. Patient has had major surgery within 14 days prior to starting treatment with alpelisib or has not recovered from major side effects.
17. Patient has any of the following cardiac abnormalities:
    - Symptomatic congestive heart failure
        i. History of documented congestive heart failure (New York Heart Association functional classification III-IV), documented cardiomyopathy
        ii. Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - Myocardial infarction ≤ 6 months prior to enrollment
    - Unstable angina pectoris
    - Serious uncontrolled cardiac arrhythmia
    - Symptomatic pericarditis

[redacted]

- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.

18. History of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.
19. Patient has a history of severe cutaneous reactions like Stevens-Johnson-Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
20. Patient who does not apply highly effective contraception during the treatment with alpelisib and through the duration as defined below after the final dose of alpelisib
    a. Sexually active males unless they are sterilized (at least 6 months prior to screening) or use a condom during intercourse while taking drug and for at least 8 months after stopping alpelisib plus fulvestrant, letrozole, goserelin or leuprolide medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
    b. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 1 year after stopping the study medication.

       Highly effective contraception methods include:
       - Total abstinence when this is in line with the preferred and usual lifestyle of the patient. 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 tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
       - Male partner sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
       - Placement of an intrauterine device (IUD).

         Note: Use of oral (estrogen and progesterone), transdermal, injected or implanted hormonal methods of contraception as well as hormonal replacement therapy is not allowed in this study; barrier method is not considered an effective method.
    c. Patient is pregnant or lactating, where pregnancy is defined as state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin (hCG) lab test prior to initiating study treatment.
21. Subjects with unresolved osteonecrosis of the jaw.

[redacted]

6 Treatment

6.1 Study treatment

For this study, the term "investigational drug" refers to Novartis study drug alpelisib. Study treatment in this protocol refers to the combination of drugs and includes investigational drug (alpelisib) as well as fulvestrant or letrozole and for men and premenopausal women goserelin or leuprolide as applicable. The storage conditions for alpelisib are described on the medication label. Novartis Global Clinical Supply (GCS) or its designee will provide alpelisib as 50 mg and 200 mg tablets as individual patient supply, packaged in bottles. Alpelisib will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area.

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

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

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

The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study drugs	Pharmaceutical form and route of administration	Dose[2]	Frequency and/or Regimen
Alpelisib	Film coated tablet for oral use	300 mg (e.g. 2 x 50 mg tablets+1x200 mg tablet) [1]	Daily (continuous) starting C1D1
Fulvestrant	Injection for i.m. administration	500 mg	Days 1, 15 on Cycle 1 and Day 1 at each cycle thereafter
Letrozole	Film coated tablet for oral use	2.5 mg	Daily (continuous) starting C1D1
Goserelin	Injectable Subcutaneous implant	3.6 mg	Every 28 days (only for men in cohort B and premenopausal women)

[redacted]

Study drugs	Pharmaceutical form and route of administration	Dose[2]	Frequency and/or Regimen
Leuprolide	Injectable Intramuscular Depot	7.5 mg	Every 28 days (only for men in cohort B and premenopausal women)

1. In case of patient supply difficulties, any combination of alpelisib (according to patient assignment) may be taken to consume the total dose.
2. Dose reduction levels for alpelisib will be administered accordingly. For example, alpelisib 250mg should preferentially be administered as 1 X 50 mg tablets + 1 x 200 mg tablet.

All eligible patients will be assigned to their respective cohorts based on prior treatment; patients whose prior treatment is CDK 4/6 inhibitor plus fulvestrant will be enrolled in Cohort B until Cohort B enrollment is closed and then in Cohort C until it is closed for enrollment.:

- Cohort A - PIK3CA mutant pre-treated with CDK 4/6i plus AI will receive:
  - Alpelisib 300 mg p.o. + fulvestrant 500 mg i.m.
- Cohort B - PIK3CA mutant pre-treated with CDK 4/6i plus fulvestrant will receive:
  - Alpelisib 300 mg p.o. + letrozole 2.5 mg p.o
- Cohort C - PIK3CA mutant pre-treated with systemic chemotherapy or ET will receive:
  - Alpelisib 300 mg p.o. + fulvestrant 500 mg i.m.

During treatment phases (during Core and Extension), alpelisib 300 mg will be administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in combination with fulvestrant 500 mg starting on Cycle 1 Day 1 and 15 and Day 1 of every cycle thereafter (+/- 3 days) in a 28 days cycle for Cohorts A and C. Similarly, alpelisib 300 mg will be administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in combination with letrozole 2.5 mg starting on Cycle 1 Day 1 of every cycle thereafter (+/- 3 days) in a 28 days cycle for Cohort B. Treatment crossovers between Cohorts will not be permitted in this study. A complete cycle of treatment is defined as 28 days of once daily continuous treatment of alpelisib in combination with fulvestrant or letrozole.

For men and premenopausal women, either goserelin will be given as an injectable subcutaneous implant or leuprolide will be given as an intramuscular injection. Either goserelin or leuprolide is recommended to be administered on day 1 starting at Cycle 1 and then every 28 days. Goserelin or leuprolide must be given as the monthly injection dosage form, as data has shown the 3-month depot dosage forms do not reliably suppress hormonal levels in all patients (NCCN 2017). If a patient is already receiving goserelin or leuprolide before C1D1, a 28 days schedule should be maintained based on the pre-existing dosing schedule. Please refer to the local approved prescribing information.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

[redacted]

6.1.1.1 Alpelisib dosing

Alpelisib at a dose of 300 mg will be administered orally once daily on a continuous dosing schedule starting on cycle 1 day 1 in combination with fulvestrant (500 mg intra muscular), or letrozole (2.5 mg).

The investigator or responsible site personnel should instruct the participant to take the study drugs as per protocol (promote compliance). Drug accountability must be performed on a regular basis. Participants will be instructed to return unused alpelisib tablets to the site at the end of each cycle or at the time of discontinuation of study treatment. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the participant with the correct amount of drugs for subsequent dosing.

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.

The following general guidelines should be followed for alpelisib administration:

- Patients should be instructed to take the dose of alpelisib once daily at approximately the same time each day after food (preferably in the morning), except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic at any later point of time.
- Alpelisib must be taken within 1 hour after a meal or snack. If, for any reason, a breakfast (or other meal) was not consumed, then the patient should take study treatment with a glass of water within 1 hour after a snack at any later point in time. If a dose of alpelisib is missed, it can be taken immediately after food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, alpelisib should be taken at the usual time.
- Alpelisib should be taken with a glass of water. 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.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF
- Should any participant enrolled on the study 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.

6.1.1.1.1 Additional dosing guidelines for fasting glucose and/or amylase/lipase and/or c-peptide and/or lipid profile sampling

On days with a pre-dose fasting (overnight) glucose and/or amylase/lipase and/or c-peptide and/or lipid profile samples as described in Table 7-1 and Section 7.2.2.5.3 the following additional guidelines should be followed:

[redacted]

The patient must be fasting overnight for 8-12 hours prior to the blood collection, but can freely drink water and coffee/tea (unsweetened and without milk). After this blood sample, the patient should have a light breakfast. Alpelisib must be taken within 1 hour after the meal in the clinic.

6.1.1.2 Letrozole dosing

Letrozole at a dose of 2.5 mg will be administered orally once daily on a continuous dosing cycle starting at cycle 1 day 1.

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.

6.1.1.3 Fulvestrant dosing

Fulvestrant 500 mg will be given at cycle 1 day 1 and 15 after cohort assignment and then at Day 1 of each subsequent cycle during the treatment phase. Fulvestrant is administered intramuscularly into the buttocks slowly as two 5mL injections, one in each buttock.

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.

6.1.1.4 Goserelin dosing

For men in cohort B and premenopausal women goserelin will be given as an injectable subcutaneous implant in a dose of 3.6 mg starting at Cycle 1 Day 1 and then every 28 days. Goserelin must be given as the monthly injection dosage form, as the 3-month depot dosage forms do no reliably suppress hormonal levels in all patients. If a patient is already receiving goserelin before C1D1, a 28 days schedule should be maintained based on the pre-existing dosing schedule.

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.

6.1.1.5 Leuprolide dosing

For men in cohort B and premenopausal women leuprolide will be given as an injectable intramuscular injection in a dose of 7.5 mg starting at Cycle 1 Day 1 and then every 28 days. Leuprolide must be given as the monthly injection dosage form, as the 3-month depot dosage forms do not reliably suppress hormonal levels in all patients. If a patient is already receiving leuprolide before C1D1, a 28 day schedule should be maintained based on the pre-existing dosing schedule.

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.

[redacted]

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to Section 6.3 Dosing modifications.

Patients who permanently discontinue one of the study drugs for any reason other than disease progression may continue the other study drug as part of the trial therapy at the investigator's discretion until disease progression, unacceptable toxicity, death or discontinuation from study treatment due to any other reason and should follow the protocol safety and efficacy assessments as scheduled. After discontinuing all study treatment, further treatment is left to the physician's discretion.

6.1.5 Treatment duration

Patients will be treated until disease progression (radiologically documented according to RECIST v1.1) or until discontinuation of study treatment due to any other reason. In the Core Phase, patients will receive treatment until disease progression, unacceptable toxicity, death, until 18 months after LPFT or discontinuation from the study treatment for any other reason and in the Extension Phase, patients will receive study treatment until discontinuation per Section 7.1.5 until 36 months.

6.2 Dose escalation guidelines

Not Applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment.

These dose modifications are summarized in Table 6-2. Deviations from mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2 or listed in Section 7.1.5.

These dose changes must be recorded on the Dosage Administration Record eCRF.

[redacted]

6.3.1.1 Fulvestrant

The established clinical dose of fulvestrant (500 mg) will be used in cohorts A and C in this study. For information on fulvestrant and management of related AEs refer to the [Faslodex® SmPC or local Prescribing Information].

6.3.1.2 Letrozole

The established clinical dose of letrozole (2.5 mg) will be used in cohort B in this study. For information on letrozole and management of related AEs refer to the latest [Femara ® Prescribing Information, Novartis].

6.3.1.3 Goserelin and leuprolide

The established clinical dose of goserelin or leuprolide will be used in men and premenopausal women patients and no dose modification is planned in this study. Patients receiving LHRH agonists will be monitored regularly per local institutional clinical guidelines to confirm a post-menopausal status, according to local laboratory ranges of FSH and estradiol levels.

Refer to the most recent regional prescribing information and/or clinical guidelines for more information on LHRH agonists.

6.3.1.4 Alpelisib

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. All dose modifications must be based on the worst preceding toxicity as graded by the NCI Common Terminology Criteria [NCI-CTCAE v4.03]. If the administration of alpelisib is interrupted for reasons other than toxicity, then treatment with alpelisib may be resumed at the same dose.

A maximum of 2 dose reductions of alpelisib from the recommended starting dose may be allowed before considering discontinuation of alpelisib treatment.

Please refer to Table 6-2 and Table 6-3 for guidance.

Table 6-2 Dose reduction sequential steps for alpelisib

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

Recommendations for dose reduction or dose interruption of alpelisib in the management of adverse reactions are summarized in Table 6-3. Adverse events for alpelisib are graded according to (Common Terminology Criteria for Adverse Events (CTCAE) v4.03 since this version is more objective with regards to hyperglycemia grading since it is based on laboratory values. Clinical judgment of the treating physician, including confirmation of lab values if deemed necessary, should guide the management plan of each patient based on individual benefit/risk assessment.

[redacted]

However, treatment must be discontinued as indicated in Table 6-3.

After treatment is resumed at a lower dose:

- If the same toxicity recurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration.
- Once the alpelisib dose has been reduced, no re-escalation will occur, even upon resolution of AE.

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

If administration of alpelisib dosing is held for more than 28 days, then alpelisib must be permanently discontinued. Grade 4 adverse events will lead to permanent discontinuation, irrespective of recovery time, unless otherwise specified. Patients requiring more than 2 dose reductions for alpelisib should be permanently discontinued.

Table 6-3 Criteria for interruption and re-initiation of alpelisib treatment

Dose Modifications for alpelisib as specified below. Fulvestrant and letrozole may be continued while alpelisib dose is being held, at the investigators discretion, and as specified in Section 6.3.1

Worst toxicity – CTCAE Grade (value)	Dose Modifications for alpelisib
Investigations (Fasting Glucose or Random blood glucose)	
Hyperglycemia (see also Section 6.3.2.1.3) 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. 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. Local standard clinical practice may be followed for monitoring and managing hyperglycemia. However dose reduction should only be based on FPG. As metformin is widely available, it is an appropriate choice as initial therapy for alpelisib-induced hyperglycemia. However, SGLT2 inhibitors as per local regulations, are acceptable as well and may be administered alone or in combination with metformin. The use of metformin XR can be considered as a suitable alternative to metformin IR, alone or in combination with an SGLT2 inhibitor, particularly for participants with at least one risk factor for the development of severe hyperglycemia, at the discretion of the Investigator and as per local regulations. (Jabbour and Ziring, 2011). Refer to Section 6.3.2.1.3 (“Guidelines for the treatment of alpelisib induced hyperglycemia”) for additional details regarding the use of metformin XR and/or SGLT2 inhibitors. In case of intolerance to or unavailability of metformin, investigator’s judgment should be exercised and as per local regulations, other oral anti-diabetic agents such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors can be used. SGLT2 inhibitor may increase the risk of euglycemic diabetic ketoacidosis and therefore, monitoring with serum / urine ketones and consultation with a healthcare expert experienced in hyperglycemia management or a diabetologist should be considered.	
Grade 1 FG > ULN - 160 mg/dL [> ULN - 8.9 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

[redacted]

Worst toxicity – CTCAE Grade (value)	Dose Modifications for alpelisib
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)	experienced in hyperglycemia management or a diabetologist. Metformin 500 mg once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg bid, with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Alternatively, metformin XR once daily dosing may be considered instead of metformin immediate release. 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 6.3.2.1.3 “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 blood glucose as clinically indicated and at least weekly for 8 weeks, then continue checking at least every two weeks until blood glucose levels are within baseline values.
Grade 2 FG > 160 - 250 mg/dL [> 8.9 - 13.9 mmol/L]	• Maintain dose level and remind patient of lifestyle changes*, exclude confounding factors like e.g. urinary tract infection, 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 > 160mg/dl (8.9 mmol/L), add an SGLT2 inhibitor if not already started, e.g. empagliflozin up to 25 mg (max. dose). Alternatively, an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose) can be added. • Monitor blood glucose as clinically indicated and at least twice weekly until FG resolves to ≤ Grade 1. • If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib by 1 dose level • Continue with anti-diabetic treatment and check fasting glucose levels at least weekly for 8 weeks, then continue checking at least every 2 weeks,

[redacted]

Worst toxicity – CTCAE Grade (value)	Dose Modifications for alpelisib
	alert treating physician if FG > 250 mg/dL (8.9 mmol/L) .
Grade 3 FG > 250 - 500 mg/dL [> 13.9 - 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 infection and consider consultation with a diabetologist. Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate. Insulin may be used for 1-2 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 blood glucose as clinically indicated and at least twice weekly until blood glucose levels resolve to ≤ Grade 1. • If FG resolves to ≤ 160 mg/dL (8.9 mmol/L) within 3-5 days, while off study treatment and on metformin, re-start alpelisib and reduce 1 dose level, continue with anti-diabetic treatment. A second or third anti-diabetic agent maybe initiated concomitantly, if needed, in consultation with a diabetologist. Check blood glucose at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FG>250mg/dl (13.9 mmol/L). • If FG does not resolve to ≤ 160 mg/dl (8.9 mmol/L) within 3-5 days while off study treatment and on metformin, consult a diabetologist for management of diabetes is strongly recommended. • If FG does not resolve to ≤ 160 mg/dL(8.9 mmol/L) 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 patient 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

[redacted]

Worst toxicity – CTCAE Grade (value)	Dose Modifications for alpelisib
	• Exclude confounding factors like e.g. urinary tract infection. • Should 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 (27.8 mmol/L) and confounding factors could be excluded, permanently discontinue patient from alpelisib.
A diabetologist consultation should always be considered For all grades: instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study, 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 In cases where there is rapidly increasing serum glucose suspicious of severe clinical presentation and/or diabetic ketoacidosis) without obvious confounding factors and potentially need close observation and monitoring, a diabetologist should be consulted with consideration of potential hospitalization and close monitoring. *specific recommendations please see Section 6.3.2.1.3.	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until resolved, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ dose level
Investigations (Renal)	
Serum creatinine	
< 2 x ULN	Maintain dose level
2 – 3 x ULN	Omit dose until resolved to ≤ grade 1, then:

[redacted]

Worst toxicity – CTCAE Grade (value)	Dose Modifications for alpelisib
	• If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue patient from alpelisib
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from alpelisib
Investigations (Hepatic)	
Isolated total Bilirubin elevation	
Grade 1 (> ULN - 1.5 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 1.5 - 3.0 x 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 - 10.0 x ULN)	Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (> 10.0 x ULN)	Permanently discontinue.
Isolated AST or ALT Elevation	
Grade 1 (> ULN – 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 (> 5.0 - 10.0 x ULN)	• Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (> 10.0 x ULN)	• Permanently discontinue
Combined elevations of AST or ALT and total Bilirubin	Please see specific instructions in Section 6.3.2.2
Investigations (Gastrointestinal)	
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements. Colitis is defined as a disorder characterized by inflammation of the colon. (see also Appendix 2)	
Grade 1 (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline) OR Asymptomatic colitis; clinical or diagnostic observations only; intervention not indicated	Maintain dose level but initiate appropriate medical therapy and monitor as clinically indicated
Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline) limiting instrumental Activities of Daily Living (ADL) OR Abdominal pain; mucus or blood in stool	Omit dose until resolved to ≤ Grade 1, initiate appropriate medical therapy then restart at same dose. If diarrhea returns as ≥ Grade 2, then omit dose until resolved ≤grade1, then decrease 1 dose level Initiate or intensify appropriate medical therapy and monitor as clinically indicated. For Grade 2 colitis consider additional treatment, such as steroids.
Grade 3 (Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL) OR	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal

[redacted]

Worst toxicity – CTCAE Grade (value)	**Dose Modifications for alpelisib**
Severe abdominal pain; peritoneal signs	medicinal products and / or fluid replacement and electrolyte supplements as clinically indicated. For Grade 3 colitis consider additional treatment, such as steroids.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from treatment. Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and /or fluid replacement and electrolyte supplements, as clinically indicated.
Investigations (Pancreatic)	
Pancreatitis	
Grade 2 (enzymatic elevation or radiologic findings only)	Omit dose until resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. If toxicity recurs, permanently discontinue patient from alpelisib
Grade 3 For patients deriving clinical benefit upon investigator's judgement: For other patients:	• Omit dose until complete resolution of symptoms and lipase resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed. • If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. • If toxicity reoccurs, permanently discontinue patient from alpelisib • Permanently discontinue patient from alpelisib
Grade 4	Permanently discontinue patient from alpelisib
Stomatitis/Oral mucositis (see also Appendix 3**)**	
Grade 1/Tolerable Grade 2	Maintain dose level Non-alcoholic or salt water mouth wash
Intolerable Grade 2 or Grade 3	First occurrence: hold until ≤ Grade 1 and ↓ 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until ≤ Grade 1 and ↓ 1 dose level.
Grade 4	Permanently discontinue patient from alpelisib
Skin and subcutaneous tissue disorders	
Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with alpelisib. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. (see also Section 6.3.2.1.2). Dermatologist consult 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	

[redacted]

Worst toxicity – CTCAE Grade (value)	**Dose Modifications for alpelisib**
Grade 1 (<10% body surface area (BSA) with active skin toxicity*)	• Maintain dose level • Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are Triamcinolone, Betamethasone as long as skin toxicity is active, during maximum 28 days • Add oral anti-histamine (sedative or non-sedative) • If active rash is not resolved within 28 days of appropriate treatment, add a low dose systemic corticosteroid (20-40 mg/d), such as prednisone 10 mg 3x/day For patients with symptoms like burning 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.
Grade 2 (10-30% BSA with active skin toxicity*)	• Maintain dose level • Initiate or intensify high potency topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone as long as skin toxicity is active, during max. 28 days • Add systemic corticosteroids 20-40mg/d. • Add oral anti-histamine (sedative or non-sedative) If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued For patients with symptoms like burning 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.
Grade 3 (>30% BSA with active skin toxicity*)	• **Omit alpelisib** dose until rash /skin toxicity is improved to Grade 1 or resolved, • **Strongly** recommend documentation by photography and performing a skin biopsy. • Initiate high potency topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone for at least 28 days • Add systemic corticosteroids 20-40mg/d • Add oral anti-histamine (sedative or non-sedative) • If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued. Re-start alpelisib dose once rash /skin toxicity is fading but is no longer active (G1): • at a 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

[redacted]

Worst toxicity – CTCAE Grade (value)	Dose Modifications for alpelisib
	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 patients with symptoms like burning 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. 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 patient from alpelisib • Consult a dermatologist, strongly recommend documentation by photography and performing a skin biopsy if clinically indicated • 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 patient from alpelisib treatment • Consult dermatologist, strongly recommend documentation by photography and performing a skin biopsy if clinically indicated. 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.	
Investigations (Pulmonary disorders)	
Pneumonitis	
Please see specific instructions in Section 6.3.2.1.1	
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation (see also **Section 6.3.2.1.4**)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥ 3 (> 2.0 x ULN)	Omit dose until resolved to baseline, then • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, then ↓ 1 dose level Note: • In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and

[redacted]

Worst toxicity – CTCAE Grade (value)	Dose Modifications for alpelisib
	continue to assess fractionated amylase) as specified in Section 6.3.2.1.4
Note: Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Investigations (any other)	
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue from alpelisib Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)

For additional details on the safety profile of alpelisib, please refer to the alpelisib Investigator Brochure.

[redacted]

6.3.2 Follow-up for toxicities

All patients must be followed up for safety (adverse events and serious adverse events) for 30 days following the last dose of study treatment. Patients should have weekly follow-up for 30 days after discontinuation of study treatment or resolution of the AE to ≤ grade 1, whichever occurs first. Post treatment follow-up (for safety) includes all study assessments appropriate to monitor the event.

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

6.3.2.1 Additional follow-up for selected toxicities

6.3.2.1.1 Management of pneumonitis/Interstitial lung disease

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

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

Patients who are suspected to have developed pneumonitis should interrupt alpelisib immediately (but may continue fulvestrant or letrozole if clinically indicated) and undergo appropriate imaging (high resolution CT scan) and broncho-alveolar lavage (BAL) and 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 study 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.

Table 6-4 Management of pneumonitis

Pneumonitis (any grade)	Immediately interrupt alpelisib for any case of suspected pneumonitis. Fulvestrant or letrozole may be continued, if clinically indicated. Obtain appropriate imaging (high resolution CT scan) and consider BAL and biopsy if appropriate based on clinical judgment. See Section 6.3.2.1.1 for details of management of pneumonitis. Treatment for pneumonitis should be initiated based on institution guidelines and generally includes high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Alpelisib should be permanently discontinued in all patients with confirmed pneumonitis

6.3.2.1.2 Guidelines for the treatment of study drug induced skin toxicity

Skin toxicity is an adverse drug reaction observed with PI3Ki agents.

[redacted]

Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as an adverse event. The most frequent skin adverse events 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. If there are no new lesions or new areas of involvement developing, and if the appearance is changing color from red to pale or light brown, it is likely the eruption has begun to fade, and not considered active any longer. 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, or Erythema multiforme or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected.

Workup for skin toxicity events includes skin photography, a complete blood count with differential, and a full chemistry panel. A paired skin biopsy should be obtained (from both affected and an unaffected skin area) for local histopathology assessment to further assess the skin toxicity, especially to confirm suspected diagnosis of any severe cutaneous reactions.

In case of a Grade 3/4 skin toxicity, Novartis strongly recommends that photographs are taken and a skin biopsy is performed and stored at the site for source documentation. Antihistamines administered prior to rash onset may decrease incidence and severity of rash based on SOLAR-1 Study; 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. Antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib.

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

- Consultation with a dermatologist should always be considered.
- 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 (GABA) Agonists: Gabapentin 300 mg every 8 hours, Pregabalin 50-75 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 GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others adverse events.

For grade 4 skin events or any grade of severe cutaneous reactions (including SJS, TEN, EM, DRESS), alpelisib treatment must be permanently discontinued without any re-challenge.

If dry skin has been reported, it is recommended that patients with dry skin use mild and fragrance free soaps and detergents. According to the severity and BSA extension patients may apply mild moisturizers, e.g. ammonium lactate cream 12%.

[redacted]

Although preclinical experiments demonstrated that alpelisib has no potential phototoxic effect, patients 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. Patients 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.

6.3.2.1.3 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 2012). Alpelisib induced hyperglycemia is generally manageable with adequate antidiabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Patients with pre-diabetes (i.e. FG 100 – 125 mg/dl; 5.6 - 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 patients, 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. Patients should always be instructed to follow dietary guidelines provided by the American Diabetes Association and/or the European Association for the study of Diabetes, e.g. 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)'.

Hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) and diabetic ketoacidosis (DKA) are two of the most serious metabolic complications associated with hyperglycemia. DKA is characterized by ketoacidosis and a comparatively lower hyperglycemic level (blood glucose 250 mg/dL-600 mg/dL), while HHNKS is characterized by more severe hyperglycemia (blood glucose > 600 mg/dL) together with hyperosmolarity and dehydration without significant ketoacidosis. HHNKS is also known as non-ketotic hyperosmolar syndrome, hyperosmolar hyperglycemic state or hyperglycemic hyperosmolar non-ketotic coma. Most patients with HHNKS have a known history of diabetes mellitus Type 2. HHNKS usually develops over a course of many days to weeks, unlike DKA which can develop over the course of a few hours or days.

Detailed guidelines for management of alpelisib induced hyperglycemia is provided in Table 6-3. This includes early administration of metformin or a sodium-glucose cotransporter 2 (SGLT2) inhibitor (alone or in combination with metformin). For more details on metformin XR, please refer to Table 6-3.

Local standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting glucose will be performed locally for rapid availability for safety evaluation and management guidance. However, it is strongly recommended that dose reduction be based on FPG only.

[redacted]

Special attention should be paid to the risk of hypoglycemia in patients 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 is highly recommended for better assessment and management of alpelisib-induced hyperglycemia.

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

Patient 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).

Patients who discontinue study 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 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 study 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.

6.3.2.2 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI. These events should be considered as clinically important 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 x ULN should be followed by repeat testing within 48 to 72 hours.

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

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

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN

[redacted]

- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x 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-glutamyltranspeptidase (GGT), Glutamate dehydrogenase (GLDH), prothrombin time (PT)/International Normalized Ratio (INR), alkaline phosphatase, albumin, and creatine kinase.

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

Perform relevant examinations (ultrasound or MRI, Endoscopic Retrograde Cholangio Pancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an Alkaline Phosphatase (ALP) elevation > 2.0 x 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 whether 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.

If DILI unlikely - interrupt treatment. Treat identified cause according to institutional guidelines. If resolved, reduce by one dose level. Re-administration of study treatment should be considered only if the investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study 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 Tests (LFT) 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

[redacted]

CMV, HSV, 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.

6.3.2.3 Guidelines for hypersensitivity

Alpelisib and combination drug are associated with hypersensitivity reactions, including anaphylaxis and angioedema. These are manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, hypotension, dizziness, tachycardiaand facial or laryngeal oedema. 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.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol (see Section 6.3 for details).

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

Medications required to treat adverse events, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed, except if specifically prohibited (see Section 14, Appendix 1).

All medications (other than study drug) and significant non-drug therapies (including vitamins, physical therapy, and blood transfusions) administered within 30 days prior to the start of study treatment and up to 30 days after the last dose of study treatment must be recorded on the Concomitant Medications or the Surgical and Medical Procedures eCRF (Core Phase only).

The investigator should instruct the participant to notify the study 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

[redacted]

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

6.4.1.1 Oral anti-diabetics

Patients who develop hyperglycemia during the study should be treated according to the ADA (American Diabetes Association) guidance and/or European Association for the study of Diabetes (EASD).

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 sodium-glucose cotransporter 2 (SGLT2) inhibitors as per standard practices/standard of care, 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 4 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.

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, 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. The decision to initiate an SGLT2 inhibitor alone in combination with metformin is at the discretion of the investigator. For more details on metformin XR, please refer to Table 6-3.

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6.4.1.2 Gastric protection agents

Alpelisib is characterized by a pH-dependent solubility but can be co-administered with acid reducing agents (ARAs, 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 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 AUC of on average by 21% when administered after a meal.

[redacted]

6.4.1.3 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 and should therefore be used with caution and patients closely monitored.

6.4.1.4 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 study should be assessed by appropriate image modalities to exclude disease progression per RECIST 1.1and the reason for its use must be clearly documented. If disease progression is documented, the participant should discontinue study treatment. No dose modification of study treatment is needed during radiotherapy.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during combined alpelisib, fulvestrant, or letrozole treatment in this study are listed below (see Table 14-1) in Appendix 1, 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:

- Sensitive substrates for CYP3A4, CYP2B6, CYP2C9 and/or which have a narrow therapeutic index (Table 14-1)
- **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 14-1) "List of CYP450 substrates to be used with caution"). Alternatively, therapeutic anticoagulation may be accomplished using low- molecular weight heparin or Direct Thrombin inhibitors (DTIs) 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, sensitive CYP2B6 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 14-1) "List of CYP450 substrates to be used with caution")

[redacted]

- **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 14-2). 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 6.4.4) for being strong inducers of CYP3A such as St. John's Wort (Hypericum perforatum) and Avasimibe (see Table 14-2) or BCRP inhibitors such as Curcumin (see Table 14-3). 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. The use/frequency of use should be documented as a concomitant medication. Subjects closely monitored for increased adverse reactions (as the relevance of this interaction in vivo is currently unknown). In case of unexpected toxicities, subjects should stop using all herbal medications. Use of all such medications (including frequency of administration) should be documented.
- Anticoagulants: Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants should be used with caution and fully avoided whenever possible because of its known interaction with many commonly used medications and certain foods. Alternatively, therapeutic anticoagulation may be accomplished using low-molecular weight heparin or Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors.

Please refer to the investigator brochure for more information.

6.4.3 Use of bone modifying agents (BMA)

The use of bone modifying agents (BMA, e.g. bisphosphonates/denosumab regardless of indication is allowed provided subjects have been on stable doses for at least 2 weeks prior to randomization. Stable dose should be maintained during the treatment period.

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

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

Participants requiring initiation of BMA treatment during the course of the study should be assessed by appropriate image modalities to exclude disease progression; if disease progression is documented, the subject should discontinue study treatment. If BMA is to be started after the first dose of study treatment, the reason for its use must be clearly documented.

Osteonecrosis of the jaw (ONJ) is a known adverse reaction for BMA. In the phase III Study C2301, 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

[redacted]

experiencing ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid). Therefore, in subjects 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 / receptor activator of nuclear factor kappa-B (RANK)-ligand inhibitors (e.g. denosumab) should be followed.

6.4.4 Prohibited concomitant therapy

The following medications are prohibited during treatment in this study (see Table 14-2 and Table 14-3 in Appendix 1), 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 inducers as it could potentially reduce the effectiveness of alpelisib (see Table 14-2).
- Inhibitors of Breast Cancer Resistance Protein (BCRP) efflux transporter: Avoid the use of BCRP inhibitors in subjects treated with alpelisib (see Table 14-3). If unable to use alternative drugs, closely monitor for increased adverse reactions.
- Other investigational and antineoplastic therapies

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Agents required for managing adverse events, cancer symptoms, and supportive care agents, such as anti-emetics, anti-diarrheal and probiotics are allowed unless listed above and/or in Appendix 1.

6.5 Patient numbering, treatment assignment

6.5.1 Patient numbering

Each patient is identified in the study by a subject number (Subject No.), that is assigned when the patient is first enrolled for molecular pre-screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The subject number is a 7 digit number that consists of a 4 digit center number (assigned by Novartis) followed by a sequential 3 digit subject numbers. Upon signing the molecular pre-screening informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to continue to the next phase or start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 10 days if the patient does not start treatment.

6.5.2 Treatment assignment

The assignment of a patient to a particular cohort will be coordinated by Novartis.

[redacted]

At the start of the Core Phase, patients will be assigned to a cohort based on previous therapy (AI, fulvestrant or systemic chemotherapy as indicated below); patients whose prior treatment is CDK 4/6 inhibitor plus fulvestrant will be enrolled in Cohort B until Cohort B enrollment is closed and then in Cohort C until it is closed for enrollment,:

Cohort A: Patients who received any CDK 4/6 inhibitor plus any AI as immediate prior treatment will receive alpelisib + fulvestrant

Cohort B: Patients who received any CDK 4/6 inhibitor plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole

Cohort C: Patients who received systemic chemotherapy or ET (as monotherapy or in combination except for CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant.

6.5.3 Treatment blinding

This is an open label study.

6.6 Study drug preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (for more details, please refer Section 6.1 “Study treatment”). Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive alpelisib on an outpatient basis.

Fulvestrant or letrozole with or without LHRH agonists (goserelin or leuprolide (if applicable)) should be dispensed according to local prescribing information and practice.

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

As per Section 2.6.4, during a Public Health emergency as declared by Local or Regional

authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant’s home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, regular phone calls or virtual contacts (every 3 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

[redacted]

6.6.1 Study treatment packaging and labeling

Study treatment, alpelisib, will be provided as global clinical open label supply and will be packed and labeled under the responsibility of Novartis, GCS.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength). Responsible site personnel will identify the study treatment package(s) to dispense by the medication number(s) assigned by IRT to the patient. Site personnel will add the patient number on the label. If the label has 2-parts (base plus tear-off label), immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the package and affix it to the patient's source document.

Table 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Alpelisib	Tablets in bottles 50 mg 200 mg	Labeled as BYL719 50mg and BYL719 200mg Once daily dosing
Fulvestrant	Refer to local product information	Refer to local product information
Letrozole	Refer to local product information	Refer to local product information
Goserelin	Refer to local product information	Refer to local product information.
Leuprolide	Refer to local product information	Refer to local product information.

Fulvestrant, letrozole or LHRH agonist (goserelin or leuprolide) packaging and labeling will be according to locally available supplies and according to local regulations.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, alpelisib should be stored according to the instructions specified on the drug labels and in the Investigator's Brochure.

Study treatments will be procured locally according to local practice and regulation, or supplied by Novartis (or its designee).

Table 6-7 Supply and storage of study treatments

Study treatments	Supply	Storage
Alpelisib	Centrally supplied by Novartis	Refer to study drug label
Fulvestrant	Supplied locally or centrally based on local regulations	Refer to local product information
Letrozole	Supplied locally	Refer to local product information
Goserelin	Locally	Refer to local product information
Leuprolide	Locally	Refer to local product information

6.6.3 Study drug compliance and accountability

[redacted]

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site. If study treatment is administered at home e.g. oral medication, participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The "S" in the table denotes the assessments that are only in the patient's source documentation and do not need to be recorded in the clinical database. No eCRF's will be used as a source document. The "D" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor.

Participants who discontinue from study treatment are to return for
reason the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

As per Section 2.6.4, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Allowed visit windows are specified as follows:

- Molecular pre-screening must occur by Day -21 before the start of treatment.
- Screening assessments, apart from those listed below, must occur before 21 days of the start of treatment as per Table 7-1.
- For visits, a general ±7 day window is allowed except for C1D1 radiological assessments must be performed as outlined in Table 7-1 and Table 7-2.

Every effort should be made to follow the schedule outlined in Table 7-1 and Table 7-2.

[redacted]

Table 7-1 Visit evaluation schedule – Core Phase

	Category	Reference to Protocol Section	Screening Phase			Treatment Phase						End of study treatment (EoT) - Core Phase	Post treatment and survival follow-up phase		
Visit Name			**Molecular Pre-screening (by Day -21)**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D15**	**Subsequent cycles (Day 1)**	**Within 21 days of last dose**	**30 days after last dose for safety**	**Every 12 weeks for efficacy applicable**	**Survival (Every 12 weeks)**
				-21 to -1	**-14 to -1**										
Obtain molecular Pre- screening informed consent	D	7.1.1	X												
Obtain main informed consent	D	7.1.2		X											
IWRS/IRT Registration	S	7.1.2.1	X												
Patient History															
Demography	D	7.1.2.3		X											
Inclusion/exclusion criteria	D	5.2 / 5.3		X											
Eligibility checklist (within IRT)	S	6.5			X										
Medical history	D	7.1.2.3		X											
Diagnosis and extent of cancer	D	7.1.2.3		X											
Prior antineoplastic therapy	D	7.1.2.3		X											

[redacted]

	Category	Reference to Protocol Section	Screening Phase			Treatment Phase						End of study treatment (EoT) - Core Phase	Post treatment and survival follow-up phase		
Visit Name			**Molecular Pre-screening (by Day -21)**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D15**	**Subsequent cycles (Day 1)**	**Within 21 days of last dose**	**30 days after last dose for safety**	**Every 12 weeks for efficacy applicable**	**Survival (Every 12 weeks)**
				-21 to -1	**-14 to -1**										
Prior/concomitant medications	D	6.4 / 7.1.2.3		X		Continuous up to 30 days after last dose of study treatment									
Surgical and medical procedures	D	7.1.2.3		X		Continuous up to 30 days after last dose of study treatment									
Antineoplastic therapies since discontinuation of study treatment	D	7.2.1.2										X	X	X	X
IWRS/IRT cohort assignment	D	6.5.2			X										
End of phase disposition	D	7.1			X							X		X	
Physical Examination															
Performance status (ECOG)	D	7.2.2.4			X				X		X	X			
Height	D	7.2.2.3			X										
Weight	D	7.2.2.3			X				X		C3D1 and then as clinically indicated	X			

[redacted]

	Category	Reference to Protocol Section	Screening Phase			Treatment Phase						End of study treatment (EoT) - Core Phase	Post treatment and survival follow-up phase		
Visit Name			**Molecular Pre-screening (by Day -21)**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D15**	**Subsequent cycles (Day 1)**	**Within 21 days of last dose**	**30 days after last dose for safety**	**Every 12 weeks for efficacy applicable**	**Survival (Every 12 weeks)**
				-21 to -1	**-14 to -1**										
Vital signs	D	7.2.2.2			X	X	X	X	X	X	X	X			
Physical examination	S	7.2.2.1			X		X	X	X	X	As clinically indicated	X			
Laboratory Assessments															
Hematology	D	7.2.2.5.1			X			X	X		X	X			
Chemistry (Full)	D	7.2.2.5.2			X				X			X			
Chemistry (Partial)	D	7.2.2.5.2						X			X				
Fasting plasma glucose	D	7.2.2.5.3			X										
Fasting or random blood glucose	D						X	X	X	X	X	X			
HbA1c	D	7.2.2.5.3			X				C2D1 and then every 3 cycles			X			
Fasting lipid panel	D	7.2.2.5.3			X							X			
Fasting lipase, Fasting amylase	D	7.2.2.5.3			X						C3D1 and then as clinically indicated	X			
Coagulation	D	7.2.2.5.4			X										
FSH and/or estradiol	D	7.2.2.5.6			X										

[redacted]

	Category	Reference to Protocol Section	Screening Phase			Treatment Phase						End of study treatment (EoT) - Core Phase	Post treatment and survival follow-up phase		
Visit Name			**Molecular Pre-screening (by Day -21)**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D15**	**Subsequent cycles (Day 1)**	**Within 21 days of last dose**	**30 days after last dose for safety**	**Every 12 weeks for efficacy applicable**	**Survival (Every 12 weeks)**
				-21 to -1	**-14 to -1**										
Urinalysis (macroscopic)	D	7.2.2.5.5			X	As clinically indicated						X			
Serum Pregnancy test (only premenopausal women)	D	7.2.2.5.6		X								X			
Urine Pregnancy test (only premenopausal women)	D	7.2.2.5.6				X every cycle									
HIV testing (only if required by local regulations	S	5.2		X											
Imaging/Other Assessments															
Tumor assessment and response by RECIST v1.1 criteria	D	7.2.1.1 /14.5		X		Every 12 weeks until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, and at EOT (If PR/CR is reported, confirmation of response is required; confirmatory assessment should be performed ≥ 4 weeks after response is first documented). **Note**: tumor assessments must be continued even after start of new antineoplastic therapy for patients that did not have progression.									
12-Lead ECG	D	7.2.2.7.1		X		X					As clinically indicated	X			

[redacted]

	Category	Reference to Protocol Section	Screening Phase			Treatment Phase						End of study treatment (EoT) - Core Phase	Post treatment and survival follow-up phase		
Visit Name			**Molecular Pre-screening (by Day -21)**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D15**	**Subsequent cycles (Day 1)**	**Within 21 days of last dose**	**30 days after last dose for safety**	**Every 12 weeks for efficacy applicable**	**Survival (Every 12 weeks)**
				-21 to -1	**-14 to -1**										
Cardiac imaging (MUGA or ECHO)	D	7.2.2.7.2		X							As clinically indicated	X			
Safety															
Adverse events	D	8.1	X	X		Continuous, up to 30 days after the last dose of study treatment									

[redacted]

[redacted]

	Category	Reference to Protocol Section	Screening Phase			Treatment Phase						End of study treatment (EoT) - Core Phase	Post treatment and survival follow-up phase		
Visit Name			**Molecular Pre-screening (by Day -21)**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D15**	**Subsequent cycles (Day 1)**	**Within 21 days of last dose**	**30 days after last dose for safety**	**Every 12 weeks for efficacy applicable**	**Survival (Every 12 weeks)**
				-21 to -1	**-14 to -1**										
[redacted]															
Study Drug Administration															
Alpelisib-oral	D	6.1.1				Daily									
Fulvestrant-injection (Cohort A & C)	D	6.1.1				X		X	X		X				
Letrozole-oral (Cohort B)	D	6.1.1				Daily									
Goserelin (men/ premenopausal only)	D	6.1.1				X			X		X				
Leuprolide (men/ premenopausal only)	D	6.1.1				X			X		X				

[redacted]

	Category	Reference to Protocol Section	Screening Phase			Treatment Phase						End of study treatment (EoT) - Core Phase	Post treatment and survival follow-up phase		
Visit Name			**Molecular Pre-screening (by Day -21)**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C2D1**	**C2D15**	**Subsequent cycles (Day 1)**	**Within 21 days of last dose**	**30 days after last dose for safety**	**Every 12 weeks for efficacy applicable**	**Survival (Every 12 weeks)**
				-21 to -1	**-14 to -1**										
Survival Follow-up	D	7.1.9													X

[redacted]

Table 7-2 Visit evaluation schedule – Extension Phase

	Category	Reference to Protocol Section	Treatment Phase						End of study treatment (EoT) Extension Phase	Post treatment extension phase
Visit Name			**EXT C1D1**	**EXT C2D1**	**EXT C3D1**	**EXT C4D1**	**EXT C5D1**	**Subsequent cycles (EXT CXD1)**	**Within 21 days of last dose**	**30 days after last dose for safety**
Antineoplastic therapies since discontinuation of study treatment	D	7.2.1.2							X	X
End of phase disposition	D	7.1							X	X
Confirmation of clinical benefit	D	7.1.4	Every 3 months **±7 days**							
Urine Pregnancy test (only premenopausal women)	S	7.2.2.5.6	X every cycle							
Adverse events	D	8.1	Continuous, up to 30 days after the last dose of study treatment							
Alpelisib-oral	D	6.1.1	Daily							
Fulvestrant-injection (Cohort A & C)	D	6.1.1	X	X	X	X	X	X		
Letrozole-oral (Cohort B)	D	6.1.1	Daily							
Goserelin (men/ premenopausal only)	D	6.1.1	X	X	X	X	X	X		
Leuprolide (men/ premenopausal only)	D	6.1.1	X	X	X	X	X	X		

[redacted]

7.1.1 Molecular pre-screening

After signing the molecular pre-screening consent, tumor tissue (archival or newly obtained) will be sent to a Novartis-designated central laboratory to either analyze or confirm PIK3CA mutational status. This will be conducted during a pre-screening phase prior to study screening and enrolling into the trial (all pre-screening activities must be completed by Day -21).

Patients with a pathology report indicating PIK3CA mutant status, by a certified laboratory using a validated PIK3CA mutation assay (either from tissue or blood); must still provide a tumor sample (either archival or newly obtained) to confirm PIK3CA status by a Novartis designated central laboratory.

It is recommended to provide a tumor sample collected after the most recent progression or recurrence. Tumor tissue requirements, along with shipping requirements, will be detailed in the laboratory manual provided by the central laboratory.

7.1.2 Screening

Once PIK3CA mutation has been confirmed (either by Novartis designated central laboratory or certified laboratory using validated PIK3CA mutation assay (see Section 7.1.1) pathology report (either from tissue or blood)) and after signing the study ICF, the screening assessment will be done within 1 to 21 days prior to start of study treatment (see Table 7-1). Any screening assessment that is done outside the screening window (day -21 to day -1) must be repeated prior to C1D1.

Re-screening of patients is only allowed once per patient. In this case, the subject number assigned to the patient initially will be used and the patient will be identified with this number throughout his/her entire participation to the study.

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

Any imaging assessments already completed during the regular work-up of the patient within 45 days prior to study treatment, including before signing the main study ICF can be considered as the baseline images for this study.

7.1.2.1 Eligibility screening

In order to determine and confirm the eligibility of the patient, once all screening procedures are completed, an eligibility checklist must be completed in the IRT system by the investigator or designee prior to study treatment assignment. Please refer and comply with detailed guidelines in the [IRT Manual].

[redacted]

7.1.2.2 Information to be collected on screening failures

Subjects who signed an ICF but failed to be started on treatment for any reason will be considered a screen failure.

The screening failures will be entered on the Screening Phase Disposition Page. Pre-screening failure information will only be entered into the IRT system.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported.

7.1.2.3 Patient demographics and other baseline characteristics

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

- Demography (Date of birth and initials (where permitted), sex, race, ethnicity, source of patient referral)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade.
- ER, PgR, and HER2 status
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.

Furthermore the following assessments will be performed:

- Vital signs
- Height, weight
- Physical examination
- Performance status (ECOG)
- Laboratory evaluations (e.g., hematology, coagulation, biochemistry, fasting plasma glucose/c-peptide/serum lipid profile/HbA_{1c}/lipase/amylase, FSH, pregnancy, urinalysis)
- ECG
- ECHO/MUGA
- Radiological assessments (e.g. CT Scan)

7.1.3 Treatment period

[redacted]

Patients will be treated with fulvestrant or letrozole plus alpelisib until disease progression, unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow-up, death, 18 months after LPFT (Core Phase) and until 36 months of the Extension Phase, discontinuation from the study treatment due to any other reason or the sponsor terminates the study. For details of assessments, refer to Table 7-1 and Table 7-2.

7.1.4 Extension Phase

Following the end of the Core Phase, patients continuing to derive benefit from study treatment who are not eligible for PSDS in their country based on local regulations will be transitioned to the Extension Phase until disease progression or any other reason for which the patient may be discontinued from study treatment (refer to Section 7.1.5). Patients will be re-consented for this amendment prior to continuing in the Extension Phase.

Patients must return to the study center on a monthly basis (4 weeks ± 7 days) for resupply of medication at which time drug dispensing information and adverse event information will be collected. A complete schedule of evaluations required for the Extension Phase is provided in Table 7-2. The procedures for patients entering the Extension Phase will proceed as follows:

- Safety laboratory assessments: chemistry, hematology, urinalysis, coagulation will be done as clinically indicated
- Treatment with assigned Cohort treatment from Core Phase will continue until lack of clinical benefit as assessed by Investigator at the site or any other reason for which the patient may be discontinued (refer to Section 7.1.5)
- Every 3 months ±7 days, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment. Although formal assessment of efficacy is not required during the Extension Phase, confirmation of continued treatment benefit as per standard of care is mandatory.
- When patients discontinue treatment for any reason, an end of treatment visit following discontinuation of the medication will be performed. The 30-day Follow-up visit will also be performed to check on continuing AEs/SAEs or any new AEs/SAEs that may have occurred.

7.1.5 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue study treatment for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

For patients who discontinue treatment during the Core Phase for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 12 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent. This does not apply to the

[redacted]

Extension Phase; once the patient enters the Extension Phase, tumor imaging is no longer required per the study schedule.

Patients may be withdrawn from the study treatment if any of the following occur:

- Adverse event or laboratory abnormalities as indicated in Section 6.3
- Lost to follow-up
- Physician decision
- Progressive disease
- Protocol deviation
- Study terminated by sponsor
- Technical problems

Patients must be withdrawn from the study treatment if any of the following occur:

- Pregnancy
- Death
- Subject/Guardian decision

Patients who discontinue study treatment should undergo an End of Treatment (EOT) visit followed by a 30 day safety follow-up. At EOT (during the Core Phase), a tumor assessment scan should be performed if the previous scan is older than 30 days.

The investigator or his/her delegate must also contact the IRT to register the patient's discontinuation from study treatment.

[redacted]

7.1.5.1 Replacement policy

Patients that enter the study based on a local pathology report without PIK3CA mutational status confirmed or if there is discordance with results will be replaced.

7.1.6 Withdrawal of consent/ opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs only when a patient:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use patient's data and biological samples), and
- No longer wishes to receive study treatment, and
- Does not want any further visits or assessments (including further study-related contacts), and
- Does not allow further collection of personal data.

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the patient therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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

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

If the patient agrees, a final evaluation at the time of the patient's study withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.1.7 Follow-up for safety evaluations

All patients who discontinue study treatment, including those who refuse to return for an EOT visit in both the Core Phase and Extension Phase, will be contacted for safety evaluations (i.e. assessment of adverse events and/or Serious Adverse Events, concomitant medications) for 30 days after the last dose of study treatment.

Patients should have weekly follow-up for 30 days after discontinuation of study treatment or resolution of the AE to ≤ grade 1, whichever occurs first. Post treatment follow-up includes all study assessments appropriate to monitor the event.

[redacted]

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc).

Data collected should be added to the Antineoplastic Therapy since Discontinuation of Study Treatment eCRF, Adverse Events eCRF and the Concomitant Medications eCRF (during the Core Phase).

7.1.8 Efficacy follow-up

During the Core Phase only: If a patient did not discontinue study treatment due to documented disease progression, death, lost to follow-up, or withdrawal of consent for efficacy follow-up, tumor assessments should continue to be performed every 12 weeks until documented disease progression, death, lost to follow-up, or withdrawn consent to efficacy follow-up or end of study. At that time, the reason for study completion should be recorded on the End of Study Disposition eCRF page for the Core Phase.

7.1.9 Survival follow-up

All patients will be followed for survival status (after progression) every 12 weeks regardless of treatment discontinuation reason (except if consent is withdrawn, death or patient is lost to follow-up) until death, lost to follow-up, or withdrawal of consent for survival follow-up or end of the Core Phase. Additional survival assessments may be performed outside the 3 months follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

7.1.10 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate eCRF.

7.1.11 End of post-treatment follow-up

Post-Treatment follow-up includes (post treatment efficacy, safety and survival). Prior to collecting survival follow-up information, the end of study disposition phase disposition eCRF page for the Core Phase will be completed once a patient has discontinued study treatment, completed safety follow-up, and can no longer perform efficacy assessment. During the Extension Phase, the end of study disposition phase disposition eCRF is completed after the safety follow-up is completed (Note: there is no efficacy or survival post treatment in the Extension Phase).

[redacted]

End of post-treatment follow-up (Core Phase) may occur due to one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by the sponsor
- Technical problems
- Subject/guardian decision
- Death

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Imaging tumor assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.1 (Appendix 5) based on RECIST v1.1 (Eisenhauer 2009) during the Core Phase. The imaging assessment collection plan is presented in Table 7-3.

Physical exam tumor assessments, photography, pathology/histology and cytology results, as well as, information regarding prior interventions, pre-existing radiographic findings that mimic metastatic disease at screening and on-study interventions should be captured in the appropriate eCRFs.

Screening imaging assessments

Imaging assessments will be performed at screening within 21 days of start of treatment (Day -21 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the patient within 45 days prior to start of treatment, including before signing the main study ICF, can be considered as the screening images for this study. Any imaging assessments obtained after study treatment cannot be considered screening images. The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain CT or MRI, if clinically indicated
- Localized bone CT, MRI or x-ray, that are not visible on the chest, abdomen and pelvis CT or MRI
- Skin visual inspection and measurement (only if skin lesions at screening)
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

If a patient is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not

[redacted]

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.

Localized CT, MRI or X-rays should be acquired for all lesions, 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, lesion will be measured and visually monitored.

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 study 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.

Core Phase Treatment phase imaging assessments

Imaging assessments as described in Table 7-3 should be performed using the same imaging modality used at screening, irrespective of study treatment interruption or actual dosing. Imaging assessments for response evaluation will be performed every 12 weeks (+/- 7 days) during the Core Phase. The 12 week interval should be followed regardless of whether study treatment is temporarily withheld or unscheduled assessments are performed.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, 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 screening 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 study 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 v1.1 (Appendix 5).

[redacted]

Extension Phase

During the Extension Phase there will be no per protocol efficacy assessments other than physician's determination as per standard of care of whether or not the patient is continuing to derive clinical benefit from the study treatment.

Table 7-3 Imaging assessment collection guidance

Procedure	Screening	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated, every 12 weeks at EOT a tumor assessment scan should be performed if the previous scan is older than 30 days
Brain CT or MRI	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Localized bone CT, MRI or x-ray	For any lesions that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Color photography (with scale/ruler)	For any skin lesions present	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

7.2.1.2 Progression on next-line therapy (PFS2)

For PFS2, the disease progression will be determined based on investigator assessment of progression on next-line therapy. For this purpose, subsequent anti-neoplastic therapies including start/end date, reason for discontinuation and date of disease progression will be captured in the antineoplastic therapy since discontinuation of treatment eCRF during the Core or Extension Phase depending on which phase the patient discontinues treatment.

7.2.2 Safety and tolerability assessments

Core Phase:

Safety will be monitored by assessing physical examination, vital signs, performance status evaluation, ECG, cardiac imaging, laboratory evaluations for hematology and biochemistry, including glucose monitoring as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

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

[redacted]

Extension Phase:

Safety assessments in the Extension Phase will consist of monitoring and recording all AEs including SAEs, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination will be performed at screening and at subsequent time points as specified in Table 7-1 during the Core Phase. The physical examination at screening can be done at Day 1 of Cycle 1 provided that it is done before the study treatment. 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 documented in the source documentation at the study site.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the adverse event page of the patient's eCRF.

7.2.2.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

7.2.2.3 Height and weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1 during the Core Phase.

7.2.2.4 Performance status

ECOG Performance status scale will be used as described in the Table 7-4 (during the Core Phase).

Table 7-4 ECOG performance status

Grade	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

7.2.2.5 Laboratory evaluations

[redacted]

Clinical laboratory analyses (hematology, fasting biochemistry (full or partial), fasting lipase, fasting amylase, fasting lipid panel/glucose/c-peptide, $HbA1_C$, coagulation, pregnancy test and urinalysis) are to be performed by the central laboratory. In case of urgent safety management of hyperglycemia, fasting or random blood glucose assessment may be done locally according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-5 for the Core Phase.

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

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

The results of the local laboratory during the Core Phase will be recorded in the eCRF if any of the following criteria are met:

- A treatment decision was made based on the local results, or
- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event severity is worse than the one reported by the central lab, or
- There are no concomitant central results available

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g. require dose modification and/or interruption of study 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 Common Terminology Criteria for Adverse events (CTCAE) version 4.03. Additional analyses are left to the discretion of the investigator.

Visit windows of +/- 7 days are allowed. Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

[redacted]

Table 7-5 Central clinical laboratory parameters collection plan during Core Phase

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, RBC morphology, White blood cells, - Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry (Full)	Calcium, Magnesium, Potassium, Sodium, C-peptide, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Gamma-glutamyl-transferase (GGT), Total Protein, Albumin, Creatinine, Creatine kinase (CK), Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Lactate dehydrogenase (LDH),
Chemistry (Partial)	Creatinine, Creatine kinase, ALT, AST, Total Bilirubin
Fasting Lipid panel	Total Cholesterol, LDL, HDL, Triglycerides
Coagulation	International normalized ratio (INR) and Activated partial thromboplastin time (aPTT) or Partial thromboplastin time (PTT)
Pregnancy	Serum and Urine
Urinalysis	Macroscopic Panel (Dipstick) (WBC, blood, protein and glucose)
Additional tests	Amylase fasting, Lipase fasting, HbA1c, FG, RBG, FSH, estradiol
All laboratory analysis will be performed centrally during the Core Phase; however for urgent safety management or inclusion criteria, laboratory assessments may be allowed to be done locally and entered on an unscheduled local eCRF page (laboratory assessment performed locally should be sent to central laboratory as well for central analysis). During the Extension Phase, all laboratory assessments needed will be done via local laboratory testing. Note: Fasting plasma glucose at Day 8 and Day 15 of Cycle 1 should be performed both locally and centrally for rapid availability for safety evaluation and dose adjustments.	

A central laboratory will be used for analysis of all specimens collected during the Core Phase. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [Laboratory Manual].

7.2.2.5.1 Hematology

Hematology tests are to be performed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 during the Core Phase and Table 7-5. The Hematology panel specifics are listed in Table 7-5.

7.2.2.5.2 Clinical chemistry

Biochemistry tests are to be performed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 during the Core Phase and Table 7-5. The full biochemistry panel specifics are listed in Table 7-5.

7.2.2.5.3 Monitoring fasting plasma glucose, random blood glucose, c-peptide, fasting lipid panel, amylase, lipase and HbA1C

Fasting c-peptide, amylase, lipase, HBA1C and lipid panel will be assessed by the central laboratory according to the schedule of assessments and collection plan outlined respectively

[redacted]

in Table 7-1 and Table 7-5 for the Core Phase. Patients must be fasting overnight for 8 to 12 hours prior to the blood draw. The study personnel will ask the patient whether she/he has been fasting, which will be captured in the eCRF as well.

Beginning with C1D8 until EOT of Core Phase, patients can have RBG testing, at the discretion of the PI.

7.2.2.5.4 Coagulation

INR and PTT or aPTT will be assessed by the central laboratory according to the schedule of assessments and collection plan during the Core Phase outlined respectively in Table 7-1 and Table 7-5.

7.2.2.5.5 Urinalysis

Urinalysis dipstick analysis (WBC, blood, protein and glucose) will be performed by the central laboratory according to Table 7-1 during the Core Phase. The full urinalysis panel specifics are listed in Table 7-5.

7.2.2.5.6 Pregnancy and Hormone Levels

Pregnancy tests are to be performed according to the Visit Evaluation Schedule for the Core Phase and Extension Phase as outlined in Table 7-1 , Table 7-2 and Table 7-5.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures)

A positive urine test is required to be confirmed by an immediate serum pregnancy test. A positive pregnancy test requires immediate interruption of study treatment until the assessment is confirmed. If positive, the patient must be discontinued from the study.

FSH and/or estradiol will be collected centrally and used for screening and confirmation of menopausal status during the Core Phase.

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above’.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements’.

Assessments of fertility:-‘Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

[redacted]

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline'.

7.2.2.6 Radiological examinations

In case of pneumonitis, patients will be monitored carefully according to Section 6.3.2.1.1. If pneumonitis develops during treatment in the Core Phase, additional chest CT scan or x-ray may be performed to follow-up on the event.

[redacted]

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed after the patient has been resting for 5-10 min prior to each time point during the Core Phase indicated in Table 7-6.

Table 7-6 Local ECG collection plan

Cycle	Patients	Day	Time	ECG Type
Screening	All	Day -21 to -1	Anytime	12 Lead
Cycle 1	All	Day 1	Pre-dose	12 Lead
EOT (Core Phase)	All	N/A	Anytime	12 Lead
Unscheduled sample as clinically indicated			Anytime	12 Lead

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

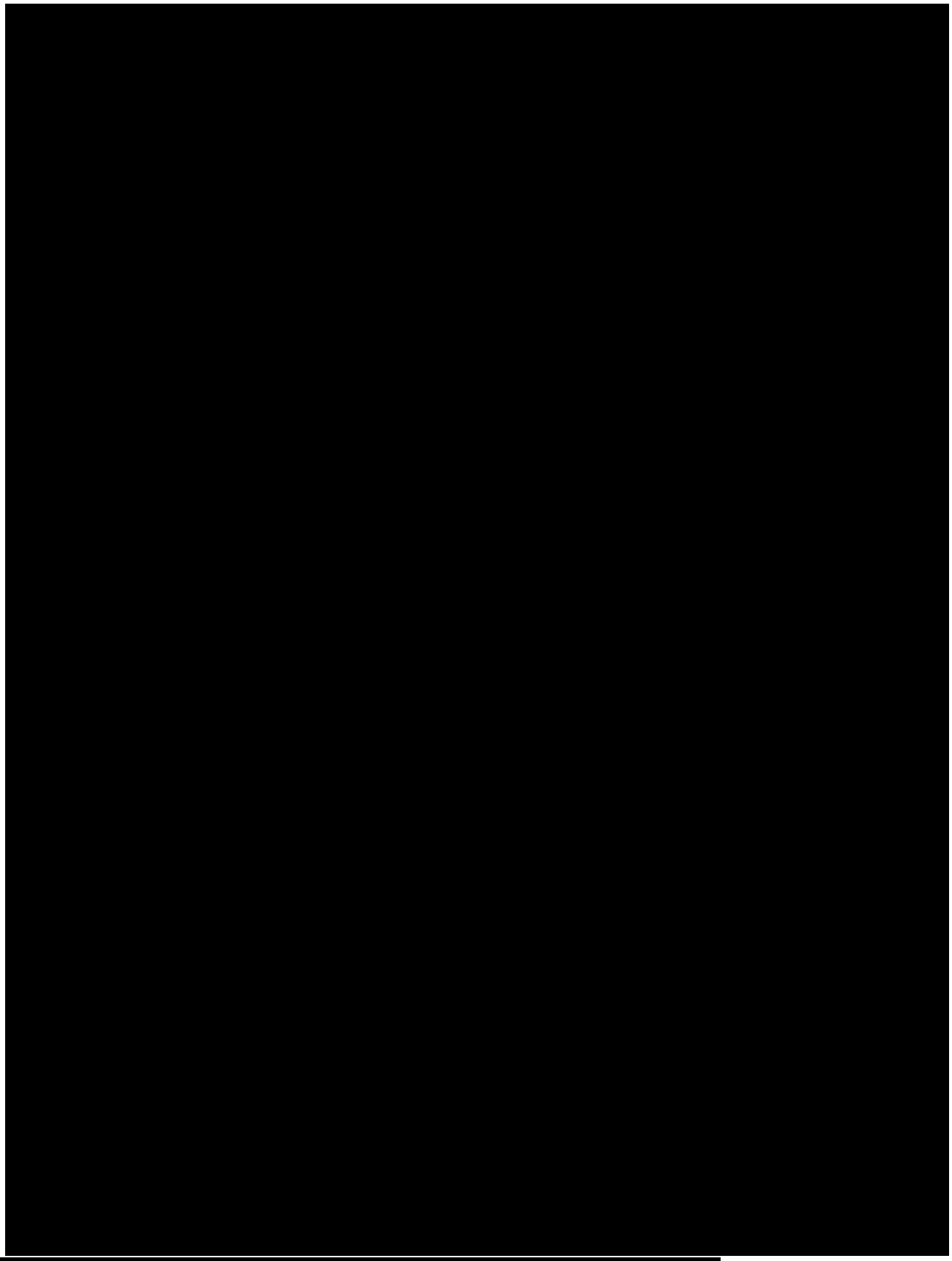
Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator.

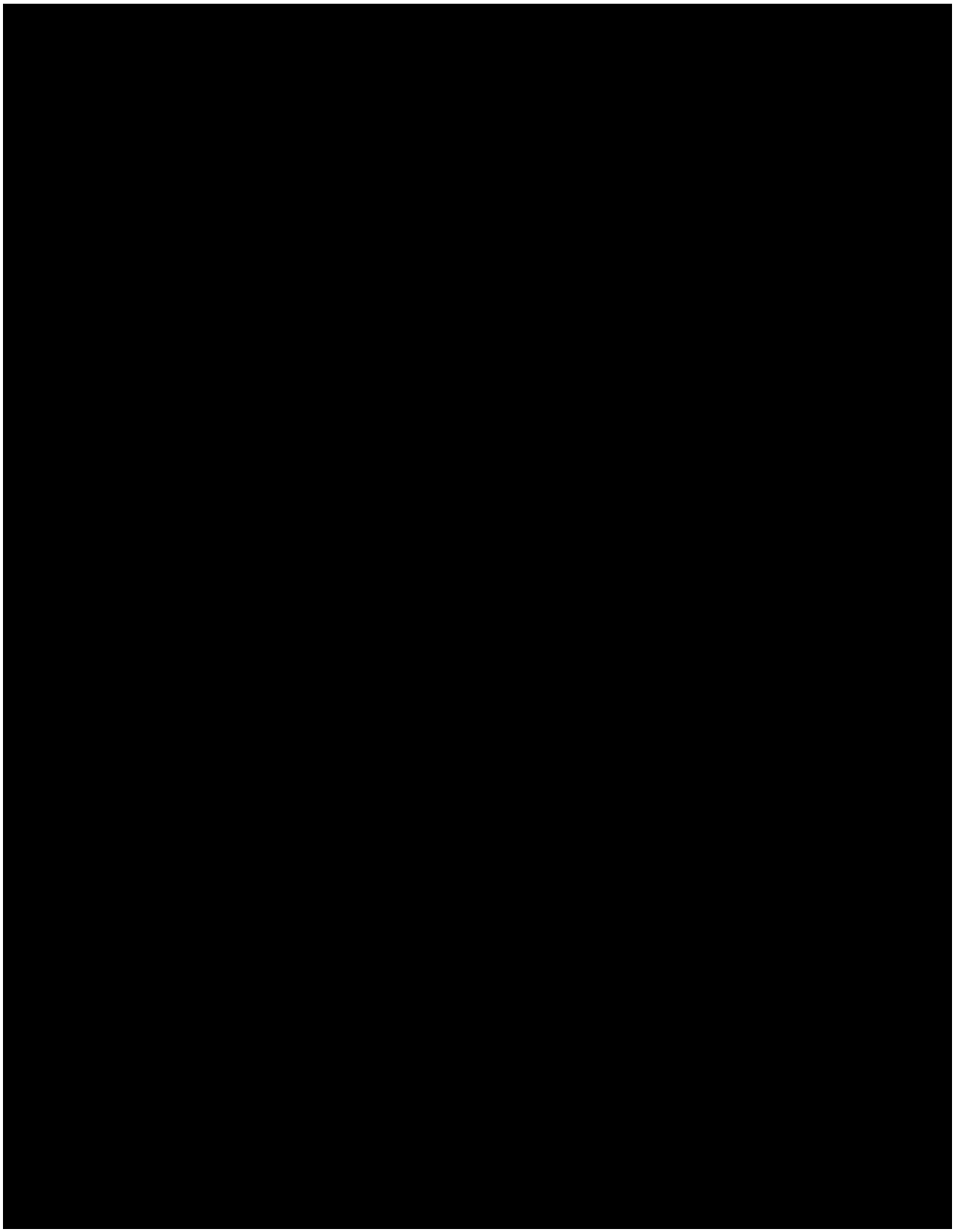
7.2.2.7.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

The left ventricular heart function will be evaluated by ECHO or MUGA at Screening and according to the Visit Evaluation Schedule for the Core Phase as outlined respectively in Table 7-1. Additional cardiac imaging during treatment is to be performed if indicated by clinical signs or symptoms. The same imaging modality should be used.

[redacted]

[redacted]





[redacted]

Other assessments

No additional tests will be performed on patients entered into this study.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear

[redacted]

diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

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

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that adverse event is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met (include for NCDS trials)
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

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

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, 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 serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will

[redacted]

be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special 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.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization

[redacted]

- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

For patients with unknown PIK3CA status and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For patients with known PIK3CA status who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis safety immediately without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail).

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: if more stringent, local regulations regarding reporting timelines prevail) An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

[redacted]

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis 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 study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable as this is an open label study.

8.4 Pregnancies

This trial is planned for men, post-menopausal women or premenopausal women with ovarian suppression. No pregnancies are expected for study patients. If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. The consent form is necessary to allow the investigator to collect and report information regarding the pregnancy.

To ensure patient safety, each pregnancy occurring while the patient is on study 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.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study 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 study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.5 Warnings and precautions

[redacted]

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

A Steering Committee (SC) will be established comprising investigators and Novartis personnel participating in the trial to ensure transparent management of the trial according to the protocol. The details of the steering committee, including roles will be defined in a steering committee charter.

A Novartis Safety Management Team (SMT) periodically reviews and evaluates all emerging data across the alpelisib program for potential safety signal assessment in a timely manner.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and

[redacted]

their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

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

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

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

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

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a

[redacted]

vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The primary analysis for each cohort will be performed 6 months after the last patient enrolled in that specific cohort has started treatment. The final analysis will be performed after LPLV of the study which include cumulative data (eg safety and clinical benefit) since the Core Phase analysis.

Prior to the final analysis, cohort specific analyses maybe performed when all patients included in the corresponding cohort have approximately 18 months of follow-up.

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

10.1 Analysis sets

10.1.1 Full analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned and who received one dose of study treatment. Patients will be analyzed according to the treatment they have been assigned to.

Modified full analysis set

The modified Full Analysis Set (mFAS) comprises all patients of the FAS population who have PIK3CA mutation confirmed by a Novartis designated laboratory. mFAS will be the primary population for the analysis of efficacy endpoints.

10.1.2 Safety set

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the assigned treatment if the patient took at least one dose of that treatment.

10.1.3 Per-protocol set

The Per-Protocol Set (PPS) consists of a subset of the patients in the mFAS who are compliant with requirements of the clinical study protocol. All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the data handling plan and statistical analysis plan. Sensitivity analyses of the primary endpoint may be performed using PPS.

[redacted]

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

Not applicable.

10.1.6 Other analysis sets

Not applicable.

10.2 Patient demographics/other baseline characteristics

The FAS will be used for the analyses below and repeated on mFAS for demographic characteristics.

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively.

Categorical data, such as gender, race will be presented by contingency type tables. Descriptive summary statistics (e.g. frequency, mean, median, range and standard deviation) will be used to present continuous data.

Relevant medical histories and current medical at baseline will be summarized separately by system organ class and preferred term in each cohort.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety set will be used for the analyses below.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th – 75th percentiles, minimum, and maximum will be presented.

The duration of exposure (in months) to "investigational drug" and combination partner (fulvestrant and letrozole) as well as the dose intensity will be summarized by means of descriptive statistics using the safety set. The duration of exposure will also be presented for the study treatment by cohort. The number of subjects with dose adjustments (reduction, interruption, or permanent discontinuation) and the reasons will be listed and summarized by cohort.

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

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

[redacted]

10.4 Primary objective

The primary objective of the study is to assess the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment per RECIST v1.1 separately in Cohorts A and C (alpelisib in combination with fulvestrant) and Cohort B (alpelisib in combination with letrozole) among patients with HR+, HER2-negative aBC harboring a PIK3CA mutation who have progressed on or after prior treatments.

The mFAS will be used for the primary efficacy analysis.

10.4.1 Variable

The primary efficacy endpoint is the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment using RECIST v1.1 in each cohort.

10.4.2 Statistical hypothesis, model, and method of analysis

A proportion of [redacted] of patients alive without progression after 6 months is considered as a clinically meaningful threshold in all the cohorts for this study. Therefore, evidence of treatment effect will be tested using the following hypothesis:

H_0: [redacted]

H_1: [redacted]

Where p is the proportion of patients who are alive without progression at 6 months.

The primary endpoint will be presented together with two-sided 95% confidence intervals using Clopper and Pearson (1934) exact method for all the cohorts separately. The null hypothesis will be rejected and evidence of treatment effect will be demonstrated if the lower bound of the 95% CI for observed proportion at 6 months is greater than [redacted] Table 10-1 displays the values of proportion of patients who are alive without any disease progression at 6 months and its 95% CI for selected number of patients alive without progressive disease out of 112 patients. To reject the null hypothesis [redacted] at least 44 patients need to be alive without progression at 6 months out of 112 patients in each cohort.

Table 10-1 Exact 95% Confidence Interval

Sample size	Number of patients alive without PD at 6 months (k)	Proportion k/N (%)	Exact 95% Confidence Interval (CI)	
			Lower (%)	Upper (%)
112	[redacted]			

[redacted]

10.4.3 Handling of missing values/censoring/discontinuations

Six months is defined in this study as 24 weeks ± 1 week. Therefore tumor assessments between week 23 and 25 will be considered for the primary analysis. For primary endpoint analysis, patients who progressed, died, or discontinued study before 6 months will be counted as a "failure".

10.4.4 Supportive and Sensitivity analyses

The primary analysis will also be performed on the FAS and may be repeated on PPS.

The primary analysis will also be repeated in patients from mFAS harboring a PIK3CA mutation as determined via ctDNA.

10.5 Secondary objectives

The secondary objectives in this study are to evaluate the progression free survival (PFS), progression free survival 2 (PFS2), overall response rate (ORR), clinical benefit rate (CBR), overall survival (OS) and duration of response (DOR), and safety. For efficacy secondary objectives, 95% confidence intervals will be provided as needed.

The secondary efficacy analysis will also be repeated in patients harboring a PIK3CA mutation as determined via ctDNA.

10.5.1 Secondary efficacy objective(s)

10.5.1.1 Progression free survival

PFS is defined as the time from the date of first dose of study medication to the date of the first documented progression or death due to any cause occurring in the study. PFS will be assessed based on local investigator's assessment according to RECIST v1.1 (see Appendix 5 for further details).

PFS will be censored if no PFS event is observed before the cut-off date. The censoring date will be the date of last adequate tumor assessment before the cut-off date. If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used (see Appendix 5). It is not intended to censor patients for new anticancer therapy prior to documented disease progression in the primary analysis.

The Kaplan-Meier estimate of the PFS survival function will be estimated and displayed. The resulting median PFS time will be given for each cohort with 95% confidence intervals, as well as 25th and 75th percentiles will be reported.

10.5.1.2 Progression free survival 2

PFS2 is defined as time from the date of first dose of study medication to the date of first documented progression on next-line therapy or death from any cause.

The first documented progression on next-line treatment is based on investigator assessment of PD (i.e. as captured on the anti-neoplastic therapy after treatment discontinuation eCRF page);

[redacted]

it is not necessary to continue to collect tumor assessments data for subsequent anti-neoplastic therapies for the purpose of PFS2.

PFS2 will be summarized using the Kaplan-Meier method on the mFAS. The resulting median PFS will be given with 95% confidence intervals for each cohort.

10.5.1.3 Overall response rate

ORR is defined as the proportion of patients with best overall response (BOR) of CR or partial response (PR), as per local investigator's assessment and according to RECIST v1.1 (see Appendix 5 for details). Patients with non-measurable lesions only at baseline will be included as 'responders' if they achieve a CR, otherwise they will be included as 'non-responders'.

ORR will be calculated based on the mFAS. ORR and its exact 95% confidence interval (Clopper and Pearson 1934) will be presented for each cohort.

10.5.1.4 Clinical benefit rate

Clinical Benefit Rate is defined as the proportion of patients with a best overall response of CR or PR or an overall lesion response of stable disease (SD) or Non-CR/ Non-PD lasting ≥ 24 weeks based on local investigator's assessment according to RECIST v1.1.

CBR will be calculated based on the mFAS. The CBR and its exact 95% confidence interval (Clopper and Pearson 1934) will be provided for each cohort.

10.5.1.5 Duration of response

DOR is the time from the date of first documented response (confirmed CR or PR) to the date of first documented progression or death due to underlying cancer. DOR only applies to patients whose best overall response is CR or PR according to RECIST v1.1 based on tumor response data per local investigator's assessment. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Patients continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment.

DOR will be listed and summarized for each cohort in the mFAS with confirmed BOR of CR or PR. DOR will be summarized using Kaplan-Meier estimates in patients with confirmed CR or PR within each cohort.

10.5.1.6 Overall Survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

OS is defined as the time from date of start treatment to date of death due to any cause. If a patient is not known to have died, then OS will be censored at the date of last known date patient alive.

[redacted]

The analyses for OS will be based on the FAS. The distribution function of OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals will be presented for each cohort.

10.5.1.7 Extension Phase Clinical Benefit

The secondary objective related to the Extension Phase of the study is to evaluate clinical benefit as assessed by the Investigator. Proportion of patients with clinical benefit as assessed by the Investigator will be summarized.

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

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

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

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication,
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication,
3. post-treatment period: starting at day 31 after last dose of study medication.

The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation, with the exception of summary table for all deaths. Those collected later than 30 days after study treatment discontinuation will be flagged in listings.

10.5.2.2 Adverse events (AEs)

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

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment. Deaths reportable as Serious Adverse Events and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and cohort.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

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

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

[redacted]

10.5.2.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (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 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following by cohort summaries will be generated separately for hematology, biochemistry tests and urinary laboratory tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges
- Listing of all notable laboratory abnormalities (i.e., newly occurring CTCAE v4.03 grade 3 or 4 laboratory toxicities)

For laboratory tests where grades are defined by CTCAE v4.03

- Number and percentage of patients with worst post-baseline CTCAE v4.03 grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE 4.03,

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

[redacted]

Laboratory values collected later than 30 days after study treatment discontinuation will be flagged in the listings.

10.5.2.4 Other safety data

Summary statistics for data from other tests will be provided, notable values will be flagged, and any other information collected will be listed as appropriate.

- ECGs: 12-lead ECGs including PR, QRS, QT, QTcF, and HR intervals will be obtained for each subject during the study. ECG data will be read and interpreted locally.
- Categorical Analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced by cohort.
- ECOG: Shift tables to compare baseline to the worst on-treatment value.

[redacted]

- Cardiac imaging: change from baseline to worst post-baseline in LVEF values.
- Vital signs: Data on vital signs will be tabulated and listed, notable values will be flagged.

10.5.2.5 Supportive analyses for secondary objectives

Not applicable.

10.5.2.6 Tolerability

Tolerability will be studied in terms of dose reductions and drug interruptions due to AE. Reasons for dose reductions and interruptions will be listed and summarized by treatment.

10.5.3 Pharmacokinetics

Not applicable.

[redacted]

10.5.5 Resource utilization

Not applicable.

10.5.6 Patient-reported outcomes

Not applicable.

10.6 Exploratory objectives

Not applicable.

10.7 Interim analysis

Three Interim Analyses (IA) are planned for this study. The first IA will be performed after at least [redacted] patients receiving alpelisib plus fulvestrant (cohort A) have at least 6 months of follow-up. The second IA will be performed when approximately [redacted] patients (50% enrolled patients) have been treated in the study (regardless of cohort) and have at least 6 months of follow-up. The third IA will be performed after the Core Phase has ended.

At the time of the first two IAs, preliminary efficacy (ORR, CBR) as well as key safety data will be analyzed in a descriptive fashion. The primary endpoint will not be analyzed and no statistical hypothesis will be tested.

The third IA will include all efficacy and safety data up to the end of the Core Phase.

Details of the IAs will be specified in the analysis plan.

10.8 Sample size calculation

A median PFS of at least 6 months (or 50% of patients who are alive without progression after 6 months) has been observed for alpelisib 300 mg plus fulvestrant 500 mg and also for palbociclib 125 mg plus fulvestrant 500 mg in PiK3CA mutant patients previously treated with AI (without CDK4/6 inhibitor) in [CBYL719X2101] and Paloma-3 (Cristofanilli 2016) studies respectively. Currently, there is no available clinical data in post-CDK4/6 inhibitor setting in PIK3CA mutant patients. Assuming that these patients after failure to CDK4/6 inhibitor will

[redacted]

have a lower median PFS than 6 months, a proportion of [redacted] of patients alive without progression after 6 months is considered as a clinically meani[redacted]l threshold in both cohorts for this study and was used for sample size calculation.

The sample size is based on an exact Binomial test for single proportion to test the null hypothesis H_0: [redacted] where p is the proportion of patients who are alive without progression at 6 months. With a one-sided 2.5% level of significance (two-sided 95% CI), a total sample size of 112 patients in each cohort is required in order to have a power of at least 90% when the true p ≥0.45. Table 10-2 provides the operating characteristics for N=112 and different true rates.

Table 10-2 Operating Characteristics

Sample size (N)	True rate	Prob (X≥44|True rate)
112	[redacted]	

The study will enroll a total of approximately 340 patients who have a PIK3CA mutation with at least 112 patients allocated into each Cohort A (alpelisib + fulvestrant), Cohort B (alpelisib + letrozole) and Cohort C (alpelisib + fulvestrant).

At the time of the first two Interim Analyses (IA) preliminary efficacy (ORR, CBR) will be analyzed in a descriptive fashion. The primary endpoint will not be analyzed and no statistical hypothesis will be tested. Therefore no multiplicity adjustment was made.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research

[redacted]

Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

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

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of 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 study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH E6 GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) and Core Data Sheet (CDS) for marketed drugs. This information will be included in the participant consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Molecular Prescreening Consent
- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for
  - Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the
- female partners of any male participants who took study treatment

[redacted]

[redacted]

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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

The study includes an optional sub studies/ DNA component which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments will in no way affect the participant's ability to join the main research study.

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

As per Section 2.6.4, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if

allowable by a local Health Authority.
Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs

by trial participant and person obtaining informed consent, etc.).

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

[redacted]

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported

on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to a paper eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic eCRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper eCRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

[redacted]

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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14 Appendices

14.1 Appendix 1 - List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or BYL719 and/or fulvestrant/letrozole. Please note that all lists in Appendix 1 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 6.4. In doubt please the contact medical monitor with any questions.

14.1.1 Permitted Medication to be used with caution

As described in this list of CYP substrates was compiled from the University of Washington's Drug Interaction Database (Updated April 2019). This list only meant to be used as a guide.

Table 14-1 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

14.1.2 Prohibited Medication

Strong inducers of CYP3A4

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

[redacted]

Table 14-2 List of prohibited strong inducers of CYP3A4

Category	Drug Name
Strong CYP3A Inducers	Apalutamide, Avasimibe[1], Carbamazepine, Enzalutamide, Ivosidenib, Lumacaftor, Mitotane, Phenobarbital, Phenytoin, Rifabutin, 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 14-3 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)

[redacted]

14.2 Appendix 2: Guidelines for the treatment of alpelisib induced diarrhea

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

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

Patient history of diarrhea

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

- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;
- Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;
- Instruct patients regarding risk of developing diarrhea;
- Perform baseline clinical/laboratory studies according to the trial protocol (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients);
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading (Table 14-4).

Table 14-4 NCI CTCAE version 4.03 grading of diarrhea for patients without colostomy

Toxicity	0	1	2	3	4
Diarrhea	None	Increase of < 4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements.					

[redacted]

First report of diarrhea

- Obtain history of onset and duration of diarrhea
- Description of number of stools and stool composition (e.g. watery, blood, mucus in stool)
- Assess patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)

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

Management of diarrhea

General recommendations:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (e.g. Metamucil®) and stool softeners (e.g. docusate sodium, Colace®)
- Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g. bananas, rice, apple sauce, toast)

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

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

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

[redacted]

with any antidiarrheal agents, the patient's response to treatment should be observed and appropriately documented in the source document and within the patient record.

Treatment of diarrhea CTCAE grade 1 or 2

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

12-24 hrs later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12 hrs diarrhea-free interval

Diarrhea unresolved

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

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

After 12-24 hrs:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12 hrs diarrhea-free interval

Diarrhea unresolved

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

[redacted]

Treatment of diarrhea CTCAE grade 3 or 4

Severe diarrhea CTCAE grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response.

After 12-24 hrs:

- If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 µg tid)
- Continue IV fluids and antibiotics as needed
- If diarrhea CTCAE grade 3 or 4 still persists patients should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea CTCAE grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg TID) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea workup

Perform appropriate tests (Fine et al 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or
- Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations

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

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

[redacted]

14.3 Appendix 3 Guidelines for the treatment of study drug induced stomatitis/oral mucositis

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

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

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

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
- Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with alpelisib metabolism (see Section 6.4 and Appendix 1).

[redacted]

14.4 Appendix 4 – Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-5 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 > 2x 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 14-6 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 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	· **No change to study 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 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	· **Interrupt study drug** · Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. · Follow- up for symptoms.

ALT	TBL	Liver Symptoms	Action
first) for more than two weeks			· Initiate close monitoring and workup for competing etiologies. · Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 14-7 Follow-up requirements for liver laboratory triggers

Criteria	***Actions required***	***Follow- up monitoring***
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	· Maintain treatment · Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	· Interrupt treatment · Repeat LFT within 48-72 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 x ULN	· Discontinue the study 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)

[redacted]

Criteria	*Actions required*	*Follow- up monitoring*
Any AE potentially indicative of a liver toxicity*	· Consider study 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.

*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

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.

[redacted]

14.5 Appendix 5 - Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

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Glossary

CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

[redacted]

1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 2 and the definition of best response in Section 3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

Indicate the assessment schedule for tumor assessments in the protocol. Frequency of tumor re-evaluation while on treatment should be adapted to the type and schedule of treatment, and the type of tumor treated. It should also be clearly stated how patients are followed for progression after discontinuation of study treatment.

It is assumed that all information which is considered for assessment of the tumor is captured in the RECIST eCRF, i.e. not merged from several sources.

2.1 Definitions

2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 3.2.9.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.

[redacted]

- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- **Cystic lesions**:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Non-measurable lesions** - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

If any lesion should be handled differently, this must be clearly stated and justified in the protocol, e.g. tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.

2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 3.2.9.

2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

[redacted]

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

If different window for baseline assessments is allowed in the protocol this must be justified in the protocol.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major “change in method” for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

If head and neck tumors and those of extremities are evaluated in the study, please specify the methods in detail in the protocol.

- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
    - If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases, PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.

[redacted]

  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Physical exams:** Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size and can be assessed using calipers.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

[redacted]

If tumor markers are used in the study for the response assessment, the criteria must be clearly stated in the protocol and the presence of abnormality in tumor markers must be entered in the eCRF page for RECIST evaluations (see also Section 2.4).

- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

When pathological response is being used, the protocol must clearly state details on how pathological responses are documented.

[redacted]

- **Clinical examination:** Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

If the protocol is considering specific symptoms as objective signs of clinical progression, e.g. bone pain or GI bleeding, then the criteria for clear worsening of these non-measurable 'lesions' indicative of PD should be clearly specified in the protocol. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the eCRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 2.1.1.
- **Nodal target:** See Section 2.1.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions:** All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

If the protocol is considering specific symptoms for assessment of the tumor, e.g. bone pain or GI bleeding, then these symptoms are to be entered as non-target lesions with either presence or absence or as a new lesion (based on protocol specified criteria). In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

For cancers which are known to metastasize to bone, the protocol should specify if and how bone lesions should be handled, e.g., if they should be followed throughout the study by CT, MRI or x-ray.

2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 2-1) and non-target lesions (Table 2-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 2-3) as well as the presence or absence of new lesions.

If tumor markers are used as non-target lesions to evaluate response, please specify criteria for CR, SD and PD in the protocol, e.g. CR='Normalization of tumor marker level', PD='Elevation of tumor markers to certain level', SD='Not qualifying for CR or PD'. These criteria are indication and study specific. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

2.4.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

[redacted]

2.4.1.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

2.4.2 Determination of target lesion response

Table 2-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 2.2).

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following possibilities:

[redacted]

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 2-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.

[redacted]

- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

2.4.3 Determination of non-target lesion response

Table 2-2 Response criteria for non- target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2]

The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail.

It is recommended that the investigator and/or central reviewer should use expert judgement to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.

[redacted]

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion eCRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 2.2.

2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 2-3.

[redacted]

Table 2-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 2.4

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 3.2.9 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

[redacted]

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- -For non-randomized trials where response is the primary endpoint, confirmation is needed.
- -For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

The protocol should state if randomization or start of treatment is used as start date (baseline). This is then used in all definitions.

If a different minimum follow-up period is required to classify for best overall response= 'stable disease', this must be specified in the protocol.

- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

If PD in a different follow-up period is considered to classify for best overall response='progressive disease', this must be specified in the protocol.

The protocol should state if discontinuation due to 'Disease progression' or death due to study indication is considered PD even if this was not accompanied by documentation of PD based on tumor measurements. This depends on Phase of the study and the primary endpoint (e.g. Phase III studies in which progression-free survival is primary endpoint should consider only documented PD, whereas Phase I and II studies may consider all clinical deteriorations PD). The following sentence therefore is only applicable if this is specified in the protocol:

Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication.

- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time

[redacted]

window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Specify which determination of best overall response will be considered primary (and delete the other terms in the text). If a central blinded review is used (e.g. in an open-label study in

[redacted]

which response is the primary endpoint), the best overall response evaluated by the central blinded review will always be considered the primary response.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

3.2 Time to event variables

The protocol should state which of the following variables is used in that study.

3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

[redacted]

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

3.2.4 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

[redacted]

3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

[redacted]

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

3.2.7 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 3.2.6. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

Indicate in the protocol whether a subgroup analysis of responders only will be performed in addition to the full population analysis (which should be included as default).

3.2.8 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

[redacted]

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

State in the protocol if date of randomization or date of start of treatment is to be used for all definitions. For randomized studies specify exactly where the randomization date comes from, e.g. from IVRS, or if start of treatment is used as randomization date. For non-randomized studies please specify which treatment start date is taken if more than one treatment is to be given.

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.

If applicable, if patients who discontinued due to 'Disease progression' are considered to be PD solely based on clinical deterioration, then add the following text in the protocol:

When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 3.2.10).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.

[redacted]

- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

In comparative studies with long follow-up period and therefore extended visit schedule, it may be useful to collect the survival status at a pre-specified cut-off within a limited timeframe for all patients with no documented death. In this case, this requires a contact to be made with the patient or with any reliable source of information on the patient's status, but not requiring a specific visit to be scheduled

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

If this is applicable for the study, it should be specified in the protocol if new cancer therapy is considered an event or endpoints are censored.

3.2.9 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

The protocol should state clearly whether patients with non-measurable disease only at baseline will be allowed into the study. If patients with non-measurable disease only are allowed to be enrolled then the statistical section should describe clearly how data from these patients will be incorporated into the primary analysis and main analyses of the key secondary endpoints. In studies where presence of measurable disease is expected to have a relatively large impact on the primary endpoint, this factor can even be considered as a stratification factor in the randomization process.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

For studies which specifically exclude patients with non-measurable disease only at baseline the pre-specified analysis plan should describe how to handle data from these types of patients if they are enrolled by error or if central readers do not identify measurable disease despite investigators having declared the contrary, or conversely perhaps they do identify measurable disease when it has not been identified at the local site. It is recommended for these types of studies that patients with non-measurable disease identified through the local site evaluation be included in the list of protocol violations. However, decisions on exclusion from a per protocol analysis should relate to whether the patient has measurable disease according to the primary data source. For example, if the primary data source is from a central independent review then patients with non-measurable disease only according to this central review should be excluded from the relevant per protocol analyses.

[redacted]

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 3-1.

Table 3-1 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 2.4

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

Study teams may also want to perform sensitivity analyses excluding patients from the analysis of ORR (e.g. possibly as part of a per-protocol type analysis). Similar considerations should be given to other endpoints which rely on a clear distinction being made between a PR and a SD response.

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

[redacted]

Based on definitions outlined in Section 3.2.8, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 3-2 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

=Definitions can be found in Section 3.2.8

=After the last adequate tumor assessment."Date of next scheduled assessment" is defined in Section 3.2.8.

=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

[redacted]

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 3-2 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

[redacted]

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment

[redacted]

- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which *"must"* lead to discontinuation of the patient from the trial.

4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible, the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgement in determining response in these types of situations, and therefore as a consequence, discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in the eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

[redacted]

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 3.2.8). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

[redacted]

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 3-2)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 3.2.8. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

[redacted]

5 References (available upon request)

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