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Novartis Research and Development

BYL719

Clinical Trial Protocol CBYL719C2202 / NCT04899349

EPIK-B4: A Phase II, multicenter, randomized, open-label, active-controlled study to assess the safety and efficacy of dapagliflozin + metformin XR versus metformin XR during treatment with alpelisib (BYL719) in combination with fulvestrant in participants with HR+, HER2-, advanced Breast Cancer with a PIK3CA mutation following progression on/after endocrine-based therapy

Document type:	Amended Protocol Version
EUDRACT number:	2021-001908-15
Version number:	01 (Clean)
Clinical Trial Phase:	II
Release date:	06-Aug-2021 (content final)

Clinical Trial Protocol Template Version 4.0 dated 15-Feb-2021

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List of abbreviations

ABC	Advanced Breast Cancer
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
AI(s)	Aromatase Inhibitor(s)
Akt	Protein Kinase B
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
ARA	Acid Reducing Agents
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AV	Atrioventricular
b.i.d.	bis in die/twice a day
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BN	Brown Norway
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CBR	Clinical Benefit Rate
CD transferrin	Carbohydrate-Deficient transferrin
CDK4/6	Cyclin-dependent kinase 4 and 6
CDx	Companion Diagnostics
CE-IVD	European In-Vitro Diagnostic Devices Directive
CFR	Code of Federal Regulation
CI	Confidence Interval
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computerized Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTT	Clinical Trial Team
CYP	Cytochrome P450
DAL	Drug Accountability Log

[redacted]

DBP	Diastolic Blood Pressure
DDE	Direct Data Entry
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DKA	Diabetic Ketoacidosis
dL	deciliter(s)
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DQF	Data Query Form
DRESS	Drug Reaction with Eosinophilia and Systemic Syndrome
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
[redacted]	[redacted]
eGFR	estimated Glomerular Filtration Rate
EM	Erythema Multiforme
EMA	European Medicines Agency
EOT	End of Treatment
ER	Estrogen Receptors
ERCP	Endoscopic Retrograde Cholangiopancreatography
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin Fixed Paraffin Embedded
FG	Fasting Glucose
FPFV	First Patient First Visit
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
GT	Glutamyl Transferase
HAV	Hepatitis A Virus
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

[redacted]

HDL	High-Density Lipoprotein
HER2	Human Epidermal growth factor Receptor-2
HEV	Hepatitis E Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Hazard Ratio
HR-positive	Hormone Receptor positive
hrs	hours
HSV	Herpes Simplex Virus
i.v.	intravenous
IB	Investigator's Brochure
IC50	half maximal inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IM	Intramuscular
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intend-To-Treat
kg	kilogram
LDH	lactate dehydrogenase
LDL	Low-Density Lipoprotein
LFT	Liver function test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
mmol	millimole
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	mammalian Target of Rapamycin
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NTI	Narrow Therapeutic Index
ONJ	Osteonecrosis of the Jaw
ORR	Overall Response Rate
OS	Overall Survival
Participant No.	Participant Number
PCR	Polymerase Chain Reaction
PD	Progressive Disease

[redacted]

PFS	Progression Free Survival
PgR	Progesterone Receptors
PI3K	Phosphatidylinositol-3-Kinase
PIK3CA	Phosphoinositide-3-Kinase Catalytic subunit Alpha
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Prothrombin Time
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RGQ	Rotor-Gene Q
RNA	Ribonucleic Acid
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	Stable Disease
SERD	Selective Estrogen Receptor Downregulator
SGLT2	Sodium GLucose co-Transporter 2
SGLT2i	Sodium GLucose co-Transporter 2 Inhibitor(s)
SJS	Steven-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SMT	Safety Management Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total bilirubin
TEN	Toxic Epidermal Necrolysis
Tmax	Time to maximum plasma concentration
ULN	Upper Limit of Normal
WHO	World Health Organization
WoC	Withdrawal of Consent
XR	Extended Release
µg	microgram

[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 participant
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis

[redacted]

Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or Electronic Source (eSource)
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
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
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 01 (06-Aug-2021)

Amendment rationale

As of the release of this amendment, this clinical trial did not start enrollment under the original protocol and no sites opened.

The main purpose of this protocol amendment is to update the immediate release (IR) metformin to extended release (XR) metformin in Arm B. For participants not randomized to dapagliflozin plus metformin XR arm, metformin XR will be initiated to explore hyperglycemia management with the extended release formulation as it is associated with slower gastrointestinal absorption, leading to less gastrointestinal toxicities, and once daily dosing, both of which may lead to better participant compliance and improved glucose management compared to the immediate release formulation (Jabbour et al 2011).

Antihyperglycemic therapy in each arm will be initiated at Cycle 1 Day 1 at low doses and require up titration every few days, based on gastrointestinal tolerability, to reach full dose after 3 weeks. Consequently, alpelisib will start on Cycle 1 Day 8 to allow the dose titration of antihyperglycemic therapy for more effective hyperglycemia control.

Additionally, the patient population has been updated to allow for prior use of fulvestrant / oral SERD and to limit the number of treatment lines in the metastatic setting to best align with SOLAR-1 and BYLieve studies.

Changes to the protocol

Changes to this protocol are considered substantial.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Throughout the protocol metformin has been replaced by metformin XR.
- Throughout the protocol the duration of treatment has been updated from 12 months to 12 cycles.
- Throughout the protocol the initiation timepoint of alpelisib has been modified from Cycle 1 Day 1 to Cycle 1 Day 8 to allow for the initiation of anti-hyperglycemic treatment prior to alpelisib administration.
- Throughout the protocol the duration of screening has been extended from 21 to 28 days to allow participants on fulvestrant prior to screening to continue their existing fulvestrant schedule.
- Throughout the protocol the timeframe for the primary endpoint (including primary objective and primary question of interest) has been updated from first two cycles (where a cycle is 28 days or 4 weeks) of alpelisib to first eight weeks of alpelisib (from Cycle 1 Day 8 to Cycle 3 Day 8) due to the change of the start date of alpelisib moving to Cycle 1 Day 8. This maintains the original intention of two cycles of alpelisib treatment (or eight weeks timeframe) for the primary endpoint.
- Throughout the protocol the timing of primary analysis has been updated in accordance with the updated timeframe of the primary endpoint.

[redacted]

- Throughout the protocol it has been clarified that the laboratory values for glucose assessment will serve as the evaluation of the primary endpoint and rationale for dose modifications.
- List of tables has been updated to add titration guidance tables in Section 6.6.2.
- *List of abbreviations has been updated per protocol amendment changes.*
- *Protocol summary has been updated to reflect the updates throughout the protocol.*
- Section 1.1.2.2: Data from CBYL719X2101 study were added to show that no negative effect with re-use of fulvestrant was observed as a justification to allow prior fulvestrant or oral SERD treatment with the current protocol amendment.
- Section 1.2: Justification provided to use metformin XR instead of metformin IR.
- Section 2: The first intercurrent event was revised to additionally consider participants without any exposure to alpelisib (similar change has been made in Section 12.4.3)
- Section 3: Baseline risk factors for the development of severe hyperglycemia have been listed without "or" and "and/or" for more clarity. "Study Design" figure and "Study Flow Chart" have been updated to match the related protocol updates. Timepoint of alpelisib treatment initiation has been updated from Cycle 1 Day 1 to Cycle 1 Day 8 (one week after the start of anti-hyperglycemic therapy). It has been clarified that randomization will be based on FPG instead of glucose. A cycle treatment definition has been added.
- Section 4.3: Rationale for choice of metformin XR has been provided. Explanation provided why treatment with antihyperglycemic agents will be initiated one week prior to alpelisib.
- Section 4.4: The timepoint of the primary analysis has been clarified following the change of the primary endpoint timeframe.
- Section 4.6: Updated based on new COVID-19 Guidance for CTTs - Protocols and Amendments for New and Ongoing Studies (Version 5.0).
- Section 5.1: Inclusion criterion 3 has been updated by removing "or" to avoid confusion.
- Section 5.1: Inclusion criterion 6 has been updated to include early relapse patients.
- Section 5.1: Previous inclusion criterion 7 (Participant has received ≤ 1 line of prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy) has been removed as participants with prior chemotherapy (except for neoadjuvant/adjuvant chemotherapy) will be excluded. New inclusion criterion 7 has been added to clarify that prior CDK4/6i therapy in adjuvant or metastatic setting is allowed. These changes were made to more closely align with the participant populations of other alpelisib studies.
- Section 5.1: Inclusion criterion 12 and has been updated to lower the absolute neutrophil count from $\geq 1.5 \times 10^9$/L to $\geq 1.2 \times 10^9$/L to allow inclusion of African American patient population known to have lower absolute neutrophil count values being normal for them.
- Section 5.2: A new exclusion criterion was added as exclusion criterion 3 and will exclude participants with more than 1 line of prior treatment in the metastatic setting
- Section 5.2: Exclusion criterion 3 became exclusion criterion 4 and has been updated to clarify that participants with prior chemotherapy (except for neoadjuvant/adjuvant chemotherapy) will be excluded.

- Section 5.2: Exclusion criterion 4 became exclusion criterion 5 and has been modified to include hypersensitivity to metformin XR.
- Section 6.1.1: It has been clarified that alpelisib treatment will start on Cycle 1 Day 8 and fulvestrant treatment on Cycle 1 Day 1. Additionally, it has been specified that fulvestrant 500 mg will consist of two 5 ml injections 250 mg each.
- Section 6.1.3: Arm 1 and Arm 2 have been replaced with Arm A and Arm B respectively for consistency with other protocol sections.
- Table 6-1: Removal of metformin (IR), clarification of pharmaceutical dosage form for fulvestrant.
- Section 6.1.5: The duration of FPG monitoring and hyperglycemia related AE collection after early discontinuation has been adjusted following updated timeframe for the primary endpoint (same update is applicable for Section 8.4.1, Section 9.1.1, Section 10.1.1).
- Section 6.2.1: Recommendation to avoid SGLTi for participants randomized to metformin XR arm updated to last until Cycle 3 Day 8.
- Section 6.3.2.2: Addition of the statement that fulvestrant injection at Cycle 1 Day 15 is not applicable for participants already being treated with fulvestrant when joining the trial.
- Section 6.3.2.3: Adjusted to highlight metformin XR treatment start.
- Section 6.3.2.4: Adjusted to highlight dapagliflozin + metformin XR treatment start.
- Table 6-3: Further details provided on management of hyperglycemia and combined ALT/AST and TBIL elevation. “Note” has been updated to clarify that dose modifications and management should only be based on fasting laboratory glucose values. For Grade 4 ≥ 27.8 mmol/L has been updated by > 27.8 mmol/L as 27.8 mmol/L is included in Grade 3.
- Erythema Multiforme added to severe skin reaction section within the table.
- Section 6.6.2.1: Metformin XR titration recommendation was updated to appear in a table format. Most common adverse reactions for metformin were removed.
- Section 6.6.2.2: Dapagliflozin + metformin XR titration recommendation was updated to appear in a table format.
- Section 6.6.3.1: The first criteria, requiring follow-up in case of ALT/AST and total bilirubin elevation, has been updated to reflect no evidence of cholestasis. Additionally, action to be taken with study treatment if DILI is confirmed or is unlikely has been added.
- Table 8-1: Update on the screening window and clarification on fulvestrant injection timepoints.
- Table 8-2:
  - Update on the screening window;
  - Addition of Cycle 3 Day 8 as a new visit;
  - [redacted]
  - Update on eligibility checklist (within IRT) to be completed on C1D1 (prior to first dose) instead of screening;
  - Addition of “Abdominal Girth” being part of metabolic syndrome (metabolic syndrome is a clustering of hyperglycemia/insulin resistance, obesity and dyslipidemia and is

[redacted]

important for several reasons, including identification of patients who are at high risk of developing atherosclerotic cardiovascular disease and type 2 diabetes);
  - Removal of "Fasting Glucose" and addition of "Fasting Plasma Glucose" at Cycle 3 Day 1, Cycle 3 Day 8, Cycle 4 Day 1 to Cycle 12 Day 1 and at EOT;
  - Addition of HbA1C at Cycle 3 Day 1,
  - Alpelisib start day has been updated from Cycle 1 Day 1 to Cycle 1 Day 8;
  - Frequency of administration of metformin XR and dapagliflozin plus metformin XR has been corrected to once daily;
  - Footnote number 3 and footnote number 4 have been updated.
- Section 8.1.2: Correction on the data collection for screen failures has been performed.
- Section 8.2: Addition of abdominal girth.
- Table 8-3: Footnote number 1 has been updated with regards to tumor evaluation at End of Treatment which has to be conducted in absence of progressive disease at previous tumor assessment and if this tumor assessment was done more than 21 days prior to EOT visit (previously 28 days). Footnote number 2 has been removed as the same language is present in the corresponding section of the protocol.
- Table 8-4: Abdominal girth added.
- [redacted]
- Section 8.4.1: The language for alternative laboratory collection has been updated based on new COVID-19 Guidance for CTTs - Protocols and Amendments for New and Ongoing Studies (Version 5.0).
- [redacted]
- Section 10.1.3 has been updated with the requirements on SAE follow-up reporting.
- Section 12.5.1: Updated summary measure for PFS to PFS rate at 24 weeks and 48 weeks, corresponding to 6 and 12 cycles.
- [redacted]
- Section 12.7: Timepoint for statistical testing of the primary endpoint has been removed.
- Section 15: Updated with additional references used in the protocol.
- Appendix 16.1: Table 16-3 was updated to align with dose modification table (Table 6-3).

In addition, editorial changes and text corrections were made for clarification in sections of the protocol, as appropriate/required.

[redacted]

IRBs/IECs

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

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

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CBYL719C2202
Full Title	EPIK-B4: A Phase II, multicenter, randomized, open-label, active-controlled study to assess the safety and efficacy of dapagliflozin + metformin XR versus metformin XR during treatment with alpelisib (BYL719) in combination with fulvestrant in participants with HR+, HER2-, advanced Breast Cancer with a PIK3CA mutation following progression on/after endocrine-based therapy
Brief title	Study of safety and efficacy of dapagliflozin + metformin XR versus metformin XR in participants with HR+, HER2-, advanced breast cancer while on treatment with alpelisib and fulvestrant
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose	Study CBYL719C2202 (EPIK-B4) will assess the safety and efficacy of the combination of dapagliflozin plus metformin extended release (XR) compared with metformin XR, during treatment with alpelisib plus fulvestrant in participants with Hormone Receptor (HR) positive, Human Epidermal growth factor Receptor-2 (HER2) negative advanced breast cancer with a Phosphoinositide-3-Kinase Catalytic subunit Alpha (PIK3CA) mutation following progression on or after endocrine-based therapy. The purpose of this study is to determine if the combination of dapagliflozin plus metformin XR, when given prophylactically to participants considered at 'high-risk' for the development of hyperglycemia, leads to a greater reduction in severe hyperglycemia events compared with the prophylactic use of metformin XR alone. In SOLAR-1, 71% of all alpelisib-treated patients and 85% of alpelisib-treated patients who developed Grade 3 or 4 hyperglycemia were considered "high-risk" for the development of hyperglycemia. Patients were considered to be "high-risk" if they had either diabetes, pre-diabetes, obesity (Body Mass Index (BMI) ≥ 30) or age ≥ 75 years. This strategy is intended to optimize prophylactic management of hyperglycemia for participants with underlying risk factors for the development of severe hyperglycemia.
Rationale	While adverse drug reactions associated with alpelisib are largely manageable and reversible, dose reductions, treatment delays and discontinuations due to hyperglycemia may ultimately impact treatment duration. In the pivotal SOLAR-1 trial, among alpelisib-treated patients, 64% of patients developed hyperglycemia of any Grade and 37% developed severe (Grade ≥ 3) hyperglycemia. Therefore, there remains an unmet need for management strategies that offer earlier and more sustained improvement of hyperglycemia than what is achieved with metformin as initial therapy after hyperglycemia has been observed. Sodium glucose co-transporter 2 inhibitors (SGLT2i) are a new class of medications, approved for use in adults with type 2 diabetes mellitus to improve glycemic control, that improve hyperglycemia primarily by promoting urinary glucose excretion and have a manageable safety profile. In the SOLAR-1 study, among 6 patients treated with SGLT2i after onset of hyperglycemia events, all subsequent hyperglycemia-related events were Grade 1/2, except one Grade 3 event which was confounded by concomitant corticosteroid use. The duration of alpelisib exposure ranged from 9.5 to 27.7 months for the [redacted] patients who discontinued alpelisib; and notably, [redacted] patients were continuing to receive alpelisib after 37.0 and 40.0 months, respectively. None of the 6 patients discontinued alpelisib due to hyperglycemia (Lu et al 2020). These data suggest that further investigation of an SGLT2i for the management of alpelisib-induced hyperglycemia is warranted. Preclinical data support the use of an SGLT2i in combination with alpelisib. The SGLT2i, dapagliflozin, has been used to test for improved glycemic control on top of Phosphatidylinositol-3-Kinase alpha (PI3Kα) inhibition with alpelisib. Based on studies conducted in Brown Norway and nude rats, the combination of dapagliflozin and alpelisib significantly reduced blood glucose levels, without concern for drug-drug interaction and notably, while maintaining the efficacy of alpelisib upon combination with dapagliflozin. Under fed conditions, a reduction in plasma insulin levels and an improvement in insulin sensitivity was observed with the combination of dapagliflozin and alpelisib. The triple

	combination of metformin plus dapagliflozin plus alpelisib resulted in further improved blood glucose level reduction with the same kinetics as dapagliflozin plus alpelisib. The triple combination of metformin plus dapagliflozin plus alpelisib was more effective in reducing plasma insulin levels when compared to double combinations with metformin plus alpelisib or dapagliflozin plus alpelisib. No sign of ketoacidosis was observed (Novartis Internal Data).
Primary Objective(s)	To evaluate the reduction in severe hyperglycemia events over the first eight weeks of alpelisib plus fulvestrant with prophylactic dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR. The primary scientific question of interest is: what is the effect on the occurrence of severe hyperglycemia (based on glucose laboratory values) over the first eight weeks of alpelisib plus fulvestrant (from Cycle 1 Day 8 to Cycle 3 Day 8) with prophylactic dapagliflozin plus metformin XR versus alpelisib plus fulvestrant with prophylactic metformin XR for participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, which progressed on or after endocrine-based therapy and have at least one risk factor for severe hyperglycemia, regardless of additional antihyperglycemic therapies as needed? Note: Among alpelisib-treated patients with severe hyperglycemia events in SOLAR-1, 87% of patients developed the events within the first two cycles of treatment. Therefore, in this proposed study, the primary endpoint will focus on the incidence of severe hyperglycemia in the first eight weeks of alpelisib plus fulvestrant treatment, starting from Cycle 1 Day 8.
Secondary Objectives	● To evaluate alpelisib plus fulvestrant with prophylactic dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR with regard to preliminary efficacy parameters ● To assess safety and tolerability
Study design	This is a Phase II, multicenter, randomized, open-label, active-controlled trial designed to assess the safety and efficacy of the combination of dapagliflozin plus metformin XR compared with metformin XR during treatment with alpelisib plus fulvestrant in participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation following progression on or after endocrine-based therapy. The study will only include participants who have at least one baseline risk factor as defined below for the development of severe hyperglycemia: ● Diabetes (FPG ≥ 126 mg/dL or ≥ 7.0 mmol/L and/or HbA1c ≥ 6.5%) ● Pre-diabetes (FPG ≥ 100 mg/dL to < 126 mg/dL or 5.6 to < 7.0 mmol/L and/or HbA1c 5.7 to < 6.5%) ● Obesity (BMI ≥ 30) ● Age ≥ 75 years Participants will be randomized in a 1:1 ratio (approximately 66 participants in each treatment arm) to receive the combination of dapagliflozin plus metformin XR or metformin XR alone starting on Cycle 1 Day 1.. Randomization will be stratified by diabetic status at baseline, i.e. normal vs pre-diabetic/diabetic (based on fasting plasma glucose (FPG) and/or hemoglobin A1c (HbA1c) laboratory values). The study will consist of a 28-day screening phase, a 12 cycle treatment phase, and a post-treatment phase which includes safety and efficacy follow-up (if applicable).
Study population	This study will include adult men and postmenopausal women with HR-positive, HER2-negative advanced (locoregionally recurrent not amenable to curative therapy or metastatic) breast cancer with a PIK3CA mutation which has progressed on or after endocrine-based therapy who plan to initiate therapy with alpelisib plus fulvestrant and have at least one baseline risk factor for severe hyperglycemia. Participants with prior CDK4/6i treatment will be included. This study population is consistent with the population for which alpelisib is approved for use.
Key Inclusion criteria	● Participant has a histologically and/or cytologically confirmed diagnosis of estrogen receptor positive (ER+) and/or progesterone receptor positive (PgR+) breast cancer by local laboratory ● Participant has a PIK3CA mutation(s) present in tumor prior to enrollment

[redacted]

	● Participant has prior treatment with an endocrine-based treatment (i.e. letrozole, anastrozole, exemestane, fulvestrant or oral SERD) and may be: • relapsed with documented evidence of progression while on (neo) adjuvant endocrine-based therapy or within 12 months from completion of (neo)adjuvant endocrine-based therapy with no treatment for metastatic disease • relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine-based therapy and then subsequently progressed with documented evidence of progression while on or after only one line of endocrine-based therapy for metastatic disease • newly diagnosed advanced breast cancer, then relapsed with documented evidence of progression while on or after only one line of endocrine-based therapy. Note: Participants with newly diagnosed endocrine-based treatment naïve advanced breast cancer will NOT be included in the study. ● Participants may or may not have received prior CDK4/6i therapy. If prior CDK4/6i therapy was administered, it may have been in the adjuvant or metastatic setting ● If female, then the participant is postmenopausal ● Participant has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 ● Participant has adequate bone marrow and organ function
Key Exclusion criteria	● Participant who relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease ● Participant had more than 1 line of prior treatment in the metastatic setting ● Participant has received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), any PI3K, Mammalian Target of Rapamycin (mTOR) or Protein Kinase B (Akt) inhibitor ● Participant has inflammatory breast cancer at screening ● Participant with an established diagnosis of diabetes mellitus type I or participants with type II diabetes mellitus requiring antihyperglycemic therapy ● Participant has a history of acute pancreatitis within 1 year of screening or a past medical history of chronic pancreatitis ● Participant has currently documented pneumonitis/interstitial lung disease ● Participant has a history of severe cutaneous reaction, such as Steven-Johnson Syndrome (SJS), erythema multiforme (EM), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Syndrome (DRESS)
Study treatment	● Arm A: Alpelisib (BYL719) + fulvestrant + dapagliflozin + metformin XR ● Arm B: Alpelisib (BYL719) + fulvestrant + metformin XR
Efficacy assessments	● Chest, abdomen, and pelvis computerized tomography (CT) or magnetic resonance imaging (MRI) with intravenous contrast enhancement at screening and every 8 weeks (+/- 7 days) until disease progression, end of treatment (EOT), death, withdrawal of consent/opposition to use data/biological samples, or lost to follow-up

[redacted]

Key safety assessments	● Physical examination ● Body weight, height, abdominal girth and vital signs ● ECOG performance status ● Laboratory evaluations, including hematology, biochemistry, coagulation, and urinalysis ● Electrocardiogram (ECG) ● Cardiac imaging (multigated acquisition scan (MUGA) or echocardiogram (ECHO)) ● Adverse events (AEs) with severity, relationship to study treatment and seriousness ● Skin photographs and skin biopsies (strongly recommended for Grade 3 and mandatory for Grade 4 skin toxicities)
Other assessments	● Tumor tissue: archival tumor block or a fresh formalin-fixed tumor biopsy block or a minimum 5-13 slides (if PIK3CA mutation status is not available) [redacted]
Data analysis	The primary analysis will assess the difference in the percentage of participants with severe hyperglycemia (Grade ≥ 3, based on glucose laboratory values) between the two treatment arms with a stratified Cochran-Mantel-Haenszel test (stratified by baseline diabetic status) at an overall one-sided 5% level of significance. The following statistical hypotheses will be tested to address the primary objective: H_{01}: $\theta_1 - \theta_2 \geq 0$ vs. H_{a1}: $\theta_1 - \theta_2 < 0$ where θ_1 is the percentage of participants with at least one occurrence of severe hyperglycemia in the study treatment arm A and θ_2 is the percentage in the study treatment arm B. The percentage of participants with severe hyperglycemia per treatment arm and the difference in percentages across the two treatment arms will be presented along with two-sided 95% standard Wald asymptotic (i.e. normal approximation) confidence intervals.
Key words	Alpelisib, fulvestrant, SERD, metformin, dapagliflozin + metformin XR, advanced breast cancer, phase II, HR+, HER2-, PIK3CA, hyperglycemia, SGLT2i

[redacted]

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Breast cancer (BC) is the most common cancer in women and is the most commonly diagnosed cancer worldwide. The estimated 2.3 million new cases indicate that 1 in every 8 cancers diagnosed in 2020 is breast cancer. The disease is the fifth-leading cause of cancer mortality worldwide, with 685,000 deaths in 2020 (Sung et al 2021). Among men, BC is much less common, accounting for <1% of all cases (Siegel et al 2018).

Subtypes of breast cancer are distinguished by the expression of estrogen receptors (ER), progesterone receptors (PgR) and human epidermal growth factor receptor-2 (HER2), as well as by distinct gene expression profiles (Perou et al 2000, Sotiriou and Pusztai 2009). Of the new breast cancers diagnosed worldwide each year, approximately 60-70% are hormone receptor positive (HR-positive), HER2-negative (Howlader et al 2021).

Alpelisib, an oral, alpha-specific phosphatidylinositol-3-kinase (PI3K) inhibitor, is indicated, in combination with fulvestrant, for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, Phosphoinositide-3-kinase catalytic subunit alpha (PIK3CA) mutated, advanced breast cancer following progression on or after an endocrine-based regimen on the basis of the pivotal study, CBYL719C2301 (SOLAR-1). Results from the SOLAR-1 study (André et al 2019), which is a Phase III, randomized, multicenter, double-blind, placebo-controlled study, showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS) in favor of the alpelisib plus fulvestrant arm (Hazard Ratio (HR)=0.65, 95% Confidence Interval (CI): 0.50, 0.85, one-sided $p < 0.001$). 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.

Alpelisib, along with other PI3K inhibitors, is associated with toxicities from both on-target and off-target effects, including hyperglycemia, diarrhea, nausea, and rash. While adverse drug reactions are largely manageable and reversible, alpelisib dose reductions, treatment delays and discontinuation may occur due to adverse drug reactions such as hyperglycemia which may ultimately impact treatment duration.

Hyperglycemia, an on-target effect, was managed primarily with metformin in the pivotal SOLAR-1 trial. Among alpelisib-treated patients, 64% of patients developed hyperglycemia of any Grade and 37% developed severe (Grade ≥ 3) hyperglycemia. Dose interruption and/or adjustment of alpelisib was required for 38% of patients and treatment discontinuation due to hyperglycemia was reported in 6% of alpelisib-treated patients. Among alpelisib-treated patients with severe hyperglycemia events, 87% of patients developed the events within the first two cycles of treatment. Baseline risk features that were associated with the development of severe hyperglycemia include prediabetes or diabetes at baseline (based on hemoglobin A1c (HbA1c) and glucose laboratory values), obesity (BMI ≥ 30) and age (≥ 75 years). In SOLAR-1, 71% of all alpelisib-treated patients and 85% of alpelisib-treated patients who developed Grade 3 or 4 hyperglycemia had at least one of these risk factors.

[redacted]

Enhanced guidance including additional glucose monitoring, earlier implementation of metformin use and faster allowance of dose reductions for alpelisib were incorporated into the BYLieve (CBYL719X2402) study, an ongoing Phase II, non-comparative study to assess the efficacy and safety of alpelisib plus fulvestrant or letrozole in patients with HR-positive, HER2-negative, advanced breast cancer with a PIK3CA mutation who have progressed on or after prior treatments. While the enhanced protocol guidance led to fewer dose reductions and treatment discontinuations due to hyperglycemia in Cohort A of the BYLieve study (Table 1-1), which consists of a patient population most similar to SOLAR-1, severe hyperglycemia events (Grade ≥ 3) were still reported in 28% of patients (Rugo et al 2021). Therefore, there remains an unmet need for management strategies that offer earlier and more sustained improvement of hyperglycemia than what is achieved with metformin as initial therapy after hyperglycemia has been observed.

Table 1-1 Comparison of hyperglycemia adverse events between SOLAR-1 and BYLieve Cohort A

Patients treated with alpelisib plus fulvestrant	SOLAR-1 N = 284	BYLieve Cohort AN = 127
% with severe (Grade ≥ 3) hyperglycemia	37%	28%
% with dose interruption and/or reduction due to hyperglycemia	38%	29%
% discontinued study treatment due to hyperglycemia	6%	2%

1.1.2 Overview of alpelisib

Alpelisib is an oral, alpha-specific class IA PI3K inhibitor belonging to the 2-aminothiazole class of compounds. Alpelisib potently inhibits p110α, in its wild-type form as well as when constitutively activated by somatic mutations, and inhibits less strongly the β, δ, and γ isoforms of PI3K.

1.1.2.1 Non-clinical experience

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 involved in deoxyribonucleic acid (DNA)-damage repair processes (IC50> 30μM on S15P-p53 and IC50> 10μM on S1981 P-ataxia-telangiectasia mutation). *In vitro*, alpelisib inhibits 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 PIK3CA lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in *in vitro* and *in vivo* models.

[redacted]

In multiple cancer indications, including breast cancer and head and neck squamous cell carcinoma (HNSCC), 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 and HNSCC (Sheng et al 2013), [Section 4.1.2.5]). More detailed information on the pharmacology of alpelisib, single and multiple dose pharmacokinetic (PK) studies conducted in multiple species and nonclinical safety evaluations can be found in the [Alpelisib (BYL719) Investigator's Brochure].

1.1.2.2 Clinical experience

Alpelisib (Piqray®) was first approved in the United States (May-2019), and later in several other countries, in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative PIK3CA mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. On 27-Jul-2020, the European Commission approved alpelisib in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR positive, HER2 negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy. Global submissions are in progress.

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 (HR=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 (HR = 0.85; 95% CI: 0.58, 1.25).

The final overall survival (OS) analysis for SOLAR-1 study in the PIK3CA mutant cohort was conducted, with a cut-off date of 23-Apr-2020, based on 181 deaths. Although OS did not meet the pre-specified efficacy boundary (one-sided $p \leq 0.0161$) for statistical significance, there was a clinically relevant improvement in median 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; HR=0.86; 95% CI: 0.64-1.15; one-sided p=0.15) (André et al 2021).

With a median duration of follow-up from randomization until the final OS data cut-off of 42.4 months, the safety profile remains consistent with that previously reported. All Grade AEs that were reported in ≥ 20% of patients in the alpelisib plus fulvestrant treatment arm were hyperglycemia(65%), diarrhea (60%), nausea (47%), decreased appetite (36%), rash (36%) (also, maculo-papular rash was 14%), vomiting (29%), weight decreased (28%), fatigue (25%), stomatitis (25%), asthenia (23%), and alopecia (20%). Grade ≥ 3 AEs in ≥ 5% of patients were hyperglycemia (37%), rash (10%), rash maculo-papular (9%), diarrhea (7%) and weight decreased 5%. All serious adverse events (SAEs) occurred in less than 3% of patients with the exception of hyperglycemia (10%). Grade ≥ 3 SAEs that occurred in ≥ 2% of patients were hyperglycemia (9%) and osteonecrosis of jaw (2%).

[redacted]

In the Phase I Study CBYL719X2101, 39 participants had prior therapy with fulvestrant before they were treated with alpelisib plus fulvestrant, 21 of these with measurable disease at baseline and PIK3CA mutations. Of these latter participants, 7 participants had a best overall response of partial response, 11 participants had stable disease, 2 participants had progressive disease, and the response for 1 participant was unknown. With no significant negative impact on efficacy observed with the re-use of fulvestrant, prior fulvestrant or oral SERD treatment will be allowed in this study.

More detailed information regarding alpelisib is available in the [Alpelisib (BYL719) Investigator's Brochure], Piqray® prescribing information.

Clinical Pharmacology

The pharmacokinetics of alpelisib has been studied in healthy volunteers and adult patients with solid tumors. Steady-state PK of alpelisib is approximately dose-proportional at clinically relevant doses under fed conditions with steady-state plasma concentrations reached within 3 days following daily dosage. 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.

Alpelisib shows a positive food effect and has to be administered after food. No clinically significant differences in alpelisib area under the curve (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 cytochrome P450 (CYP) 3A4 in vitro. 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 Breast Cancer Resistance Protein (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 co-administered with alpelisib. Alpelisib has a low potential to inhibit BCRP, MRP2, BSEP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1, and MATE2K at clinically relevant concentrations.

For more detailed information please refer to [Alpelisib (BYL719) Investigator's Brochure].

1.2 Purpose

While adverse drug reactions associated with alpelisib are largely manageable and reversible, dose reductions, treatment delays and discontinuation due to hyperglycemia have been reported which may ultimately impact treatment duration.

Among alpelisib-treated patients in SOLAR-1, 64% of patients developed hyperglycemia of any Grade, 37% developed severe (Grade ≥ 3) hyperglycemia and 10% developed hyperglycemia as serious adverse events. Dose interruption and/or adjustment of alpelisib was

required for 38% of patients and treatment discontinuation due to hyperglycemia was reported in 6% of alpelisib-treated patients.

Based on the SOLAR-1 experience, enhanced protocol guidance was incorporated into the BYLieve study, which led to fewer dose reductions and treatment discontinuations due to hyperglycemia in Cohort A of the BYLieve study (i.e. 29% and 2% respectively in BYLieve), which consists of a patient population most similar to SOLAR-1. However, severe hyperglycemia events (Grade ≥ 3) were still reported in 28% of patients in Cohort A and in 6% of patients as serious adverse events. Therefore, there remains an unmet need for management strategies that offer early and sustained improvement of hyperglycemia than what is achieved with metformin as initial therapy after hyperglycemia has been observed. In addition to frequent monitoring and early recognition of treatment-related toxicities, management strategies including both active and prophylactic intervention for hyperglycemia should be explored and optimized.Study CBYL719C2202 (EPIK-B4) will assess the safety and efficacy of the combination of dapagliflozin plus metformin extended release (XR) compared with metformin XR alone, during treatment with alpelisib plus fulvestrant in participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation following progression on or after endocrine-based therapy.

While the adverse drug profile of metformin IR (immediate release) and metformin XR are generally similar, up to 25% of patients on metformin IR may experience gastrointestinal toxicities that lead to treatment discontinuation in 5-10% of patients (Jabbour et al 2011). Metformin XR was developed to allow a slower release of drug into the upper gastrointestinal tract to reduce toxicities such as diarrhea. The use of metformin XR instead of metformin IR is justified by its better tolerability and once daily dosing (Jabbour et al 2011). The targeted patient population for EPIK-B4 is expected to be at high risk to develop drug-induced hyperglycemia and the better tolerability of metformin XR versus metformin IR will potentially allow a more rapid dose titration and improved adherence. In order to achieve a better glycemic control while on alpelisib treatment, the antihyperglycemic agents will be initiated one week before alpelisib treatment and will be titrated to the dose that is tolerated by the participant.

The purpose of this study is to determine if the combination of dapagliflozin plus metformin XR, when given prophylactically to participants considered at ‘high-risk’ for the development of hyperglycemia, leads to a greater reduction in severe hyperglycemia events compared with the prophylactic use of metformin XR alone. This strategy is intended to optimize prophylactic management of hyperglycemia for participants with underlying risk factors for the development of severe hyperglycemia.

2 Objectives, endpoints and estimands

Objectives and related selected endpoints are described in Table 2-1.

[redacted]

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To evaluate the reduction in severe hyperglycemia events over the first eight weeks of alpelisib plus fulvestrant with prophylactic dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR	● Occurrence of severe hyperglycemia (grade ≥ 3, based on glucose laboratory values) over the first eight weeks of alpelisib plus fulvestrant treatment (from C1D8 to C3D8)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To evaluate alpelisib plus fulvestrant with prophylactic dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR with regard to preliminary efficacy parameters	● PFS, ORR with confirmed response and CBR with confirmed response, based on local radiology assessments and using RECIST 1.1 criteria
● To assess the safety and tolerability	● Safety: Incidence, type, and severity of adverse events per CTCAE version 4.03 criteria including changes in laboratory values, ECOG, vital signs, liver assessments, renal and cardiac assessments Tolerability: dose interruptions, reductions, dose intensity, and duration of exposure for all drug components

[redacted]

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary scientific question of interest is: what is the effect on the occurrence of severe hyperglycemia (based on glucose laboratory values) over the first eight weeks of alpelisib plus fulvestrant (from Cycle 1 Day 8 to Cycle 3 Day 8) with prophylactic dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR, for participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, which progressed on or after endocrine-based therapy and have at least one risk factor for severe hyperglycemia, regardless of additional antihyperglycemic therapies as needed?

The justification for targeting this treatment effect is the intent to assess the treatment effect based on the occurrence of severe hyperglycemia while the participants are exposed to alpelisib plus fulvestrant as well as after the discontinuation and interruption of prophylactic antihyperglycemic medications, since any discontinuation or interruption will reflect clinical practice.

[redacted]

The primary estimand is characterized by the following attributes:

1. Population: participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after endocrine-based therapy and have at least one risk factor for severe hyperglycemia; randomized and received at least one dose of study treatment.
2. Treatment: the first study treatment is alpelisib plus fulvestrant with prophylactic dapagliflozin plus metformin XR (plus additional antihyperglycemic therapies as needed). The second study treatment is alpelisib plus fulvestrant with prophylactic metformin XR (plus additional antihyperglycemic therapies as needed).
3. Variable: occurrence of severe hyperglycemia (Grade ≥ 3, based on glucose laboratory values) over the first eight weeks of alpelisib plus fulvestrant treatment (from Cycle 1 Day 8 to Cycle 3 Day 8).
4. Handling of remaining intercurrent events:
   - Discontinuation of alpelisib for any reason or not receiving any alpelisib will be handled using treatment policy strategy.
   - Discontinuation and/or interruption of prophylactic antihyperglycemic medication for any reason will be handled using treatment policy strategy.
   - Dose interruption and/or reduction of alpelisib for any reason will be handled using treatment policy strategy.
5. Summary measure: difference between treatment arms in percentage of participants with severe hyperglycemia.

2.2 Secondary estimands

Not applicable.

3 Study design

Study CBYL719C2202 is a Phase II, multicenter, randomized, open-label, active-controlled trial designed to assess the safety and efficacy of the combination of dapagliflozin plus metformin XR compared to metformin XR alone during treatment with alpelisib plus fulvestrant in participants with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation following progression on or after endocrine-based therapy. The study will only include participants who have at least one of the following baseline risk factors for the development of severe hyperglycemia:

- Diabetes (fasting plasma glucose (FPG) ≥ 126 mg/dL or ≥ 7.0 mmol/L and/or HbA1c ≥ 6.5%)
- Pre-diabetes (FPG ≥ 100 mg/dL to < 126 mg/dL or 5.6 to < 7.0 mmol/L and/or HbA1c 5.7 to < 6.5%)
- Obesity (BMI ≥ 30)
- Age ≥ 75 years

Participants will be randomized in a 1:1 ratio (approximately 66 participants in each treatment arm) to receive the combination of dapagliflozin plus metformin XR or metformin XR

[redacted]

alone starting on Cycle 1 Day 1. Randomization will be stratified by diabetic status at baseline, i.e. normal vs pre-diabetic/diabetic (based on FPG and/or HbA1c laboratory values).

Figure 3-1 Study Design

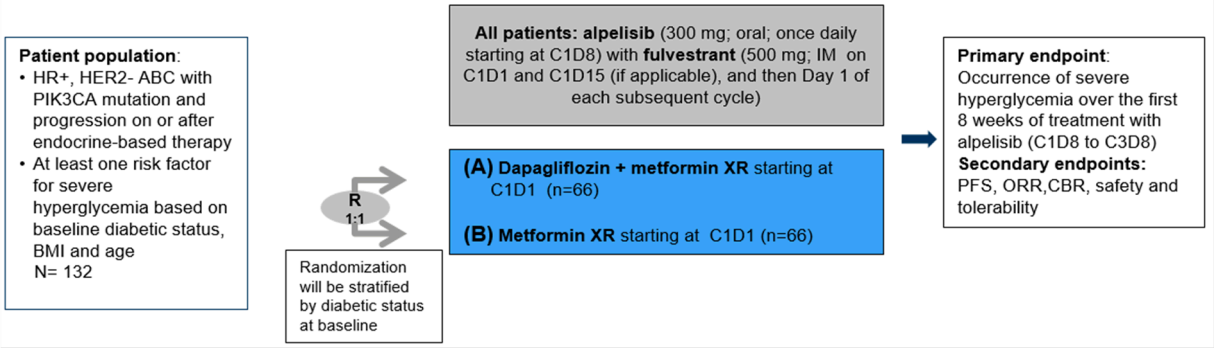
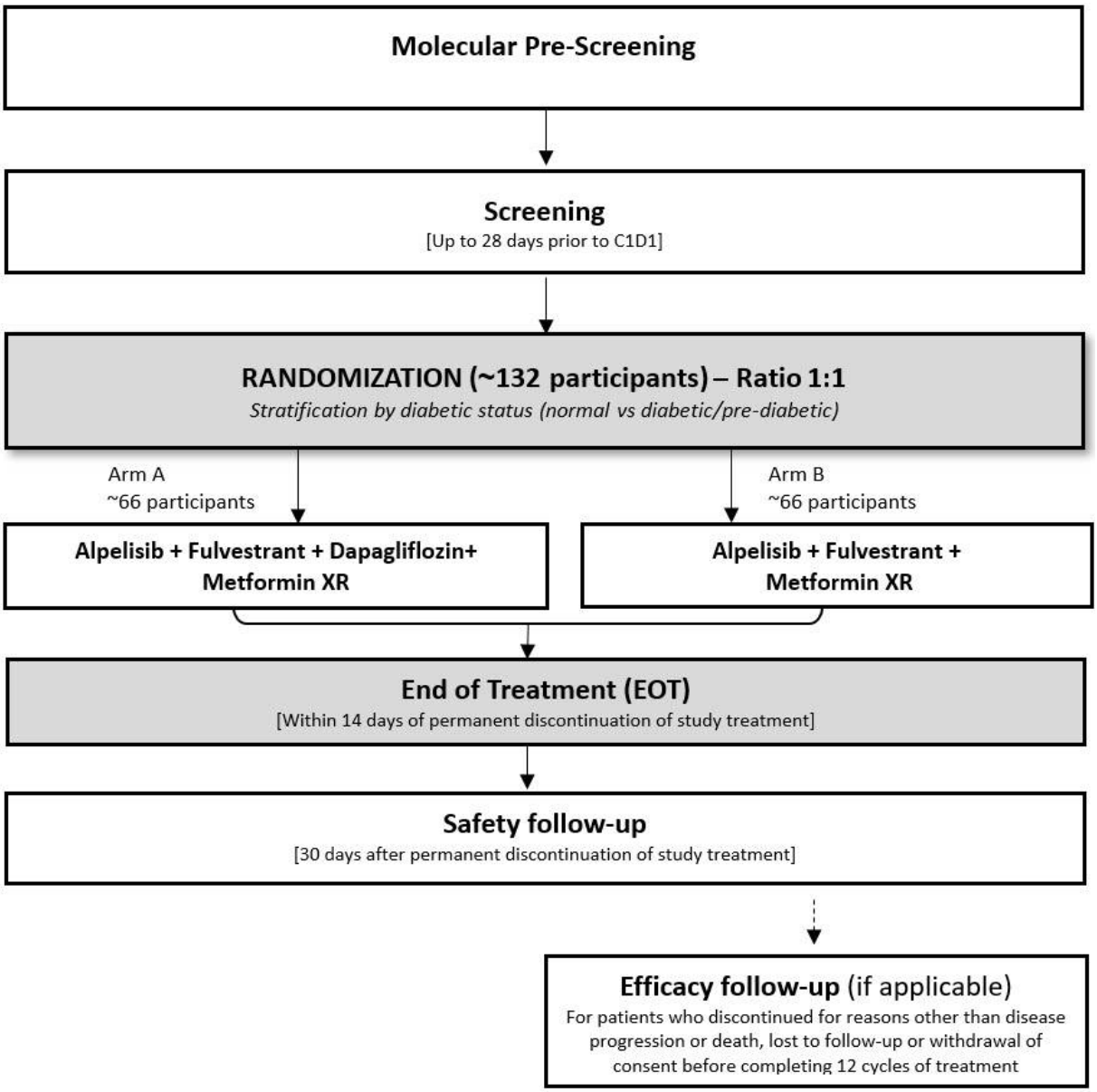


Figure 3-2 Study Flow Chart



The primary endpoint is the occurrence of severe (Grade ≥ 3) hyperglycemia events (based on glucose laboratory values) over the first eight weeks of alpelisib plus fulvestrant (from Cycle 1 Day 8 to Cycle 3 Day 8) with prophylactic treatment with dapagliflozin plus metformin XR compared to alpelisib plus fulvestrant with prophylactic metformin XR in participants who have at least one baseline risk factor associated with severe hyperglycemia.

The study will consist of 4 phases: molecular pre-screening, screening (28 days), randomized treatment, and post-treatment follow-up (safety follow-up and efficacy follow-up if applicable) as described in the study flow chart (Figure 3-2).

Treatment with fulvestrant and dapagliflozin plus metformin XR or metformin XR will be initiated on Cycle 1 Day 1 and be administered continuously. Alpelisib treatment begins one

[redacted]

week after the start of antihyperglycemic therapy (Cycle 1 Day 8) to allow for initial titration prior to alpelisib dosing.

The duration of treatment with alpelisib and fulvestrant will be 12 cycles or until disease progression, unacceptable toxicity, or discontinuation from study treatment for any other reason, whichever comes first. A cycle of treatment is defined as 28 days.

After treatment discontinuation, all participants will enter the safety follow-up which will end 30 days after participant discontinues from study treatment.

Participants who discontinue for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use of data/biological samples before completing 12 cycles of treatment will additionally enter post-treatment efficacy follow-up. Post-treatment efficacy follow-up will end 12 cycles after randomization.

After the 12 cycles treatment period for alpelisib plus fulvestrant, participants who, in the opinion of the Investigator, are benefiting from study treatment may switch to commercially available supply.

4 Rationale

4.1 Rationale for study design

This Phase II, multicenter, randomized, open-label, active-controlled trial is intended to include only participants who have at least one baseline risk factor for the development of severe hyperglycemia as defined in Section 3.

In SOLAR-1, 71% of all alpelisib-treated patients and 85% of alpelisib-treated patients who developed Grade 3 or 4 hyperglycemia had at least one of these risk factors.

Based on these data, the proposed study will include participants more likely to develop severe hyperglycemia, which include those with impaired glucose tolerance at baseline, a higher BMI grouping and older age, as defined above.

Among alpelisib-treated patients with severe hyperglycemia events in SOLAR-1, 87% of patients developed the events within the first two cycles of treatment. Therefore, in this proposed study, the primary endpoint will focus on the incidence of severe hyperglycemia in the first eight weeks of alpelisib plus fulvestrant treatment, starting from Cycle 1 Day 8.

In order to control for strong risk factors and avoid imbalance between the two arms while considering the sample size, randomization will be stratified (Kernan et al 1999) by diabetic status at baseline, i.e. normal vs pre-diabetic/diabetic (based on glucose and/or HbA1c laboratory values). In the SOLAR-1 study, among the risk factors identified for severe hyperglycemia, baseline diabetic status was most strongly associated with increased blood glucose.

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Rationale for dose/regimen and duration of treatment with alpelisib

The dose of alpelisib used in this study is 300 mg once daily.

[redacted]

In the Phase Ia study CBYL719X2101 alpelisib doses of 30 mg - 450 mg were explored; the maximum tolerated dose (MTD) for single-agent treatment was declared at 400 mg alpelisib under fed conditions. Clinical responses for alpelisib monotherapy were observed at doses of ≥ 270 mg once daily, though signs of tumor growth suppression were observed at doses ≥ 180 mg based on pharmacodynamic markers (Juric et al 2018). The dose and regimen in combination with the approved dose of fulvestrant was informed by the available safety, efficacy, and pharmacokinetic data from the combination part of study X2101 and taken forward into a Phase III study (SOLAR-1). SOLAR-1 confirmed that 300 mg alpelisib has a positive benefit-risk ratio with respect to efficacy and safety leading to substantial clinical benefit with manageable toxicities. In addition, alpelisib 300 mg once a day (QD) was also the selected starting dose or emerged to be the best tolerated dose in other studies in combination with aromatase inhibitors (AIs) (Shah et al 2014, Munster et al 2014, Mayer et al 2017, Study CBYL719A2201).

4.2.2 Rationale for combination treatment with fulvestrant

The dose of fulvestrant used in this study is 500 mg given intramuscularly at one month intervals, with an additional 500 mg dose given two weeks after the initial dose.

In the second line setting, several acceptable options are available (Gradishar et al 2015) and include fulvestrant. In addition, fulvestrant is currently approved for the treatment of HR+ metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. Hence, fulvestrant is considered a standard therapy for patients who have progressed on or after treatment with other endocrine agents and who require a well-tolerated alternative therapy (Ciruelos et al 2014).

Alpelisib (Piqray®) is approved in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor HR-positive, HER2-negative PIK3CA mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

4.3 Rationale for choice of antihyperglycemic agents

While current management strategies for hyperglycemia associated with PI3K inhibition primarily involve metformin and close observation of fasting glucose (FG) values, there remains an unmet need for strategies that offer early and sustained improvement of hyperglycemia than what is achieved with metformin as initial monotherapy. SGLT2i are a new class of medications, approved for use in adults with type 2 diabetes mellitus to improve glycemic control, that improve hyperglycemia primarily by promoting urinary glucose excretion and have a manageable safety profile. The combination of an SGLT2i plus metformin XR (extended release) administered on Cycle 1 Day 1 of treatment has the potential to not only maintain the efficacy observed with metformin monotherapy, but with enhanced rapidity of onset and durable management. From the mechanistic perspective, a particular advantage of SGLT2i is that they carry a limited risk of hypoglycemia which is often associated with glucose-lowering agents, as they function through a novel mechanism of reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating a compensatory increase in insulin. Therefore, SGLT2i are an appropriate addition to standard treatment with metformin, which also has a limited risk of hypoglycemia.

[redacted]

There are preclinical and clinical data to support the investigation of adding an SGLT2i to the standard antihyperglycemic agent, metformin, to treat and potentially prevent severe hyperglycemia associated with PI3K inhibition with alpelisib.

Brown Norway (BN) rat and Rat1-myr-p110α tumor bearing nude rat *in vivo* models were used to further investigate the degree of glucose and insulin control achievable upon treatment with alpelisib and the SGLT2i, dapagliflozin, with and without the addition of metformin and its subsequent effects on the tolerability and efficacy of alpelisib.

In both rat models tested, the addition of dapagliflozin to alpelisib nearly suppressed alpelisib-induced hyperglycemia, was associated with insulin level reduction and insulin sensitivity improvement. Notably, no signs for ketoacidosis upon single agent nor combination were observed under fed conditions. Alpelisib single agent efficacy in the Rat1-myr-p110α tumor bearing nude rats was maintained when used in combination with dapagliflozin and there was no influence of dapagliflozin on alpelisib-induced body weight loss. In BN rats, when combining metformin with alpelisib, a delay in blood glucose reduction was observed compared with the combination of dapagliflozin and alpelisib. The triple combination of metformin plus dapagliflozin plus alpelisib resulted in further improved blood glucose level reduction with the same kinetics as dapagliflozin plus alpelisib. The triple combination of metformin plus dapagliflozin plus alpelisib was more effective in reducing plasma insulin levels when compared to double combinations with metformin plus alpelisib or dapagliflozin plus alpelisib (Novartis Internal Data).

In terms of clinical data, in the SOLAR-1 study, among the 284 patients who were randomized to receive alpelisib plus fulvestrant, 181 patients (64%) developed hyperglycemia, with 18 patients (6%) discontinuing alpelisib treatment due to hyperglycemia, as of 12-Jun-2018.

Among those with hyperglycemia, 166 patients received concomitant anti-diabetic medications, primarily consisting of metformin (87%). However, in addition to metformin, 6 patients also received an SGLT2 inhibitor, consisting of empagliflozin, ipragliflozin, or dapagliflozin. All 6 patients 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 patients was Grade 3 (n = 5). After initiating an SGLT2 inhibitor, all subsequent hyperglycemia events were Grade 1/2, except one Grade 3 event with steroids as a confounding factor. The duration of alpelisib ranged from 9.5 to 27.7 months in [redacted] patients who discontinued alpelisib; and notably, [redacted] patients were continuing to receive alpelisib after 37.0 and 40.0 months, respectively. None of the 6 patients discontinued alpelisib due to hyperglycemia (Lu et al 2020).

Based on these data, participants may benefit from the initiation of an SGLT2i with metformin. Particularly in participants with at least one risk factor for the development of severe hyperglycemia, defined as prediabetes/diabetes, and/or obesity (BMI ≥ 30), and/or age ≥ 75 years, early or prophylactic initiation of an SGLT2i in combination with metformin may help to reduce the incidence and frequency of severe hyperglycemia events.

There are several available SGLT2i, including the combination of dapagliflozin and metformin XR, which is indicated for use in adults with type 2 diabetes mellitus. By utilizing a combination agent of dapagliflozin and metformin XR, there is an opportunity to optimize the safety profile of alpelisib with respect to hyperglycemia with a single oral medication. Among the

[redacted]

combination agents that are approved and available, the single oral combination of dapagliflozin and metformin XR is one of the most preferred agents, making it an appropriate treatment choice for this proposed study. Additionally, it is available in multiple strengths, which would allow for dose titration to target fasting glucose values. However, it is acceptable for participants randomized to the dapagliflozin plus metformin XR arm to receive these medications as two separate tablets, at the discretion of the Investigator, provided that the starting dose and dose titration guidance included in Section 6.3.2.4 can be achieved.

For participants not randomized to the dapagliflozin plus metformin XR arm, metformin XR will be initiated to explore hyperglycemia management with the extended release formulation as it is associated with slower gastrointestinal absorption, leading to less gastrointestinal toxicities, and once daily dosing, both of which may lead to better participant compliance and improved glucose management (Jabbour et al 2011).

Metformin XR and dapagliflozin plus metformin XR are initiated at low doses and require up-titration every few days, based on gastrointestinal tolerability, to reach full dose after 3 weeks. Hence, these antihyperglycemic agents will be started one week prior to alpelisib to allow for more effective hyperglycemia control.

4.4 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned for this trial. The primary analysis will be performed after all participants have completed at least eight weeks of alpelisib plus fulvestrant (from Cycle 1 Day 8 to Cycle 3 Day 8) or have discontinued treatment prior to completing eight weeks of alpelisib plus fulvestrant without further glucose assessment, whichever is earlier

4.5 Risks and benefits

4.5.1 Potential benefits to trial participants

Based on the results of the SOLAR-1 study, treatment with alpelisib in combination with fulvestrant has been shown to result in prolongation of PFS compared to fulvestrant alone in men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer, which progressed on or after AI treatment. Based on preclinical and clinical data, treatment with alpelisib in combination with fulvestrant is well tolerated. All participants enrolled in this trial will receive active therapy for their disease with alpelisib in combination with fulvestrant.

For further details on clinical safety, please refer the latest version of [Alpelisib (BYL719) Investigator's Brochure].

While adverse drug reactions associated with alpelisib are largely manageable and reversible, dose reductions, treatment delays and discontinuation due to hyperglycemia may ultimately impact treatment duration. All participants enrolled in this trial will receive an active treatment regimen for hyperglycemia starting on Cycle 1 Day 1, which may result in reduced hyperglycemia events and may improve tolerability to alpelisib treatment.

4.5.2 Potential risks to trial participants

Participants in this study will be carefully monitored using periodic laboratory and cardiac assessments (ECG, ECHO/MUGA) for key toxicities that have been observed with study

[redacted]

treatment (see Section 1.1.2.2). Specific guidance for overlapping toxicities for alpelisib and combination partner and other possible side effects is provided in Section 6.6.3.

Risks will be minimized by adherence to inclusion/exclusion selection criteria (Section 5), avoidance of prohibited medication (see Section 6.2.2), close safety monitoring (see Section 6.6.3 and Section 10), adherence to dose adjustment guidelines (see Section 6.6), and training of site personnel.

Sexually active males must be informed that taking this study treatment may involve potential embryo-fetal risk to the fetus if pregnancy were to occur (during the study and up to the period required after the last dose of study treatment) and they must agree that in order to participate in the study they must 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.

A Steering Committee (SC) (see Section 10.3.1) comprising of Investigators, and Novartis representatives from the Clinical Trial Team (CTT) will support the scientific integrity and conduct of the trial according to the protocol. A Novartis Safety Management Team (SMT) will regularly review and evaluate all emerging data in this study and across the alpelisib program for potential safety signal assessments in a timely manner.

4.6 Rationale for Public Health Emergency mitigation procedures

In the event of 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 of the study protocol. Notification of the Public Health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

The study will include adult men and postmenopausal women with HR-positive, HER2-negative advanced (locoregionally recurrent not amenable to curative therapy or metastatic) breast cancer with a PIK3CA mutation which has progressed on or after endocrine-based therapy who plan to initiate therapy with alpelisib plus fulvestrant and have at least one baseline risk factor for severe hyperglycemia. This study population is consistent with the population for which alpelisib is approved for use. A total of approximately 132 participants will be enrolled and randomized to receive the combination of dapagliflozin plus metformin XR or metformin XR alone during treatment with alpelisib plus fulvestrant.

5.1 Inclusion criteria

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

1. Signed informed consent(s) must be obtained prior to participation in the study.
2. Participant is an adult ≥ 18 years old at the time of informed consent(s) (man or postmenopausal woman) before any trial related activities and according to local guidelines.

[redacted]

3. Participant is fulfilling at least one of the below criteria (risk factors for severe hyperglycemia):
   - Diabetes (FPG ≥ 126 mg/dL or ≥ 7.0 mmol/L and/or HbA1c ≥ 6.5%)
   - Pre-diabetes (FPG ≥ 100 mg/dL to <126 mg/dL or 5.6 to <7.0 mmol/L and/or HbA1c 5.7 to <6.5%)
   - Obesity (BMI ≥ 30)
   - Age ≥ 75 years.
4. Participant has a histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ breast cancer by local laboratory.
5. Participant has a PIK3CA mutation(s) present in tumor prior to enrollment, as determined by a Novartis designated laboratory. A formalin fixed paraffin embedded (FFPE) tumor block from a new or archival biopsy or unstained FFPE glass sides (5 slides minimum from a surgical specimen, 13 slides minimum from a biopsy) must be provided. It is recommended to provide a tumor sample collected after the most recent progression or recurrence.

   Note: Local confirmation of the PIK3CA mutation status is acceptable, provided that the tumor PIK3CA mutation assessment (tissue or plasma) was performed by a local laboratory using either a food and drug administration (FDA)-approved PIK3CA Companion Diagnostics (CDx) test for alpelisib or the European In-Vitro Diagnostic Devices Directive (CE-IVD) QIAGEN therascreen PIK3CA Rotor-Gene Q (RGQ) polymerase chain reaction **(**PCR) test.
6. Participant has advanced (locoregionally recurrent not amenable to curative therapy or metastatic) breast cancer.
7. Participant has prior treatment with an endocrine-based treatment (i.e. letrozole, anastrozole, exemestane, fulvestrant or oral SERD) and may be:
   - relapsed with documented evidence of progression while on (neo) adjuvant endocrine-based therapy or within 12 months from completion of (neo)adjuvant endocrine-based therapy with no treatment for metastatic disease
   - relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine-based therapy and then subsequently progressed with documented evidence of progression while on or after only one line of endocrine-based therapy for metastatic disease
   - newly diagnosed advanced breast cancer, then relapsed with documented evidence of progression while on or after only one line of endocrine-based therapy.

   Note: Participants with newly diagnosed endocrine-based treatment naïve advanced breast cancer will NOT be included in the study.
8. Participants may or may not have received prior CDK4/6i therapy. If prior CDK4/6i therapy was administered, it may have been in the adjuvant or metastatic setting
9. Participant has HER2-negative breast cancer defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing.

[redacted]

10. Participant has either measurable disease, i.e., at least one measurable lesion as per response evaluation criteria in solid tumors (RECIST) 1.1 criteria OR if no measurable disease is present, then at least one predominantly lytic bone lesion must be present.
11. If female, then the participant is postmenopausal. Postmenopausal status is defined either by:
    - Prior bilateral oophorectomy
    - Age ≥60
    - Age <60 and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and Follicle-stimulating Hormone (FSH) and estradiol in the postmenopausal range per local normal range

    Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status. Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression in this trial (see Section 8.4.3).
12. Participant has an ECOG performance status 0 or 1.
13. Participant has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory for eligibility):
    - Absolute neutrophil count ≥ 1.2×10^9/L
    - Platelets ≥ 100×10^9/L
    - Hemoglobin ≥ 9.0 g/dL
    - Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ grade 1 according to National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 if judged clinically not significant by the Investigator
    - Potassium within normal limits, or corrected with supplements
    - International Normalized Ratio (INR) ≤ 1.5
    - Total bilirubin < 2 x upper limit of normal (ULN) (any elevated bilirubin should be asymptomatic at enrollment) except for participants with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
    - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 × ULN. If the participant has liver metastases, ALT and AST ≤ 5 × ULN, he/she will be eligible for the study
    - Fasting Serum amylase ≤ 2 × ULN
    - Fasting Serum lipase ≤ ULN

5.2 Exclusion criteria

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

[redacted]

1. Participant who relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease.
2. Participant with symptomatic visceral disease or any disease burden that makes the participant ineligible for endocrine therapy per the Investigator's assessment.
3. Participant had more than 1 line of prior treatment in the metastatic setting
4. Participant has received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), any PI3K, mTOR or Akt inhibitor.
5. Participant has a known hypersensitivity to alpelisib, fulvestrant, dapagliflozin and metformin XR alone or in combination or to any of their excipients.
6. Participant has inflammatory breast cancer at screening.
7. Participant is concurrently receiving other anti-cancer therapy.
8. Participant has had major surgery within 14 days prior to study treatment start and/or has not recovered from major side effects.
9. Participant has not recovered from all toxicities related to prior anticancer therapies to NCI CTCAE version 4.03 Grade ≤ 1. Exception to this criterion: participant with any grade of alopecia are allowed to enter in the study.
10. Participant with Child Pugh score B or C.
11. Participant has received radiotherapy≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia).
12. Participant has a concurrent malignancy or malignancy within 3 years prior to randomization, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
13. Participants with previously untreated central nervous system (CNS) involvement are ineligible for this study, unless they fulfill the following 3 criteria:
    - completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study entry
    - and CNS tumor is clinically stable at the time of screening and
    - participant is not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases
14. Participants with an established diagnosis of diabetes mellitus type I or participants with uncontrolled type II diabetes mellitus (FPG > 160 mg/dL and/or HbA1c > 8%) or type II diabetes mellitus requiring antihyperglycemic therapy.
15. Moderate to severe renal impairment (e.g., estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2).
16. Participant 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.
17. Participant has a history of acute pancreatitis within 1 year of screening or a past medical history of chronic pancreatitis.

[redacted]

18. Participant has uncontrolled hypertension, defined as 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 anti-hypertensive medication(s) is allowed prior to screening.
19. Participant has any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator's judgment, contraindicate participant participation in the clinical study (e.g., chronic active hepatitis [testing not mandatory unless required by local regulations or requirements], severe hepatic impairment, etc.).
20. Participant has currently documented pneumonitis/interstitial lung disease (the chest Computerized Tomography (CT) scan performed before start of study treatment for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).
21. Participant has clinically significant, uncontrolled heart disease and/or recent cardiac events including any of the following:
    - History of angina pectoris, coronary artery bypass graft (CABG), symptomatic pericarditis, or myocardial infarction within 6 months prior to the start of study treatment
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Left Ventricular Ejection Fraction (LVEF) < 50% at screening as determined by MUGA or ECHO
    - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high grade atrioventricular (AV) block (e.g., bifascicular, Mobitz type II and third degree AV block without pacemaker in place)
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or Fridericia QT correction formula (QTcF) > 470 msec at screening.
22. Participant has a history of severe cutaneous reaction, such as Steven-Johnson Syndrome (SJS), erythema multiforme (EM), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Syndrome (DRESS.
23. Participant has unresolved osteonecrosis of the jaw (ONJ).
24. Participant is currently receiving any of the following medications and cannot be discontinued at least 7 days prior to the start of study treatment:
    - Strong CYP3A4 inducers
    - Inhibitors of BCRP
25. Participant is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.

    Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
26. Participant is a sexually active male not sterilized (at least 6 months prior to screening) or unwilling to use a condom during intercourse while taking study treatment, and for at least 1 year after stopping fulvestrant or for at least 1 week after stopping alpelisib. A condom is required for all sexually active male participants to prevent them from fathering a child

[redacted]

AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm during the study and up to the time period specific above.

27. Participant participated in a prior investigational study within 30 days prior to randomization or within 5 half-lives of the investigational product, whichever is longer.
28. Participant is not able to understand and to comply with study instructions and requirements, including oral administration of study treatment

6 Treatment

6.1 Study treatment

In this study, the term "study treatment" or "investigational treatment" refers to both combinations:

- Arm A: Alpelisib + fulvestrant + dapagliflozin + metformin XR
- Arm B: Alpelisib + fulvestrant + metformin XR

Participants randomized to Arm A will be allowed, at the discretion of the Investigator, to receive dapagliflozin + metformin XR as a single tablet combination or as two separate tablets, provided that the starting dose and dose titration guidance included in Section 6.3.2.4 can be achieved.

Refer to Section 6.3.2 for guidance related to the dispensation of study treatment.

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

6.1.1 Investigational and control drugs

Alpelisib will be administered at a dose of 300 mg, orally once daily on a continuous basis immediately after food starting on Cycle 1 Day 8 in combination with fulvestrant 500 mg i.m. (as two 5 ml injections 250 mg each) starting on Cycle 1 Day 1 and 15, and Day 1 of every cycle thereafter (+/- 3 days) in a 28-day cycle.

A non-sedating antihistamine, such as cetirizine once daily, is recommended to start on Cycle 1 Day 1 for approximately 8 weeks for the prevention of rash associated with PI3K inhibition. The antihistamine can be continued beyond the first 8 weeks, if clinically indicated at the Investigator's discretion (Wang et al 2020). Refer to Table 6-3 and Section 6.6.3.3 for additional information on antihistamine treatment and incidence/severity of rash based on alpelisib clinical trial experience.

For participants randomized to receive dapagliflozin + metformin XR, the starting dose is 5 mg dapagliflozin + 500 mg metformin XR orally once daily, which can be titrated to a maximum dose of 10 mg dapagliflozin + 2000 mg metformin XR orally once daily, as outlined in Section 6.3.2.4. For participants randomized to receive metformin XR monotherapy, the starting dose is 500 mg orally once daily and can be titrated to a maximum dose of 2000 mg orally once daily, as outlined in Section 6.3.2.3.

[redacted]

A complete cycle of treatment is defined as 28 days (+/- 3 days) of once daily continuous treatment of alpelisib (starting at Cycle 1 Day 8) in combination with fulvestrant (starting at Cycle 1 Day 1). The last day of a complete treatment cycle is Day 28 (+/- 3 days). Day 1 of the next cycle starts on Day 29 (+/- 3 days).

Table 6-1 Study treatment

Study treatment (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation
Alpelisib 50 mg[1]	Tablet	Oral use	Open label participant packs
Alpelisib 200 mg[1]	Tablet	Oral use	Open label participant packs
Fulvestrant 500 mg	Prefilled syringe (two 5 ml syringes 250 mg each)	Intramuscular (IM) injection	Commercial supply or open label participant packs
Dapagliflozin 5 mg + metformin 500 mg XR (single combination tablet)[2]	Tablet	Oral use	Commercial supply or open label participant packs
Dapagliflozin 5 mg + metformin 1000 mg XR (single combination tablet)[2]	Tablet	Oral use	Commercial supply or open label participant packs
Dapagliflozin 10 mg + metformin 1000 mg XR (single combination tablet)[2]	Tablet	Oral use	Commercial supply or open label participant packs
Dapagliflozin 5 mg[2]	Tablet	Oral use	Commercial supply or open label participant packs
Dapagliflozin 10 mg[2]	Tablet	Oral use	Commercial supply or open label participant packs
Metformin 500 mg XR[2]	Tablet	Oral use	Commercial supply or open label participant packs
Metformin 1000 mg XR[2]	Tablet	Oral use	Commercial supply or open label participant packs

[1] Dose for alpelisib will be administered accordingly (see Table 6-2)

[2] Participants randomized to the dapagliflozin + metformin XR arm may, at the discretion of the Investigator, receive dapagliflozin and metformin XR as a single tablet combination or as two separate tablets, provided that the starting dose and dose titration guidance included in Section 6.3.2.4 can be achieved.

6.1.2 Additional study treatments

The study treatment consists of alpelisib plus fulvestrant for the treatment of breast cancer, and dapagliflozin + metformin XR or metformin XR alone for the management/prevention of hyperglycemia. Additional guidance regarding permitted concomitant therapy is included in Section 6.2.

6.1.3 Treatment arms/group

Participants will be randomized in an unblinded fashion at the time of initiation of treatment with fulvestrant (visit Cycle 1 Day 1) to one of the following 2 treatment arms/groups in a 1:1 ratio:

- Arm A: alpelisib + fulvestrant + dapagliflozin + metformin XR

[redacted]

- Arm B: alpelisib + fulvestrant + metformin XR

Participants randomized to the dapagliflozin + metformin XR arm may, at the discretion of the Investigator, receive dapagliflozin and metformin XR as a single tablet combination or as two separate tablets, provided that the starting dose and dose titration guidance included in Section 6.3.2.4 can be achieved.

Refer to Section 6.3.2 for guidance related to the dispensation of study treatment.

6.1.4 Guidelines for continuation of treatment

For guidelines for continuation of treatment, refer to Section 6.6.1.

Patients who permanently discontinue alpelisib and/or fulvestrant for any reason other than disease progression may continue the other study drug (alpelisib or fulvestrant) as part of the trial therapy at the Investigators 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

The planned duration of treatment with alpelisib + fulvestrant is 12 cycles. Participants will continue to receive study treatment until disease progression is radiologically documented according to RECIST 1.1, unacceptable toxicity that precludes further treatment, or discontinuation from study treatment for any other reason, whichever comes first (see Section 9.1.1).

Alpelisib and fulvestrant may be discontinued independently of each other for unacceptable toxicities that precludes further treatment, or at the discretion of the Investigator.

If alpelisib is discontinued, treatment with antihyperglycemic agents (dapagliflozin + metformin XR or metformin XR alone) may also be discontinued as hyperglycemia typically resolves following discontinuation of alpelisib. The timing of discontinuation of the antihyperglycemic agents (dapagliflozin + metformin XR or metformin XR alone) is at the discretion of the Investigator and should be based on the participant's normalization (or return to baseline) of fasting glucose values.

Participants who discontinue alpelisib and fulvestrant (EOT) prior to Cycle 3 Day 8 will continue to have FPG monitored and hyperglycemia-related AE collected for a maximum of 9 weeks (+/- 3 days) depending on the time point of study treatment discontinuation (e.g., discontinuation after 1 week treatment would require FPG monitoring and hyperglycemia-related AE collection for another 8 weeks; discontinuation after 2 weeks would require FPG monitoring and hyperglycemia-related AE collection for 7 weeks etc.).

After the 12 cycles treatment period for alpelisib + fulvestrant, participants who, in the opinion of the Investigator, are benefiting from study treatment may switch to commercially available supply.

[redacted]

6.1.5.1 Treatment beyond disease progression

Study treatment beyond disease progression per RECIST 1.1 as assessed locally by the Investigator is not permitted in this study.

6.1.6 Supply of study treatment

Novartis Global Clinical Supply or its designee will provide alpelisib as tablets in dosage strengths of 50 mg and 200 mg. The tablets will be differentiated through different tablet sizes and/or colors. Alpelisib will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area (BSA). Alpelisib tablets will be administered orally immediately after food once daily on a continuous basis.

Fulvestrant, dapagliflozin + metformin XR, and metformin XR will be provided locally by the study site, subsidiary or designee in each participating country according to local practices and local regulations. Storage conditions are described in the prescribing information. Prescribing information will comply with the legal requirements of each country and should be printed in the local language.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The use of any concomitant medications/non-drug therapies deemed necessary 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 16.5.2).

All medications, procedures, and significant non-drug therapies (including vitamins, physical therapy, herbal/natural medications and blood transfusions) administered within 30 days prior to the start of study treatment and up to 30 days after the last dose of study treatment must be recorded on the appropriate eCRF.

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

Oral antihyperglycemics

Participants who develop hyperglycemia during the study should be treated according to the American Diabetes Association and/or European Association for the study of Diabetes guidance. Participants receiving oral anti-diabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, should be monitored with respect to their effectiveness as alpelisib was found to be an inducer of CYP2C9 in vitro.

[redacted]

If additional antihyperglycemic agents are required prior to Cycle 3 Day 8 to achieve adequate control of fasting blood glucose levels, it is recommended that participants randomized to the metformin XR alone arm avoid the use of SGLT2i, as this may impact the primary endpoint assessment. However, beyond Cycle 3 Day 8 , SGLT2i are acceptable. In case of intolerance to metformin XR or dapagliflozin + metformin XR, or persistent hyperglycemia, Investigator's judgment should be exercised and other oral anti-diabetic agents such as thiazolidinediones, dipeptidyl peptidase-4 inhibitors, or insulin treatment can be used, as clinically indicated.

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 agent drug-drug interaction **(**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.

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 1.1 and 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.

Hematopoietic growth factors

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

Corticosteroids

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

See exclusion criteria number 25 (Section 5.2) for further details of use.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during combined alpelisib and fulvestrant treatment in this study are listed below and in Section 16.5.1. 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 fulvestrant interruption, as appropriate, if the concomitant medication is only needed for a short time.

[redacted]

Medications to be used with caution include:

- **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 (see Table 16-10). Alternatively, therapeutic anticoagulation may be accomplished using low- molecular weight heparin or Direct Thrombin inhibitors and Factor Xa inhibitors.
- **CYP2B6 sensitive substrates or CYP2B6 substrates with NTI:** Based on a static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib. In absence of clinical data, 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 (see Table 16-10).
- **Selected CYP3A4 substrates:** Alpelisib can be co-administered with sensitive CYP3A4 substrates (e.g., everolimus, midazolam) and CYP3A4 substrates with narrow therapeutic window (e.g., fentanyl). Caution is recommended when alpelisib is used in combination with CYP3A4 substrates that also possess an additional time dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g., ribociclib, encorafenib, refer to Table 16-10). 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 16.5.2) for being strong inducers of CYP3A such as St. John's Wort (Hypericum perforatum) and Avasimibe (see Table 16-11) or BCRP inhibitors such as Curcumin (see Table 16-12). Medications such as Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng should be avoided if possible due to their potential for complex interactions. Since cannabinoids have been shown to inhibit BCRP in vitro, medical cannabis should be used with caution. Participants should be closely monitored for increased adverse reactions (as the relevance of this interaction in vivo is currently unknown). In case of unexpected toxicities, participants should stop using all herbal medications. Use of all such medications (including frequency of administration) should be documented.

6.2.1.2 Use of bisphosphonates/RANK-ligand inhibitors

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

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

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

[redacted]

Participants requiring initiation of bisphosphonate/RANK-ligand inhibitors (e.g., denosumab) treatment during the course of the study should be assessed by appropriate image modalities to exclude disease progression; if disease progression is documented, the participant should discontinue study treatment. If bisphosphonate/ RANK-ligand inhibitors (e.g., denosumab) therapy 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 bisphosphonates/RANK-ligand inhibitors. In SOLAR-1, ONJ was reported in 4.2% participants (12/284) in the alpelisib plus fulvestrant arm compared to 1.4% participants (4/287) in the placebo plus fulvestrant arm. All participants experiencing ONJ were also exposed to prior or concomitant bisphosphonates (e.g., zoledronic acid). Therefore, in participants receiving alpelisib and bisphosphonates, an increased risk of development of ONJ cannot be excluded. For prevention and clinical management of ONJ, prescribing information of bisphosphonates should be followed.

6.2.2 Prohibited medication

The following medications are prohibited during combined alpelisib and fulvestrant treatment in this study (see Appendix Section 16.5.2), this list is not comprehensive and is only meant to be used as a guide. Please contact Novartis 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, refer to Table 16-11.
- **Inhibitors of BCRP**: Avoid the use of BCRP inhibitors in participants treated with alpelisib. If unable to use alternative drugs, closely monitor for increased adverse reactions, refer to Table 16-12.
- **Other investigational and antineoplastic therapies.**

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

Participants will be provided with an adequate supply of alpelisib, dapagliflozin + metformin XR, and metformin XR for self-administration at home, including instructions for administration, until at least their next scheduled study visit.

Participants will receive alpelisib, dapagliflozin + metformin XR or metformin XR alone on an outpatient basis.

Participants randomized to the dapagliflozin + metformin XR arm may, at the discretion of the Investigator, receive dapagliflozin and metformin XR as a single tablet combination or as two separate tablets, provided that the starting dose and dose titration guidance included in Section 6.3.2.4 can be achieved.

Only qualified and personnel trained to the preparation procedure will handle, prepare and dispense fulvestrant as described in the local Prescribing Information.

A unique medication number is printed on the study medication label.

[redacted]

For drugs managed by Interactive Response Technology (IRT), Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

As per Section 4.6, 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 investigational medicinal product (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 (as per visit frequency describe in Table 8-2) 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.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

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.

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.

[redacted]

6.3.2 Instruction for prescribing and taking study treatment

6.3.2.1 Alpelisib administration

Alpelisib 300 mg is taken orally once daily on a continuous dosing schedule starting on Cycle 1 Day 8 under fed conditions. Dose reductions to 250 mg and 200 mg will be permitted (see Section 6.6.1.1). If further dose reductions are indicated, the participant will be permanently discontinued from alpelisib.

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 BSA. There will be no breaks between dosing cycles. Participants should be instructed to take the dose of alpelisib at approximately the same time each day immediately after food (preferably in the morning), except on the days blood collection is scheduled at the clinic, at which time the participants should take their doses at the clinic at any later point of time.

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

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

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.

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

6.3.2.1.1 Additional dosing guidelines for scheduled visits days

On days when pre-dose fasting safety samples are collected as described in Table 8-2, participants should be instructed to arrive at the site in s fasted state. The additional guidelines below should be followed.

- The participants must have fasted overnight for at least 8-12 hours prior to the blood collection for fasting glucose, lipid profile, amylase/lipase samples. Water, coffee/tea (unsweetened and without milk) is allowed during all fasting periods; however, juices (fruit or vegetable) are not permitted during the fasting period.

[redacted]

- On scheduled visit days, participants must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days participants will take alpelisib at home.
- The participants must take alpelisib immediately after food.
- If a pre-dose ECG measurement should be collected, then the ECG measurement should occur before dosing of alpelisib and all study treatment

6.3.2.2 Fulvestrant administration

Fulvestrant 500 mg will be given at Cycle 1 Day 1 and Cycle 1 Day 15 after randomization and then at Day 1 of each subsequent cycle during the randomized treatment phase (+/- 3 days). Fulvestrant injection at Cycle 1 Day 15 is not applicable for participants already being treated with fulvestrant when joining the trial.

Fulvestrant is administered intramuscularly into the buttocks slowly as two 5 mL injections (of 250 mg each), one in each buttock.

No dose modification is allowed for fulvestrant. Please refer to the local approved prescribing information. Any planned variance from these guidelines in the view of the patient safety must be previously discussed with the Sponsor unless there is an urgent need for action.

6.3.2.3 Metformin XR administration

Participants who are randomized to receive metformin XR alone will initiate metformin XR on Cycle 1 Day 1. Metformin XR treatment will be administered during the first week of Cycle 1 and continue for the duration of treatment with alpelisib. The starting dose of metformin XR is 500 mg orally once daily, which can be titrated to a maximum dose of 2000 mg orally once daily.

For dose titration guideline please refer to Section 6.6.2.1.

[redacted]

6.3.2.4 Dapagliflozin + metformin XR administration

Participants who are randomized to receive dapagliflozin + metformin XR will initiate combination therapy on Cycle 1 Day 1.

Participants randomized to dapagliflozin + metformin XR arm will be allowed, at the discretion of the Investigator, to receive the medication as a single tablet combination or as two separate tablets, provided that the starting dose and dose titration guidance included in Section 6.6.2.2. can be achieved.

Treatment with dapagliflozin + metformin XR will be administered during the first week of Cycle 1 and continue for the duration of treatment with alpelisib. The starting dose is 5 mg dapagliflozin + 500 mg metformin XR orally once daily, which can be titrated to a maximum dose of 10 mg dapagliflozin + 2000 mg metformin XR orally once daily.

For dose titration guideline, please refer to Section 6.6.2.2.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available at each site.

The Investigator or designated staff will contact the IRT and provide the requested identifying information to register the participant into the IRT. Once assigned, the Participant No. must not be reused for any other participant and the Participant No. for that individual must not be changed. If the participant fails to be enrolled, to be randomized or to start treatment for any reason, the reason will be entered into the appropriate eCRF.

IRT must be notified within 2 days if the participant did not start treatment or isn't randomized.

A participant who has any laboratory test result that does not satisfy the eligibility criteria may have the test(s) repeated once. These test(s) may be repeated as soon as the Investigator believes the retest result(s) is/are likely to be within the acceptable range to satisfy the eligibility criteria, but should be completed within 14 days of screening period. In this case, the participant will not be required to sign another informed consent form (ICF), and the original Participant No. assigned by the Investigator will be used. In the event that the laboratory test(s) cannot be performed within 14 days of screening period or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant will be considered a screen failure.

It is permissible to re-screen a participant if s/he fails the initial screening. A new informed consent form must be signed only if there is an interruption in the participant's eligibility evaluation and the Investigator chooses to re-screen the participant following screen failure.

[redacted]

Re-screening of participant is only allowed once per participant if the subject was not registered as entering the randomized treatment phase before (i.e. IRT randomization/treatment assignment). In this case a new Participant No. will be generated, and a specific rescreen form will be added in the eCRF, to collect the original Participant No. This data will be used to link the two Participant No. for reporting and validation.

All required screening activities must be performed when the participant is re-screened to satisfy the requirements defined in Table 8-2. Once the number of participants screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the participants who have screen failed will not be permitted to re-screen.

6.4.2 Treatment assignment, randomization

At visit Cycle 1 Day 1 all eligible participants will be randomized via IRT to one of the two treatment arms specified in Section 6.1.3. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion and none of the exclusion criteria.

The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm. At each visit, the IRT will specify specific medication number(s) of alpelisib to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing alpelisib.

Randomization of participants will be stratified by diabetic status (normal versus diabetic/pre-diabetic based on glucose and/or HbA1c laboratory values) at baseline in order to control for an important hyperglycemia risk factor and to avoid imbalance between the two treatment arms. Of note, all participants will have at least one risk factor associated with the development of hyperglycemia (as listed in Section 3).

The randomization scheme for participants will be reviewed and approved by a member of the Novartis Randomization Office.

6.5 Treatment blinding

Treatment will be open to participants, Investigator staff, persons performing the assessments and the Novartis CTT. However, in order to minimize the potential impact of knowledge of treatments, the randomization list will be kept strictly confidential. No aggregate statistical analyses (efficacy or safety across the study) by treatment shall be performed prior to the primary analysis.

[redacted]

6.6 Dose escalation and dose modification

Alpelisib and fulvestrant dose escalations are not permitted.

6.6.1 Dose modifications

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

These dose modifications are summarized in Table 6-3. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent discontinuation from study treatment is mandatory for specific events indicated as such in Table 6-3 or listed in Section 9.1.

These dose changes must be recorded on the appropriate eCRF.

Additionally dose escalations of antihyperglycemic medication as described in Section 6.6.2 must also be recorded on the appropriate eCRF.

6.6.1.1 Alpelisib dose modifications

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 CTCAE v4.03 since this version is more objective than CTCAE v5 with regard to hyperglycemia grading as it is based on laboratory values. Clinical judgment of the treating physician, including confirmation of laboratory values if deemed necessary, should guide the management plan of each participant based on individual benefit/risk assessment.

A maximum of 2 dose reductions of alpelisib will be allowed after which treatment must be discontinued as indicated in Section 6.3.2.1. Deviations to stepwise dose reductions are not allowed.

After treatment is resumed at a lower dose:

- If the same toxicity reoccurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration, except if specified in Table 6-3.
- Once the alpelisib dose has been reduced by the Investigator, no re-escalation is allowed, even upon resolution of AE.

If a participant requires a withholding of alpelisib dose, the participant may continue fulvestrant, per Investigator discretion. As the half-life of alpelisib is approximately 9 hours, if alpelisib is interrupted, then consideration should be given to any antihyperglycemic medications. All scheduled assessments will continue to be performed as per protocol.

Permanent discontinuation of alpelisib treatment is mandatory for specific events indicated as such in Table 6-3 or listed in Section 9.1. These dose changes must be recorded on the appropriate eCRF.

[redacted]

Table 6-2 Stepwise dose reduction 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

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

Worst toxicity - CTCAE grade (value)	**Dose Modifications for alpelisib**
Investigations (Fasting Glucose)	
Hyperglycemia • 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 and/or European Association for the study of Diabetes, 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). • Local standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting glucose testing may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance. • **Note:** this table provides dose management recommendations. **Dose modifications and management should only be based on fasting** laboratory **glucose values.** • If additional antihyperglycemic agents are required prior to Cycle 3 Day 8 to achieve adequate control of fasting blood glucose levels, it is recommended that participants randomized to the metformin XR arm avoid the use of SGLT2i, as this may impact the primary endpoint assessment. However, beyond Cycle 3 Day 8 , SGLT2i are acceptable. In case of intolerance to metformin XR or dapagliflozin + metformin XR, or persistent hyperglycemia, Investigator's judgment should be exercised and other oral anti-diabetic agents such as thiazolidinediones, dipeptidyl peptidase-4 Inhibitors, or insulin treatment can be used, as clinically indicated. • SGLT2i may increase the risk of euglycemic diabetic ketoacidosis and therefore, monitoring with serum ketones will be performed as outlined in Table 8-2. Refer to Section 6.6.2 for additional information regarding euglycemic diabetic ketoacidosis. • If antihyperglycemic treatment is interrupted for radiologic assessments or another reason, then alternative hyperglycemia management should be considered for those days to ensure optimal hyperglycemia management.	
Grade 1 (FG > ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For participants with baseline values between > ULN – 140 mg/dL (ULN – 7.7 mmol/L) this applies only for values > 140 mg/dL (7.7 mmol/L)	● Maintain dose level, and remind participant on lifestyle changes. ● Intensify dapagliflozin + metformin XR or metformin XR as per guidance in Section 6.6.2 in cooperation with a healthcare expert experienced in hyperglycemia management or a diabetologist. ● Monitor fasting glucose levels as clinically indicated and at least twice weekly for 8 weeks, then continue checking at least weekly until FG is within baseline values.
Grade 2 (FG > 160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	● Maintain dose level and remind participant on lifestyle changes, exclude confounding factors like e.g., urinary tract infection, and consider consultation with a healthcare expert experienced in hyperglycemia management or a diabetologist. ● Intensify dapagliflozin + metformin XR or metformin XR as per guidance in Section 6.6.2 ● If fasting glucose levels are still rising on maximum tolerated doses of dapagliflozin + metformin XR or metformin XR (depending on treatment arm), persistently > 160mg/dl (> 8.9 mmol/L), additional oral antihyperglycemic agent may be initiated, at the discretion of the Investigator. For example, an insulin-sensitizer, e.g., pioglitazone 30 mg (max. dose) can be added.

Worst toxicity - CTCAE grade (value)	**Dose Modifications for alpelisib**
	Monitor fasting glucose levels as clinically indicated and at least twice weekly until FG resolves to ≤ Grade 1. If FG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate antihyperglycemic treatment, reduce alpelisib by 1 dose level. Continue with antihyperglycemic treatment and check fasting glucose levels at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FG > 250 mg/dL.
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 antihyperglycemic treatment and titrate as outlined for Grade 2. Monitor fasting glucose levels as clinically indicated and at least twice weekly until FG resolves to ≤ Grade 1. If FG resolves to ≤ 160 mg/dL within 3-5 days, while off alpelisib and on antihyperglycemic treatment, restart alpelisib and reduce 1 dose level, continue with antihyperglycemic treatment. A second and third oral antihyperglycemic agent may be initiated concomitantly, if needed, in consultation with a diabetologist. Check FG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG > 250 mg/dL. If FG does not resolve to ≤ 160 mg/dL within 3-5 days while off alpelisib and while on antihyperglycemic treatment consultation a diabetologist for management of diabetes is strongly recommended. If FG does not resolve to ≤ 160 mg/dL within 21 days after institution of appropriate antihyperglycemic treatment in cooperation with diabetologist and exclusion of confounding factors e.g., urinary tract infection, permanently discontinue participant from alpelisib treatment.
Grade 4 (FG > 500 mg/dL) [> 27.8 mmol/L]	● **Omit alpelisib**, confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Regardless of fasting status, consider IV fluids. ● Exclude confounding factors like e.g., urinary tract infection. ● Consult with diabetologist, initiate or intensify medication with appropriate antihyperglycemic treatment (see Grade 3), re-check within 24 hours. ● If grade improves then follow specific grade recommendations ● If FG is confirmed as > 500 mg/dL and confounding factors could be excluded, permanently discontinue participant from alpelisib.
CTCAE v 4.03 is modified to allow fasting blood glucose values in addition to fasting plasma glucose values.	
Investigations (Hepatic). Note: this is for newly occurred or worsened from baseline	
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.

[redacted]

Worst toxicity - CTCAE grade (value)	**Dose Modifications for alpelisib**
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 - 20.0 x ULN)	● Interrupt dose until recovery to Grade ≤ 1, then decrease dose level.
Grade 4 (> 20.0 x ULN)	● Permanently discontinue.
Combined ALT/AST and TBIL elevation	●
For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x upper limit of normal (ULN) combined with total bilirubin > 2.0 x ULN without evidence of cholestasis For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 3.0 x baseline] or [ALT or AST > 8.0 x ULN], whichever occurs first, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN] Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin.	● Interrupt treatment and adjudicate for DILI: Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTsb, or as clinically indicated, until AST, ALT, or total bilirubin have resolved ≤ ULN or to baseline. (Refer to the Section 6.6.3.1 for additional follow-up evaluations as applicable.) ● If causality assessment indicates that DILI is probable: Permanently discontinue participant from treatment. ● If not DILI: Treat the identified cause according to institutional guidelines. Once resolved, reduce by one dose level.
Gastrointestinal	
Diarrhea is defined as: a disorder characterized by frequent and watery bowel movements.	
Grade 1 (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline)	● Maintain dose level but initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental Activities of Daily Living (ADL))	● Omit dose until resolved to ≤ Grade 1, then restart at same dose. ● If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then decrease 1 dose level ● Initiate or intensify appropriate medical therapy and monitor as clinically indicated.
Grade 3 (Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL)	● Omit dose until resolved to ≤ Grade 1, then decrease dose level. ● Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	● Discontinue participant from treatment. ● Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.

[redacted]

Worst toxicity - CTCAE grade (value)	**Dose Modifications for alpelisib**
Investigations (Pancreatic)	
Pancreatitis	
Grade 2 or Grade 3	● Omit dose until resolved to Grade ≤ 1, then resume treatment at decreased dose level. If toxicity recurs, permanently discontinue participant from alpelisib
Skin and subcutaneous tissue disorders	
Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity (see Section 6.6.3.3). Dermatologist consultation is mandated for serious cutaneous reactions (i.e. fulfilling seriousness criteria for AE Reporting) and for severe cutaneous reactions like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme, DRESS.	
Rash	
Grade 1 (< 10% BSA with active skin toxicity*)	● Maintain dose level. ● Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are triamcinolone, betamethasone for up to 28 days, as long as skin toxicity is active. ● If active rash is not resolved within 28 days of appropriate treatment, add low dose systemic corticosteroid (20-40 mg/d), such as prednisone 10 mg 3 x daily. For participants with symptoms like burning and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating antihistamine such as diphenhydramine once daily at night.
Grade 2 (10-30% BSA with active skin toxicity*)	● Maintain dose level. ● Initiate or intensify topical corticosteroids 3-4 x daily, preferred compounds to use are triamcinolone or betamethasone for up to 28 days, as long as skin toxicity is active. ● Add systemic corticosteroids 20-40 mg/d. If rash improves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued. For participants with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night.
Grade 3 (> 30% BSA with active skin toxicity*)	● **Omit alpelisib** dose until rash/skin toxicity has improved to ≤ Grade 1 or resolved, strongly recommend documentation by photography and performing a skin biopsy. ● Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are triamcinolone or betamethasone for at least 28 days. ● Add systemic corticosteroids 20-40 mg/d. ● If rash improves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued. ● restart alpelisib dose once rash/skin toxicity is fading but no longer active (Grade 1): - at reduced dose in case of first occurrence - If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with alpelisib; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued. For participants with symptoms like burning, stinging and/or pruritus, add a non-sedating antihistamine such as cetirizine once daily during daytime and a sedating antihistamine such as diphenhydramine once daily at night. Antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib
Grade 4 ● (any % BSA associated with extensive superinfection, with IV	● Permanently discontinue participant from alpelisib. ● Consult a dermatologist. ● Treatment may follow guidelines for Grade 3 above with the exception

[redacted]

Worst toxicity - CTCAE grade (value)	**Dose Modifications for alpelisib**
antibiotics indicated; life-threatening consequences)	of rechallenge. ● Additional measures may be taken as per local treatment guidance.
Any grade of Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis/ Erythema Multiforme/ DRESS or other SJS/TEN/EM/DRESS like severe skin reactions	● Permanently discontinue participant from alpelisib. ● Consult a dermatologist. ● Follow local treatment guidelines for SJS/TEN/EM/DRESS.
* “Active” skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered “active” any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.	
Immune system disorders	
Hypersensitivity	
Please see specific instructions in Section 6.6.3.5	
Investigations (Pulmonary disorders)	
Pneumonitis	
Please see specific instructions in Section 6.6.3.2.	
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation (see Section 6.6.3.4)	
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 decrease dose level. Note: In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase) as specified in Section 6.6.3.4.
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 decrease dose level.
Grade 4	● Permanently discontinue participant from alpelisib. ● Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice).

6.6.1.2 Fulvestrant dose modification

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

[redacted]

6.6.2 Dose titration guideline for antihyperglycemic agents

6.6.2.1 Dose titration guideline for metformin XR

The starting dose of metformin XR is 500 mg orally once daily with dinner.

Titrate to MTD over a period of 3 weeks as described in Table 6-4.

Table 6-4 Metformin XR Titration Recommendations

Metformin XR Titration	Remarks
500 mg once daily with dinner	If no gastrointestinal intolerance after several days, increase to next level
1000 mg once daily with dinner	If tolerated, increase to next level
1500 mg once daily with dinner	If tolerated, increase to next level
2000 mg once daily with dinner	If not tolerated, reduce to prior tolerated dose.

If additional antihyperglycemic agents are required prior to Cycle 3 Day 8 to achieve adequate control of fasting blood glucose levels, it is recommended that participants randomized to the metformin XR arm avoid the use of SGLT2i, as this may impact the primary endpoint assessment. However, beyond Cycle 3 Day 8, SGLT2i are acceptable.

For additional information on metformin XR dosing and management of related AEs refer to the local Prescribing Information.

6.6.2.2 Dose titration guideline for dapagliflozin + metformin XR

The starting dose of dapagliflozin + metformin XR is 5 mg dapagliflozin + 500 mg metformin XR orally once daily. If tolerated after several days, increase to dapagliflozin 5 mg +1000 mg metformin XR once daily in the morning with food. If tolerated, increase to dapagliflozin 10 mg +1000 mg metformin XR once daily in the morning with food. If tolerated, increase to the maximum daily dose of dapagliflozin 10 mg + 2000 mg metformin XR once daily in the morning with food. If not tolerated, reduce to prior tolerated dose.Titrate to the MTD over a period of 3 weeks as described in Table 6-5.

[redacted]

Table 6-5 Dapagliflozin + Metformin XR Titration Recommendations

Dapagliflozin + Metformin XR Titration	Remarks
5 mg dapagliflozin + 500 mg metformin XR once daily with breakfast	If tolerated after several days, increase to next level
5 mg dapagliflozin + 1000 mg metformin XR once daily with breakfast	If tolerated, increase to next level
10 mg dapagliflozin + 1000 mg metformin XR once daily with breakfast	If tolerated, increase to next level
10 mg dapagliflozin + 2000 mg metformin XR once daily with breakfast	If not tolerated, reduce to prior tolerated dose

In case of intolerance to either the dapagliflozin or metformin XR component of treatment, it is acceptable to continue monotherapy with dapagliflozin or metformin XR, as tolerated.

The risk of diabetic ketoacidosis (DKA) must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Participants should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment with dapagliflozin should be discontinued immediately.

The most common adverse reactions associated with dapagliflozin + metformin XR (5% or greater incidence) were female genital mycotic infection, nasopharyngitis, urinary tract infection, diarrhea, and headache.

Adverse reactions reported in > 5% of patients treated with metformin XR and more commonly than in patients treated with placebo are: diarrhea and nausea/vomiting.

A higher incidence of adverse reactions related to reduced intravascular volume and renal function has been observed in the specific population of patients with renal impairment receiving dapagliflozin + metformin XR. Therefore, in this study, those with moderate to severe renal impairment are not eligible for study participation. During course of the study, chemistry panels including creatinine will be obtained at regular interval, as per Table 8-2. At the discretion of the investigator, further clinical evaluation may be needed for participants with observed increases in serum creatinine, which may be indicative of renal impairment.

For additional information on dapagliflozin + metformin XR and management of related AEs refer to the local Prescribing Information.

6.6.3 Follow-up for toxicities

All participants must be followed up for safety (adverse events and serious adverse events) for 30 days following the last dose of study treatment.

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.

[redacted]

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

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x upper limit of normal (ULN) combined with total bilirubin > 2.0 x ULN without evidence of cholestasis
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 3.0 x baseline] or [ALT or AST > 8.0 x ULN], whichever occurs first, combined with [total bilirubin > 2.0 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 review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/INR, alkaline phosphatase (ALP), albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

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 cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-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. For children, there are caveats to calculating the R-ratio as normal levels of ALP are higher than in adults with standard ranges varying by developmental age. 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. Table 6-6 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed liver function test (LFT) abnormalities.

[redacted]

Table 6-6 Alternative causes of liver disease

Disease	Assessment
Hepatitis A, B, C, E	● IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	● IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	● Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	● Ethanol history, GGT, MCV, carbohydrate-deficient (CD)-transferrin
Nonalcoholic steatohepatitis	● Ultrasound or MRI
Hypoxic/ischemic hepatopathy	● Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	● Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if < 40 yrs old)	● Caeruloplasmin
Hemochromatosis	● Ferritin, transferrin
Alpha-1-antitrypsin deficiency	● Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, Thyroid-stimulating hormone; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; glycogenic hepatitis).

If DILI confirmed: permanently discontinue study treatment.

If DILI is 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.

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

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6.3.2 Management of Pneumonitis/Interstitial lung disease

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

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

Participants who are suspected to have developed pneumonitis should interrupt alpelisib immediately (but may continue fulvestrant if clinically indicated) and undergo appropriate imaging (high resolution computerized tomography (CT) scan) and broncho-alveolar lavage;

[redacted]

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.

6.6.3.3 Guidelines for the treatment of study drug induced skin toxicity

Skin toxicity is a class-effect adverse event observed with PI3Ki agents.

Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as 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. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity at any Grade, and mandated if severe cutaneous reaction like Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected.

Workup for skin toxicities 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.

Skin photographs must be taken and skin biopsy must be performed in case of grade 4 skin toxicity and any grade of suspected severe cutaneous reactions and stored at site as source document. In case of Grade 3 skin toxicity, Novartis strongly recommends that photographs are taken and a skin biopsy is performed and stored at site as source documentation. Skin biopsy will be sent to a Novartis designated laboratory, together with dermatologist and pathologist reports, if available, for further research purpose on the pathology and mechanism of PI3K inhibitor treatment induced skin toxicity.

In Study CBYL719C2301 (SOLAR-1), among the 86 alpelisib-treated patients who received prophylaxis prior to rash onset, 73% did not develop a rash, while among the 198 alpelisib-treated patients who did not receive prophylaxis, 36% did not develop a rash. Similar trends were observed in the BYLieve study, where 70% of patients who received prophylaxis (n=10) did not develop a rash compared with 53% of patients who did not receive prophylaxis (n=117) did not develop a rash (Patel et al 2020). Additionally, in a single center retrospective analysis of 102 patients receiving alpelisib, prophylaxis with non-sedating antihistamines (n=43) was correlated with a reduction in Grade 1/2 rash events (OR 0.39, p=0.09) (Wang et al 2020). Based on these data, prophylactic treatment with non-sedating antihistamines (e.g., cetirizine (Zyrtec©), fexofenadine (Allegra), loratadine (Claritin) can be started on Cycle 1 Day 1 and continued for approximately 8 weeks in all participants, especially in those with a history of

[redacted]

atopy such as allergic rhinitis, asthma, atopic dermatitis, or drug allergies, at the discretion of the Investigator. Preventive strategies, including the administration of non-sedating, oral antihistamines prior to rash onset and before starting alpelisib, may decrease incidence and severity of rash based on alpelisib clinical trial experience.

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 300mg 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 is reported, it is recommended that participants with dry skin use mild and fragrance free soaps and detergents.

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

6.6.3.4 Follow-up on amylase or lipase elevation (CTCAE Grade 3 or superior)

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

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

Participants who discontinue 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 v4.03 Grade change over 4 weeks).

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

[redacted]

See also dose modification guidelines described in Table 6-3.

6.6.3.5 Guidelines for hypersensitivity

Alpelisib, fulvestrant, dapagliflozin + metformin XR, and metformin XR alone are associated with hypersensitivity reactions, which may include anaphylaxis. These are manifested by symptoms including, but not limited to dyspnea, flushing, rash, fever or tachycardia. In participants with serious hypersensitivity reactions, the specific study treatment responsible for the reaction should be permanently discontinued and should not be re-introduced. Appropriate treatment should be promptly initiated.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the Investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log (DAL).

6.7.2 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, insulin and/or amylase/lipase and/or c-peptide and/or lipid profile samples as described in Table 8-2 and Table 8-8 the following additional guidelines should be followed:

The patient must be fasting overnight for 8-12 hours prior to the blood collection, but can freely drink water. After this blood sample, the patient should have a light breakfast. Alpelisib must be taken within 1 hour after the meal in the clinic.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-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.

[redacted]

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

Novartis will provide to Investigators in a separate document a proposed informed consent form that complies with the international council for harmonization of technical requirements for pharmaceuticals for human use (ICH) E6 good clinical practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the [Alpelisib (BYL719) Investigator's Brochure (IB)] and/or prescribing information for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of alpelisib 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 pre-screening 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:

- Female Partner Consent Form
- Pregnancy Outcomes Reporting Consent for female participants
- Pregnancy Outcomes Reporting Consent for the female partners of any male participants who took study treatment

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.

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

8 Visit schedule and assessments

The Assessment Schedule Table 8-2 lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Treatment cycles are intended to be 4 weeks (28 days), but the treatment can be delayed in order to manage toxicities according to the alpelisib dose modification criteria in Section 6.6.1.1 and

[redacted]

the locally approved label and local practice for fulvestrant, dapagliflozin + metformin XR, and metformin XR.

Participants should be seen for all visits/assessments as outlined in the assessment schedule Table 8-2 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to return for 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 eCRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Additional visits may be needed based on the Investigator's discretion and are permitted at any time throughout the study.

At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications should be up to date on the eCRF.

As per Section 4.6, 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 allowed by 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.

During the course of the study visits, test procedures should occur on schedule whenever possible as per allowable visit windows specified in Table 8-1 below:

Table 8-1 Allowable visit windows

Visit name	Window
Screening	-28 to -1 or -14 to -1 days as detailed in Table 8-2
Fulvestrant injection	Cycle 1 Day 1 and Cycle 1 Day 15 (if applicable) and on Day 1 ± 3 days of every subsequent cycle
Tumor assessments	+/- 7 days
All other assessments during the treatment period	+/- 3 days
Safety follow-up	+/- 3 days
Efficacy follow-up	+/- 7 days
End of Treatment (EOT)	≤ 14 days after permanent discontinuation of study treatments

[redacted]

Table 8-2 Assessment Schedule

Period	**Pre-screening**	**Screening**		**Cycle 1**				**Cycle 2**				**Cycle 3**		**Cycle 4 to 12**	**EOT**	**Post-Treatment follow-up**	
Visit Name	**Molecular Pre-screening**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D 1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C4D1 to C12D1**	**EOT**	**Safety follow-up**	**Efficacy follow-up (if applicable)**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**1**	**14 days after last dose**	**30 days after last dose**	**see section 8.3**
Molecular pre-screening informed consent	X																
Tumor tissue: New/recent biopsy or archival tumor block/slides or tumor tissue PIK3CA mutation status available [1]	X																
[redacted]																	
IRT Registration (after Molecular pre-screening ICF)		S															
Informed consent		X															
Eligibility checklist (within IRT)				S													
Randomization				X													
Demography		X															
Inclusion/Exclusion criteria		X															

[redacted]

Period	**Pre-screening**	**Screening**		**Cycle 1**				**Cycle 2**				**Cycle 3**		**Cycle 4 to 12**	**EOT**	**Post-Treatment follow-up**	
Visit Name	**Molecular Pre-screening**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D 1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C4D1 to C12D1**	**EOT**	**Safety follow-up**	**Efficacy follow-up (if applicable)**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**1**	**14 days after last dose**	**30 days after last dose**	**see section 8.3**
Medical history/current medical conditions		X															
Diagnosis and Extent of Cancer		X															
ER/PgR status		X															
HER2 status		X															
Prior antineoplastic therapies		X															
Prior or concomitant non-drug therapies/procedures		X		Continuous up to 30 days after last dose of study treatment													
Prior/concomitant medications		X		Continuous up to 30 days after last dose of study treatment													
Performance status (ECOG)			X					X				X		X	X		
Body Height			X														
Body Weight			X					X				X		C4D1 then as clinically indicated	X		
Abdominal Girth			X									X			X		

[redacted]

Period	**Pre-screening**	**Screening**		**Cycle 1**				**Cycle 2**				**Cycle 3**		**Cycle 4 to 12**	**EOT**	**Post-Treatment follow-up**	
Visit Name	**Molecular Pre-screening**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D 1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C4D1 to C12D1**	**EOT**	**Safety follow-up**	**Efficacy follow-up (if applicable)**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**1**	**14 days after last dose**	**30 days after last dose**	**see section 8.3**
Physical Examination			S		S	S		S		S		S		S	S		
Vital Signs			X	X		X		X		X		X		X	X		
Hematology			X			X		X		X		X		X	X		
Fasting Chemistry (Full)			X					X				X		X	X		
Fasting Chemistry (Partial)[2]						X				X							
Fasting Plasma Glucose[3]			X	X	X	X	X	X	X	X	X	X	X	X	X		
Ketones			X	X		X		X		X		X		X	X		
HbA1c			X					X				X		C5D1 + C8D1 + C11D1	X		
Fasting Insulin level			X	X	X	X	X	X	X	X	X	X	X	X	X		
Fasting Lipid Panel			X												X		
Coagulation			X	As clinically indicated											X		
Fasting Lipase, Fasting Amylase			X					X				X		X	X		
Urinalysis (Macroscopic)[5]			X	As clinically indicated											X		
Tumor Assessment		X		Every 8 weeks until disease progression, death, loss to follow-up, withdrawal of consent/oppose the use of their data											X		Every 8 weeks until disease

[redacted]

Period	**Pre-screening**	**Screening**		**Cycle 1**				**Cycle 2**				**Cycle 3**		**Cycle 4 to 12**	**EOT**	**Post-Treatment follow-up**	
Visit Name	**Molecular Pre-screening**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D 1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C4D1 to C12D1**	**EOT**	**Safety follow-up**	**Efficacy follow-up (if applicable)**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**1**	**14 days after last dose**	**30 days after last dose**	**see section 8.3**
																	progression, death, loss to follow-up, withdrawal of consent/oppose to use their data
Whole body bone scan		Within 42 days prior to randomization (X)		As clinically indicated													
Electrocardiogram (ECG)			X	X[6]		X		X				X		X	X		
Cardiac Imaging (MUGA or ECHO)		X												C5D1 and C9D1	X		
Skin photography and skin biopsies of toxicity sites				Strongly recommended for Grade 3 skin toxicity and mandatory for Grade 4 skin toxicity and suspected severe cutaneous reactions													
Adverse Events[3]				Continuous up to 30 days after last dose of study treatment													
Alpelisib					Daily starting at C1D8												
Fulvestrant				X		X[4]		X				X		X			

[redacted]

Period	**Pre-screening**	**Screening**		**Cycle 1**				**Cycle 2**				**Cycle 3**		**Cycle 4 to 12**	**EOT**	**Post-Treatment follow-up**	
Visit Name	**Molecular Pre-screening**	**Screening**		**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D 1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C4D1 to C12D1**	**EOT**	**Safety follow-up**	**Efficacy follow-up (if applicable)**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**1**	**14 days after last dose**	**30 days after last dose**	**see section 8.3**
Metformin XR or Dapagliflozin + Metformin XR				Once daily starting at C1D1													
Disposition		X													X[7]		X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Local confirmation of the PIK3CA mutation status is acceptable, provided that the tumor PIK3CA mutation assessment (tissue or plasma) was or will be performed by a local laboratory using either a FDA-approved PIK3CA Companion Diagnostics (CDx) test for alpelisib or the CE-IVD QIAGEN therascreen PIK3CA RGQ PCR test
[2] Creatinine, Creatine Kinase, ALT, AST, Total Bilirubin
[3] Participants who discontinue alpelisib and fulvestrant (EOT) prior to C3D8 will continue to have FPG monitored and hyperglycemia-related AE collected for a maximum of 9 weeks (+/- 3 days) depending on the time point of study treatment discontinuation (see Section 6.1.5 & Section 9.1.1) Fulvestrant injection at C1D15 is not applicable for participants already being treated with fulvestrant prior to joining the trial.
[5] Macroscopic Panel Dipstick: Leukocytes, Blood, Protein and Glucose
[6] If the ECG assessment is performed more than 7 days before the C1D1 visit, the assessment must be repeated at the C1D1 visit prior to the first dose of study treatment.
[7] Completed upon end of study treatment or when a participant exits the study for any reason

[redacted]

8.1 Screening

Molecular pre-screening

All participants must sign the molecular pre-screening informed consent form for the testing of PIK3CA mutation status or for sharing the PIK3CA mutational status based on local test results with Novartis**.**

The molecular pre-screening informed consent form only addresses consent for the collection of tumor sample for molecular testing or sharing molecular test results, if PIK3CA mutational status was already assessed (based on the FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN therascreen® PIK3CA RGQ PCR test) and is known.

The molecular pre-screening informed consent does not include consent to start screening activities or undergo any other study-specific procedures aside from molecular pre-screening. This consent form is intended to facilitate molecular mutation testing, and to allow the Investigator to submit the required samples for testing, based on when it is most clinically appropriate at his/her discretion. To start screening activities, all participants must sign the main study informed consent.

Molecular pre-screening and main screening are recommended to occur sequentially; it is at the discretion of the site to perform these in parallel.

The steps required for participant enrollment are as follows:

1. PIK3CA mutational status confirmation (central or local) upon participant signature of the molecular pre-screening ICF:

A)* A tumor tissue sample (newly obtained or archival) must be collected and sent for central assessment of the PIK3CA mutation status to the Novartis designated laboratory located in the US at Navigate BioPharma Services, Inc. (a Novartis subsidiary) located at 1890 Rutherford Road, Carlsbad, CA 92008. Remaining tumor samples from participants who will not be randomized into the study due to screen failure will be returned to the site.

OR

B)A tumor or plasma sample has to be provided to a local laboratory using a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN therascreen® PIK3CA RGQ PCR test.

*If more than one archival sample is available, tumor sample from the most recent archival biopsy is preferred.

Please refer to the laboratory manual for tumor sample shipping requirements. Assessments can be performed during the screening however it is recommended to provide the tumor sample early in the screening process (preferably at least 14 to 28 days prior to randomization) to allow adequate time for processing.

Note: If a tumor PIK3CA mutation status is available, and was assessed by a local laboratory using either a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN therascreen® PIK3CA RGQ PCR test, this mutation status can be used for enrolment into this study.

[redacted]

PIK3CA mutation results generated by laboratory-developed tests, including research use only version of the QIAGEN test, are not acceptable.

2. The participant will be assigned a participant number by the Investigator (see Section 6.4.1) and be registered into the IRT system.

3. PIK3CA mutation status and demographic information will be collected in the eCRF (see Section 8.2).

4. The Novartis designated laboratory will provide the PIK3CA mutation results to the investigational site.

Screening

All study participants must be thoroughly informed about all aspects of the study, including the study treatment, visit schedule, required evaluations, and all regulatory requirements for informed consent. Written informed consent must be obtained before any study specific assessments are performed, including screening. If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion.

All screening assessments must be performed within 1 to 28 days prior to randomization or within 1 to 14 days prior to randomization for selected assessments (see Table 8-2 for the list of assessments to be performed) to confirm patient's eligibility.

Any screening assessment that is done outside the screening window, as defined in Table 8-2, must be repeated prior to randomization.

A new ICF will need to be signed if the Investigator chooses to re-screen the participant after a participant has screen failed. In case of re-screening, a new participant ID will be generated, however, site has to provide original participant ID in respective re-screening eCRF to link the two participants for reporting and validation.

All required screening activities must be performed when the participant is re-screened for participation in the study to satisfy the requirements defined in Table 8-2. An individual participant may only be re-screened once for the study. Once the number of participants screened and enrolled/randomized is likely to ensure target enrollment, Novartis may close the study to further screening. In this case, the participants who screen failed will not be permitted to re-screen.

A participant who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the Investigator believes the retest result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within 14 days of screening period, as defined in Table 8-2. In this case, the participant will not be required to sign another ICF, and the original participant ID number assigned by the Investigator will be used. In the event that the laboratory test(s) cannot be performed within 14 days of screening period, as defined in Table 8-2 or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screen failure. Unused tumor samples for screen failure participants will be returned, unless otherwise directed. In case re-screening occurs, all evaluations re-assessed should meet the eligibility criteria.

[redacted]

Any imaging assessments already completed during the regular work-up of the participant and within 28 days prior to randomization (42 days prior to randomization for whole body scan), including before signing the main study ICF can be considered as the baseline images for this study.

8.1.1 Eligibility screening

Following IRT registration at molecular pre-screening and screening, participants' eligibility will be checked according to study inclusion and exclusion criteria as described in Section 5 once all screening procedures are completed.

A list of procedures to be performed during the 28-day screening period is summarized in Table 8-2.

Results of all screening/baseline evaluations must be reviewed by the Investigator or his/her designee prior to start study treatment of each participant to ensure that all inclusion and exclusion criteria have been satisfied. When all screening procedures are completed and the participant's eligibility is confirmed (i.e. all inclusion/exclusion criteria have been verified), the key eligibility criteria checklist embedded in the IRT system will be completed prior to the first dose of study drug. Please refer to Section 6.4.2 and as well as comply with detailed guidelines in the IRT user guide.

8.1.2 Information to be collected on screening failures

Participants who signed an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. This can be either after the signature of the molecular pre-screening ICF or after the signature of the main study ICF.

The screening phase discontinuation status should be recorded on the appropriate eCRF. Demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered as early terminators. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

[redacted]

The following participant demographics and baseline characteristics are to be collected on all enrolled/randomized participants:

- Demographic information age, sex, race/predominant ethnicity (if permitted). Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we need to assess the diversity of the study population as required by Health Authorities.
- Medical history (e.g., important medical, surgical, and allergic conditions from the participant's medical history which could have an impact on the participant's evaluation)/current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade. Where possible, the diagnosis and not symptoms should be recorded.
- Disease baseline characteristics including diagnosis, history, extent of cancer with ER, PgR and HER2 status, staging of cancer, 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
- Prior/concomitant therapy: all prescription medications, over-the 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 Prior or Concomitant non-drug therapies/procedures eCRF page and updated on a continual basis if there are any new changes to the medications. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

Furthermore, the following assessments will be performed to assess the eligibility of the participant:

- Body height, body weight and abdominal girth
- Vital signs including blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature
- ECOG Performance Status
- 12-Lead ECG
- Cardiac imaging (MUGA or ECHO)
- Tumor evaluation (e.g., CT Scan)
- Whole body bone scan
- Laboratory evaluations (e.g., hematology, coagulation, biochemistry, fasting insulin level, fasting glucose/serum lipid profile/HbA1c/lipase/amylase, ketones, urinalysis)
- The presence of a PIK3CA mutation(s) in the tumor (tissue or plasma)
- Complete physical examination

[redacted]

8.3 Efficacy

8.3.1 Efficacy assessment 1

Efficacy assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.2 (Section 16.4) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 8-3.

Imaging data for all participants will be assessed locally and the results of the local evaluations will be used to support the secondary objective.

The local Investigator's assessment will be used for treatment decision making.

If needed imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. Central review of the imaging data may be performed if deemed necessary.

Information regarding prior interventions (e.g., radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO via the Baseline Clinical Form along with the baseline images. Sites will ensure the data entered on the form is consistent with the data entered in the clinical database.

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 baseline/screening and on-study interventions should be captured in the appropriate eCRFs.

All known lesions (measurable, non-measurable) should be accounted for at screening within 28 days (42 days for whole body bone scan) before Cycle 1 Day 1 when assessing objective tumor status. Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) after randomization. The 8-week interval should be respected regardless of whether study treatment is temporarily withheld or unscheduled assessments are performed. Assessment modality must remain the same throughout the study (e.g., contrast CT or MRI scan) using RECIST 1.1 criteria.

Table 8-3 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated, every 8 weeks (+/- 7 days) until disease progression, EOT[1], death, withdrawal of consent/opposition to use data/biological samples, or lost to follow-up
Brain CT or MRI	Mandated at screening only if existing or suspected brain metastasis	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole body bone scan	Mandated, within 42 days (6 weeks) prior to randomization	If clinically indicated

[redacted]

Procedure	Screening/Baseline	During Treatment/Follow-up
Localized bone CT, MRI, or x-ray	Mandated for skeletal abnormalities identified on the whole body bone scan 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)	Mandated if any skin lesions present at screening	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)	Mandated if suspected lesion at screening	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

[1] Tumor evaluation at End of treatment (EOT) is required for participants who discontinue study treatment before the first scheduled post-baseline tumor assessment (week 8) and for participants whose previous tumor assessment did not demonstrate progressive disease (PD) and was done more than 21 days prior to EOT visit

Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1).

The whole body bone scan can be performed within 42 days prior to start of study treatment.

Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images. The following assessments are required at screening/baseline:

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

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

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

If clinically indicated, a whole body bone scan should be performed per institutional standard of care (e.g., Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET), or sodium fluoride PET). Localized CT, MRI, or X-rays should be

[redacted]

acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen, and pelvis CT/MRI.

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

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

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

Each lesion that is measured at baseline must be measured by the same method (either same radiologic/nuclear method or by physical exam) throughout the 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.

Post baseline imaging assessments

Imaging assessments as described in Table 8-3 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-2). Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) until disease progression, death, lost to follow-up or withdrawal of consent/opposition to use data/biological samples. Imaging assessments should be scheduled using the randomization date as the reference date (not the date of the previous tumor assessment), and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

All participants who discontinue from study treatment due to disease progression must have their progression clearly documented according to RECIST 1.1 as assessed by Investigator. If a participant did not discontinue study treatment due to disease progression per RECIST 1.1 assessed by Investigator, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, then tumor assessments should continue to be performed according to the planned schedule during efficacy follow-up for 12 cycles after randomization or until disease progression (per Investigator), death, lost to follow-up or withdrawn consent/opposition to use data/biological samples.

An additional tumor assessment must be performed to confirm response (complete response (CR) or partial response (PR)) no less than 4 weeks after the criteria for response are first met.

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

[redacted]

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the 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 PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (see Section 16.4).

If participants start on a new antineoplastic therapy before documented progression, every effort should be made to continue to collect tumor assessment according to the planned schedule. In instances where alpelisib is discontinued and fulvestrant is continued, participants can remain on study and will continue to be followed according to the study schedule.

8.3.2 Appropriateness of efficacy assessments

The measurements are standard based on the new response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) (Eisenhauer et al 2009).

8.4 Safety

Safety assessments and their timepoints are specified in the Table 8-4 below.

For details on AE collection and reporting, refer to AE section.

As per Section 4.6, 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, regular phone or virtual calls can occur (as per visit frequency describe in Table 8-2) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-4 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination will be completed at screening, C2D1 and EOT A short physical exam will be performed at all visits as indicated in Table 8-2 during treatment except where a complete physical examination is required. It will include at least the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). If indicated based on symptoms, additional exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event (see Section 10).
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

[redacted]

Assessment	Specification
Height, weight, and abdominal girth	Height in centimeters (cm), body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes), and abdominal girth in centimeters (cm) (at the midpoint of the line between the rib or costal margin and the iliac crest in the midaxillary line) will be measured as specified in Table 8-2.

The performance status will be assessed according to the ECOG performance status scale as describe in Table 8-5 following the schedule given in Table 8-2.

Table 8-5 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

8.4.1 Laboratory evaluations

Clinical laboratory analyses are to be performed by the central laboratory.

Safety samples that can be collected remotely will be collected and analyzed in line with the study laboratory manual. Where samples are collected and analyzed at a local laboratory instead of the central laboratory, Novartis will ensure the results reported are equivalent to central laboratory collection and analysis.

In case of urgent safety management of hyperglycemia, fasting plasma glucose assessment can be done locally according to the schedule of assessments and collection plan outlined respectively in Table 8-2 and Table 8-6.

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). 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.

As per Section 4.6, 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, if participants cannot visit the site for protocol specified safety laboratory assessments, an alternative laboratory (local) collection site may be used.

[redacted]

The results of the local laboratory 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 laboratory results document an adverse event not reported by the central lab, or
- Local laboratory results document an adverse event severity that is worse than the one reported by the central lab, or
- There are no concomitant central results available

For assessment of participants' eligibility for the study, only laboratory results from the central laboratory will be used with the exception of the following where local laboratory results are acceptable:

- **Postmenopausal status (FSH and estradiol) if applicable and**
- **PIK3CA mutational status (if done locally using FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN therascreen PIK3CA RGQ PCR test)**

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 in the eCRF. Additional analyses are left to the discretion of the Investigator. Visit window of +/-3 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 participant 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 participants in the study and evaluating any abnormalities for clinical significance.

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the central Laboratory Manual.

Table 8-6 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Erythrocytes, Leukocytes, , Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, (absolute value preferred, %s are acceptable)
Fasting Chemistry	Albumin, Alkaline phosphatase, ALT , AST , GGT, Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphate, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Plasma Glucose
Fasting chemistry (partial)	Creatinine, Creatine Kinase, ALT, AST, Total Bilirubin
Fasting lipid panel	Total Cholesterol, low-density lipoprotein (LDL) Cholesterol, high-density lipoprotein (HDL) Cholesterol, Triglycerides
Urinalysis	Macroscopic Panel (Dipstick) (Blood, Glucose, Leukocytes, Protein)

[redacted]

Test Category	Test Name
Coagulation	INR, Activated partial thromboplastin time (APTT)
Additional tests	HbA1c, Fasting Insulin Level, Serum Ketones

Participants who discontinue alpelisib and fulvestrant (EOT) prior to Cycle 3, Day 8 will continue to have FPG monitored and hyperglycemia-related AE collected for a maximum of 9 weeks (+/- 3 days) depending on the time point of study treatment discontinuation (e.g., discontinuation after 1 weeks of treatment would require FPG monitoring for another 8 weeks; discontinuation after 2 weeks would require FPG monitoring for 7 weeks etc.).

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit (refer to flow diagram below).

Figure 8-1 Timing of study procedures

The QTcF must be used for clinical decisions, e.g., at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility. The Investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

Single local 12 lead ECGs are collected as detailed in Table 8-7.

Table 8-7 Local ECG collection plan

Cycle/Visit	Day	Time	Number of ECG Type Replicates
Screening	-14 to -1	Anytime	12 Lead, Single
1 to 12*	1	Pre-dose	12 Lead, Single
1	15	Pre-dose	12 Lead, Single
EOT	NA	Anytime	12 Lead, Single
Unscheduled (as clinically indicated or as deemed appropriate by the Investigator e.g., if the participant takes drugs that prolong the QT interval and/or induce Torsades de Pointes)		Anytime	12 Lead, Single

* If the screening ECG assessment is performed more than 7 days before the Cycle 1 Day1 visit, the assessment must be repeated at the Cycle 1 Day 1 visit prior to the first dose of study treatment.

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate eCRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the

[redacted]

study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECGs on non-heat-sensitive paper and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

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

The left ventricular heart function will be evaluated by cardiac imaging (ECHO or MUGA) at Screening to confirm eligibility, at Cycle 5 Day 1, Cycle 9 Day 1 and at EOT.

Additional cardiac imaging during treatment is to be performed if indicated by clinical signs or symptoms. The same imaging modality should be used.

8.4.3 Pregnancy and assessments of fertility

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.

Male participants must use a condom during intercourse while taking study treatment, and for at least 1 week after stopping alpelisib and 1 year after stopping fulvestrant. In addition, male participants should not donate sperm for the time period specified above.

Female participants must be postmenopausal as per inclusion criteria 11 in order to be eligible for the study.

If a female participant or the female partner of a male participant becomes pregnant while in the trial, please refer to Section 10.1.4 for reporting.

Assessments of fertility

Medical documentation of 12 or more months of natural (spontaneous) amenorrhea with an appropriate clinical profile AND/OR prior surgical bilateral oophorectomy must be retained as source documents to confirm post-menopausal status.

In case of 12 or more months natural amenorrhea FSH and estradiol will be done locally at screening to confirm the woman is postmenopausal.

In case of therapy-induced amenorrhea serial measurements of FSH and/or estradiol will be done locally at screening to confirm the woman is postmenopausal.

Note: unilateral oophorectomy, hysterectomy, or tubal ligation do not induce postmenopausal status and therefore cannot serve to meet inclusion criteria 11.

[redacted]

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population and known safety profile of the study treatment.

8.5 Additional assessments

8.5.1 Biomarkers

A tumor tissue sample must be provided for all participants for the analysis of the PIK3CA mutational status, except if a PIK3CA mutation status has been assessed by a local laboratory using either a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN therascreen PIK3CA RGQ PCR test. It is recommended to provide a tumor sample collected after the most recent progression or recurrence, in order to ensure that the submitted sample is representative of the molecular status of the tumor at study entry. A newly obtained tumor biopsy is preferred, if feasible. If not feasible, a recent archival tumor sample can be provided. Blocks are preferred but if not possible, 5 to 13 slides (5 slides minimum from a surgical specimen, 13 slides minimum from a biopsy) are requested. It is recommended to involve the site pathologist in the selection of a high quality tumor sample (following the Guide for Local Pathologist) in order to minimize the risk of sample rejection. A pathology report and a requisition form should also be provided.

As an enrollment criterion, PIK3CA mutational status will be assessed through analysis of hotspots located in the C2, namely: C420R on exon 7; E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R on exon 9; and H1047L, H1047R, H1047Y on exon 20; which are all critical for PI3K function. These hotspots, known to increase PI3K function, are anticipated to cover the majority of all the PIK3CA mutations identified in breast cancer patients based on data from publicly available databases such as The Cancer Genome Atlas (Koboldt et al 2012).

The presence of a PIK3CA mutation is required prior to randomization (please refer to Section 8.1 for details). If a PIK3CA mutation status is available, and was assessed by a local laboratory using either a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN therascreen® PIK3CA RGQ PCR test, confirmation of its status via a Novartis designated laboratory is not required prior to randomization. PIK3CA mutation results generated by research use only version of the Qiagen test, or other laboratory-developed tests, are not acceptable. In this case, participants must submit tumor samples for assessment of PIK3CA mutation status by a Novartis designated central laboratory.

[redacted]

[redacted]

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g. inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of Novartis. Additional markers or methods may be utilized if indicated by new findings from the literature as well as from Novartis internal data.

Instructions for collection, preparation and shipment of all biomarker samples can be found in the central laboratory manual. Required sample collection information must be entered on the appropriate eCRF pages and central laboratory requisition forms.

Table 8-8 Biomarker sample collection plan

	Sample Type	Volume	Visit
Tumor samples			
Mandatory[1]	Either an archival tumor block or a fresh formalin-fixed tumor biopsy block or a minimum 5-13 slides	1 block or 5 slides minimum from a surgical specimen, 13 slides minimum from a core needle biopsy	Pre-screening or screening
[redacted]			
Skin samples			
Mandatory	Skin biopsy for central assessment	N/A	Anytime at the appearance of Grade 4 skin toxicity and suspected severe cutaneous reactions
Strongly recommended	Skin biopsy for central assessment	N/A	Anytime at the appearance of Grade 3 skin toxicity

1 Mandatory to provide an archival tumor block or a fresh formalin-fixed tumor biopsy block if PIK3CA mutation status is not available i.e. was not assessed by a local laboratory using either a FDA-approved PIK3CA CDx text for alpelisib or the CE-IVD QIAGEN therascreen PIK3CA RGQ PCR test.

Assessments in skin

A skin biopsy and photographic images is strongly recommended from all participants at the appearance of Grade 3 and mandatory at the appearance of Grade 4 skin toxicity or any Grade of suspected severe cutaneous reactions. Skin biopsy at Grade 3, 4 or suspected severe cutaneous reactions is not needed if in a location which is not able to be biopsied, or at Grade 4 if a biopsy was taken at Grade 3 skin toxicity. Skin biopsies will be used to confirm molecular underpinnings of alpelisib induced skin toxicity.

[redacted]

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the Investigator.

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

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which continued study participation might result in a safety risk to the participant
- Adverse event or laboratory abnormalities requiring permanent discontinuation of study treatment as per Section 6.6.3
- Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the participant’s overall status, prevents the participant from continuing participation in the study
- Progressive disease per RECIST 1.1 as per Investigator's assessment (see Section 8.3).
- Protocol deviation that results in significant risk to participant’s safety
- Study terminated by sponsor

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New/concomitant treatments
- Adverse Events/Serious Adverse Events

The Investigator must also contact the IRT to register the participant’s discontinuation from study treatment (only applicable for medication managed through IRT).

[redacted]

If a participant did not discontinue study treatment due to disease progression per RECIST 1.1 assessed by Investigator, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, then tumor assessments should continue to be performed according to the planned schedule during efficacy follow-up for 12 cycles after randomization or until disease progression (per Investigator), death, lost to follow-up or withdrawn consent/opposition to use data/biological samples.

Participant whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first.

Participants who discontinue alpelisib and fulvestrant (EOT) prior to Cycle 3, Day 8 will continue to have FPG monitored and hyperglycemia-related AE collected for a maximum of 9 weeks (+/- 3 days) depending on the time point of study treatment discontinuation (e.g., discontinuation after 1 weeks' of treatment would require FPG monitoring and hyperglycemia-related AE collection for another 8 weeks; discontinuation after 2 weeks would require FPG monitoring and hyperglycemia-related AE collection for 7 weeks etc.).

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants 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 participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

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

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant'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)

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

[redacted]

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw 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 participant 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 participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study completion and post-study treatment

The duration of treatment with alpelisib and fulvestrant is 12 cycles or until disease progression is radiologically documented according to RECIST 1.1, unacceptable toxicity that precludes further treatment, or discontinuation from study treatment for any other reason, whichever comes first.

All participants who discontinue study treatment, including those who refuse to return for an EOT visit, will be contacted for safety evaluations (i.e., assessment of AEs and/or SAEs, concomitant medications) 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3.

Participants whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory values, must be followed until resolution or stabilization of the event, whichever comes first.

Participants who permanently discontinue alpelisib/placebo for any reason other than disease progression should continue fulvestrant until disease progression, unacceptable toxicity, death or discontinuation from study treatment due to any other reason and continue to be followed for safety as described in Section 8.4.

If participants 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 participant should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.). Continuing care should be provided by the Investigator and/or referring physician based on participant availability for follow-up.

[redacted]

After the 12 cycles treatment period for alpelisib plus fulvestrant, participants who, in the opinion of the Investigator, are benefiting from study treatment may switch to commercially available supply.

The primary analysis will be conducted after all participants have completed at least eight weeks of alpelisib plus fulvestrant treatment (from Cycle 1 Day 8 to Cycle 3 Day 8) or have discontinued prior to completing eight weeks of alpelisib plus fulvestrant treatment without further glucose assessment, whichever is earlier. Following the cut-off date for the primary analysis, the study will remain open. Ongoing participants will continue to receive study treatment and be followed as per the schedule of assessments.

Study completion is defined as when the last participant finishes their safety and efficacy follow-up periods (as applicable) and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

The final analysis will occur at the end of the study. All available data from all participants up to this cut-off date will be analyzed and summarized in a Clinical Study Report (CSR).

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include

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

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment (instructions will be provided to the Investigator for contacting the participant, when the participant should stop taking drug and when the participant should come for a final visit). The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

[redacted]

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

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

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

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

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

1. The Common Terminology Criteria (CTC) AE (Version 4.03). Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, including Grade 5 (AEs leading to deaths)
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been me
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose reduced/increased
   - Drug interrupted/permanently discontinued
6. Its outcome

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.

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

[redacted]

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

In general, adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

For participants who discontinue study treatment before Cycle 3, Day 8 hyperglycemia related adverse events should be collected up to 9 weeks after first dose of study treatment.

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

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, except if the Investigator considers that progression of malignancy is related to study treatment.

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

Information about adverse drug reactions for alpelisib can be found in the [Alpelisib (BYL719) Investigator's Brochure (IB)].

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

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity

[redacted]

- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

When the molecular screening occurs before the main screening assessments, SAEs that occur during the molecular screening period 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).

[redacted]

When the molecular screening and the main screening assessments occur in parallel, SAEs that occur during the screening period will be reported regardless of relationship to study procedure.

SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

For participants who failed the molecular screening or screening, SAEs will be collected until the time the participant is deemed a molecular screening or screen failure.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form (eSAE with paper back up); all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, under no circumstances later than within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification to inform all Investigators involved in any study with the same study treatment 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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

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. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent 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 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

[redacted]

form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. 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.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE (see Table 10-1). Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

For more information on AE and SAE definition and reporting requirements, please see the respective Section 10.1.1 and Section 10.1.2.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Section 16.1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below.

[redacted]

Additional details on actions required in case of liver events are outlined in Table 16-1. Repeat liver chemistry tests (i.e. ALT, AST, TBIL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver even
- Thorough follow-up of the liver event should include
    - These investigations can include based on Investigator's discretion: 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

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.3 Committees

10.3.1 Steering Committee

A Steering Committee will be established comprising Investigators participating in the trial, and Novartis representatives from the CTT.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the Clinical Trial Team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

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

[redacted]

The Investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. Data collected by third parties (such as safety lab, biomarker, IRT) will be sent electronically to Novartis.

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

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

11.2 Database management and quality control

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

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

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture/data entry, the adherence to the protocol and to 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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical

[redacted]

information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

The primary analysis will be conducted after all participants have completed at least eight weeks of alpelisib plus fulvestrant treatment (from Cycle 1 Day 8 to Cycle 3 Day 8) or have discontinued prior to completing eight weeks of alpelisib plus fulvestrant treatment without further glucose assessment, whichever is earlier.

A final, descriptive (non-inferential) analysis will be conducted after all participants who are still receiving study treatment have completed 12 cycles of treatment with alpelisib plus fulvestrant.

It is planned that the data from all centers participating in the study will be combined, so that an adequate number of participants are available for analysis. Novartis and/or a designated CRO will perform all analyses.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Safety Set includes all participants who received at least one dose of study treatment (i.e. at least one dose of any component of alpelisib, fulvestrant, dapagliflozin + metformin XR, metformin XR). Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received. The safety set will be the analysis set for the primary analysis and all safety analyses.

The Full Analysis Set (FAS) is comprised of all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. The FAS will be the population for all efficacy analyses.

[redacted]

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the FAS and Safety Set (if the latter differs from the FAS).

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

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term by treatment group.

12.3 Treatments

The Safety set will be used for the following analyses. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to alpelisib, fulvestrant, dapagliflozin + metformin XR, metformin XR as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

The number of participants with dose adjustments (reductions, titrations, interruption, or permanent discontinuation) and the reasons will be summarized by treatment group and all relevant dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group.

12.4 Analysis supporting primary objectives

The primary objective is to determine whether prophylactic dapagliflozin plus metformin XR compared to prophylactic metformin XR alone reduces the occurrence of severe hyperglycemia events over the first eight weeks of alpelisib plus fulvestrant treatment (from Cycle 1 Day 8 to Cycle 3 Day 8) .

12.4.1 Definition of primary endpoint(s)

The primary endpoint (variable attribute of the primary estimand; refer to Section 2) is occurrence of severe (Grade ≥ 3) hyperglycemia over the first eight weeks of alpelisib plus fulvestrant treatment, defined as any glucose laboratory values > 250 mg/dL (> 13.9 mmol/L) from Cycle 1 Day 8 to Cycle 3 Day 8. Censoring conventions (i.e. handling of missing values/censoring/discontinuations) are provided in Section 12.4.4.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will assess the difference in the percentage of participants with severe hyperglycemia between the two treatment arms with a stratified Cochran-Mantel-Haenszel test at an overall one-sided 5% level of significance.

The following statistical hypotheses will be tested to address the primary objective:

$H_{01}: \theta_1 - \theta_2 \geq 0$ vs. $H_{a1}: \theta_1 - \theta_2 < 0$

where θ_1 is the percentage of participants with at least one occurrence of severe hyperglycemia in the study treatment arm A and θ_2 is the percentage in the study treatment arm B .

The primary endpoint, occurrence of severe hyperglycemia (variable attribute of the primary estimand; refer to Section 2.1), will be analyzed based on the Safety Set according to the treatment participants actually received. The percentage of participants with severe hyperglycemia per treatment arm and the difference in percentages across the two treatment arms will be presented along with two-sided 95% standard Wald asymptotic (i.e. normal approximation) confidence intervals.

12.4.3 Handling of intercurrent events of primary estimand

The primary estimand will account for different intercurrent events as explained in the following:

1. **Discontinuation of alpelisib or not receiving any alpelisib:** occurrence of severe hyperglycemia events collected after discontinuation of alpelisib or without any exposure to alpelisib will be used for the primary analysis (treatment policy strategy)
2. **Discontinuation and/or interruption of prophylactic antihyperglycemic medication:** occurrence of severe hyperglycemia events collected after discontinuation and/or interruption of prophylactic antihyperglycemic medication will be used for the primary analysis (treatment policy strategy)
3. **Dose interruption and/or reduction of alpelisib:** occurrence of severe hyperglycemia events collected after dose interruption and/or reduction of alpelisib will be used for the primary analysis (treatment policy strategy)

12.4.4 Handling of missing values not related to intercurrent event

Missing data will not be imputed. The primary analysis includes all participants in the safety set.

The occurrence of severe hyperglycemia during the first eight weeks of alpelisib plus fulvestrant treatment documented after the initiation of additional antihyperglycemic therapies will be counted for the primary analysis (refer to Section 2.1 for more information on primary estimand).

12.4.5 Sensitivity analyses

Additional sensitivity analyses on the primary estimand may be conducted if appropriate and described in the Statistical Analysis Plan.

[redacted]

12.4.6 Supplementary analysis

As a supplementary analysis, the occurrence of either severe hyperglycemia or the initiation of additional antihyperglycemic therapies during the first eight weeks of alpelisib plus fulvestrant treatment will be considered. The percentage of participants with severe hyperglycemia or additional antihyperglycemic therapies per treatment arm and the difference in percentages across the two treatment arms will be presented along with two-sided 95% standard Wald asymptotic (i.e. normal approximation) confidence intervals.

Additionally, subgroup analyses will be performed on each level of randomization stratification factors. Further supplementary analyses will be provided in the statistical analysis plan (SAP).

12.5 Analysis supporting secondary objectives

The secondary objectives are to compare the two treatment groups with respect to progression-free survival (PFS), and to evaluate the overall response rate (ORR), clinical benefit rate (CBR) and safety. No inferential testing is planned for secondary endpoints.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via Investigator assessment according to RECIST 1.1 (Section 16.4). If a participant has not had an event, PFS will be censored at the date of the last adequate tumor assessment (see RECIST 1.1 in Section 16.4 for further details). Clinical deterioration without objective radiological evidence will not be considered as documented disease progression in the PFS analysis.

PFS will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The PFS rate at 24 and at 48 weeks will be calculated, along with its 95% confidence intervals.

Overall response rate (ORR) with confirmed response is defined as the proportion of participants with best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR), as per local review and according to RECIST 1.1 (see Section 16.4 for details). For this study with imaging assessments performed every 8 weeks (+/- 7 days), BOR for each participant will be 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.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD (Stable Disease) assessment (or better) > 7 weeks after randomization (and not qualifying for CR or PR).
- PD = progression ≤ 17 weeks after randomization (and not qualifying for CR, PR or SD).

ORR with confirmed response will be calculated based on the FAS according to the intent-to-treat (ITT) principle. ORR with confirmed response will be presented by treatment group along with approximate 95% confidence intervals. In addition, ORR with unconfirmed response will

[redacted]

also be calculated and presented by treatment group together with approximate 95% confidence intervals.

Clinical benefit rate (CBR) with confirmed response is defined as the proportion of participants with a best overall response of confirmed CR or PR, or SD lasting for a duration of at least 24 weeks. CR, PR and SD are defined as per local review according to RECIST 1.1 (see Section 16.4 for details).

CBR with confirmed response will be calculated based on the FAS and according to the ITT principle. CBR with confirmed response and its 95% confidence interval will be presented by treatment group. In addition, CBR with unconfirmed response will also be calculated and presented by treatment group together with approximate 95% confidence intervals.

12.5.2 Safety endpoints

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

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

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

1. Pre-treatment period: from day of participant'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 safety period: starting at day 31 after last dose of study medication.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

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

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

A participant with multiple adverse events within a primary system organ class will only be counted once towards the total of the primary system organ class.

[redacted]

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 version 4.03 grades), type of adverse event, relation to study treatment.

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.

The number (and proportion) of participants with AESI will be summarized by treatment. AESI consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). AESI will be defined at the project level and may be regularly updated. The grouping of AEs in AESI according to project standards will be specified in the Case-Retrieval Sheet and/or the SAP.

For each specified AESI, the number and percentage of participants with at least one event part of the AESI will be reported by treatment group.

Vital signs

All vital signs data will be summarized by treatment and visit/time.

12-lead ECG

1. PR, QRS, QT, QTcF, RR intervals, heart rate and overall interpretation will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally.
2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented.

All ECG data will summarized by treatment and visit/time.

Cardiac imaging (MUGA/ECHO)

Shift tables comparing baseline to worst post-baseline cardiac imaging (MUGA or ECHO) overall interpretation will be provided. Percentages will be based on all participants in the Safety set.

Note: If there is any change in the methodology used throughout the study compared to baseline, the post-baseline values for which the methodology differs from baseline will be discarded in the tables presenting comparisons to baseline.

Descriptive statistics of the LVEF at baseline, worst post-baseline value and change from baseline to worst post-baseline value will be provided.

[redacted]

A listing of participants with newly occurring clinically significant abnormality will be produced by treatment group.

Clinical laboratory evaluations

All laboratory data will be summarized by treatment group and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI 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 is not applicable for laboratory data.

For laboratory tests where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

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

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

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

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

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

[redacted]

12.7 Interim analyses

No formal interim analysis is planned for this trial.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary endpoint: occurrence of severe hyperglycemia. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

The incidence of severe hyperglycemia adverse events over the first eight weeks of alpelisib plus fulvestrant treatment in the study treatment arm B (i.e. prophylactic metformin XR alone) is assumed to be 40% based on data from the SOLAR-1 study in HR-positive, HER2-negative, advanced breast cancer patients with a PIK3CA mutation treated with alpelisib plus fulvestrant.

It is expected that treatment with prophylactic dapagliflozin plus metformin XR will result in a 20% reduction in the incidence rate. Approximately 124 participants (62 in each arm) will be required to detect a 20% difference in incidence rate with 80% power using the difference of proportion test at a one-sided 5% level of significance (Table 12-1). Assuming a 5% dropout rate (patients without adequate assessment of glucose laboratory values per protocol from Cycle 1 Day 8 to Cycle 3 Day 8) at the time of primary analysis, approximately 132 participants will need to be randomized to the two treatment arms in a 1:1 fashion.

Table 12-1 Sensitivity of power to changes in assumptions for N=124

Expected reduction in incidence rate	Observed reduction in incidence rate	Power
20%	30%	99.2%
	25%	93.8%
	20%	**79.1%**
	15%	56.1%
	10%	32.0%
	5%	14.2%

Note: Simulations are performed in East 6.4 with number of simulations = 100,000 and randomization seed = 2020.

[redacted]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines.

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

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

[redacted]

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication

14 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

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

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

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant 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.

[redacted]

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 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 > 3x baseline or > 300 U/L (whichever occurs first)

Table 16-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBIL -

ALT	**TBIL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBIL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, total bilirubin (TBIL), INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBIL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
If normal at baseline:	Normal	None	

<table>
<tr><th>ALT</th><th>TBIL</th><th>Liver Symptoms</th><th>Action</th></tr>
<tr><td>ALT > 8 x ULN</td><td></td><td></td><td rowspan="6">• 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.</td></tr>
<tr><td colspan="3">ALT increase with bilirubin increase:</td></tr>
<tr><td>If normal at baseline:
ALT > 3 x ULN</td><td rowspan="2">TBIL > 2 x ULN (or INR > 1.5)
For participants with Gilbert’s syndrome: Doubling of direct bilirubin</td><td rowspan="2">None</td></tr>
<tr><td>If elevated at baseline:
ALT > 2 x baseline
or > 300 U/L (whichever occurs first)</td></tr>
<tr><td>If normal at baseline:
ALT > 3 x ULN</td><td rowspan="2">Normal or elevated</td><td rowspan="2">Severe fatigue, nausea, vomiting, right upper quadrant pain</td></tr>
<tr><td>If elevated at baseline:
ALT > 2 x baseline
or > 300 U/L (whichever occurs first)</td></tr>
</table>

Table 16-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Interrupt treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution 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 eCRF	Monitor LFTs weekly until resolution 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 eCRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate	Investigator discretion

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF	

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.

16.2 Appendix 2: Guidelines for the treatment of study drug induced diarrhea

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

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

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 6-3).

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.

[redacted]

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, applesauce, 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 eCRF.

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

Treatment of diarrhea CTCAE grade 1 or 2

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

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

[redacted]

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). 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.

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 subcutaneous (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.

[redacted]

Diarrhea workup

Perform appropriate tests (Fine and Schiller 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)

Blood examination

- Blood cultures to evaluate for septicemia
- C-reactive protein
- other inflammatory markers, as clinically indicated

  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 to evaluate for colitis/sigmoiditis
  - Biopsy: Histopathological examination of colonic mucosa and immunophenotyping may be performed to confirm the etiology of colitis

16.3 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®).

[redacted]

- 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 BYL719 metabolism (see Section 6.2 and Section 16.5).

16.4 Appendix 4: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

Document type:	TA Specific Guideline
Document status:	Version 3.2: February 11, 2016 Version 3.1: November 29, 2011 Version 3: October 19, 2009 Version 2: January 18, 2007 Version 1: December 13, 2002
Release date:	11-Feb-2016
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Table 16-4 Glossary

CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
eCRF	Electronic Case Report Form
FPFV	First participant first visit
ITT	Intent-to-treat
LPLV	Last participant last visit
MRI	Magnetic resonance imaging
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]

16.4.1 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 16.4.2 and the definition of best response in Section 16.4.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response.Section 16.4.3.2 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 16.4.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.4.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria by (Therasse et al 2000) and revised RECIST guidelines (version 1.1) by Eisenhauer et al 2009).

16.4.2.1 Definitions

16.4.2.1.1 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 participants without measurable disease, even if not expected as per eligibility criteria in this protocol, see Section 16.4.3.2.9.

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 5 mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- 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.

[redacted]

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 participant, 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.

16.4.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the subject 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 subjects be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how subjects with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.4.3.2.9

16.4.2.2 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:

- 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.
- 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 subjects, 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 subject 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

[redacted]

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.

- 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.
- 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. Ultrasound 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

[redacted]

normalize for a subject to be considered in complete clinical response when all lesions have disappeared.

- 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).
- Clinical examination: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes).

16.4.2.3 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) should be at least 10 mm in longest diameter. See Section 16.4.2.1.1.
- Nodal target: See Section 16.4.2.1.1. 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.

[redacted]

16.4.2.4 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 16-5) and non-target lesions (Table 16-6) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-7) as well as the presence or absence of new lesions.

16.4.2.4.1 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

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.

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

[redacted]

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.

16.4.2.4.2 Determination of target lesion response

Table 16-5 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 16.4.3.2.2).
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:

- 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 16-5 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 subjects who have not achieved target response of CR. For subjects who have achieved CR, please refer to last bullet in this section.
- For those subjects 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

[redacted]

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.
- 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.

[redacted]

16.4.2.4.3 Determination of non-target lesion response

Table 16-6 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].

1. 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 prevails.
2. It is recommended that the investigator and/or central reviewer should use expert judgment 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.
- The response for non-target lesions is C 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 16.4.2.4.3 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

[redacted]

16.4.2.4.4 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 subject in which case the response should be UNK, as for any of this subject's assessment Section 16.4.2.5
- 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 16.4.2.2

16.4.2.5 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 16-7.

Table 16-7 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 16.4.2.4.

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.

[redacted]

16.4.3 Efficacy definitions

The following definitions primarily relate to subjects who have measurable disease at baseline. Section 16.4.3.2.9 outlines the special considerations that need to be given to subjects with no measurable disease at baseline in order to apply the same concepts.

16.4.3.1 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 subject'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.

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 subject 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) > 6weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression <=12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

[redacted]

- 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 based on a 6 week tumor assessment frequency taking into account assessment windows.

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 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 subject 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 subject 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 subject. 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 subject 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 subject 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)

[redacted]

The primary analysis of the best overall response will be based on the sequence of investigator overall lesion responses.

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

Overall response rate (ORR) is the proportion of subjects 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 subjects with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize subjects 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 subjects 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 subjects 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 (Dent et al 2001) and counts all subjects 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. Subjects 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, subjects 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 intent-to-treat(ITT) approach).

16.4.3.2 Time to event variables

16.4.3.2.1 Progression-free survival

Usually in all Oncology studies, subjects 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.

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 subject has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

[redacted]

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.

16.4.3.2.2 Overall survival

All subjects should be followed until death or until subject has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the subject was last seen alive / last known date subject 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 subject is not known to have died, survival will be censored at the date of last known date subject alive.

16.4.3.2.3 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 subject has not had an event, time to progression is censored at the date of last adequate tumor assessment.

16.4.3.2.4 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.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues with respect to censoring foreseen.

16.4.3.2.5 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

[redacted]

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 subjects who did not experience treatment failure will be censored at last adequate tumor assessment.

16.4.3.2.6 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 subjects: a good risk group and a poor risk group. Good risk subjects tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk subjects 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 subjects. Less potent agents induce a response mainly in good risk subjects only. This is described in more detail by (Morgan 1988).

It is recommended that an analysis of all subjects (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 subjects (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis 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-subject analysis of these endpoints are not appropriate since the status of subjects throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For subjects 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.

Duration of overall complete response (CR): For subjects 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.

[redacted]

Duration of stable disease (CR/PR/SD): For subjects 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.

16.4.3.2.7 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 16.4.3.2.6. It is recommended that an analysis of all subjects (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 subjects should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all subjects, subjects 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 subjects 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 subject 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 subjects 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.

16.4.3.2.8 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.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

[redacted]

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.
- 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 backdating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol Section 16.4.3.2.8.

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.
- Date of last contact is defined as the last date the subject 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 subject 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.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

16.4.3.2.9 Handling of patients with non-measurable disease only at baseline

It is possible that subjects with only non-measurable disease present at baseline are entered into the study, 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.

It is recommended that any subjects with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to subjects with measurable disease at baseline, subjects without measurable disease should also

[redacted]

be incorporated in an appropriate manner. The overall response for subjects with non-measurable disease is derived slightly differently according to Table 16-8 .

Table 16-8 Overall lesion response at each assessment: subjects 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

As defined in Section 16.4.2.4

In general, the **non-CR/non-PD response** for these subjects is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response subjects 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 subjects 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 subjects with only non-measurable disease at baseline, handling subjects with a best response of CR as "responders" with respect to ORR and all other subjects as "non-responders".

For **PFS**, it is again recommended that the main ITT analyses on these endpoints include all subjects with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular subjects. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from subjects with only non- measurable disease.

16.4.3.2.10 Sensitivity analysis

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 subject being lost to follow-up? It is important that the protocol and SAP 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.

Based on definitions outlined in Section 16.4.3.2.8 , and using the FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics 2005)
as a reference, the following analyses can be considered:

[redacted]

Table 16-9 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)

1 =Definitions can be found in Section 16.4.3.2.8.
2 =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.4.3.2.8.
3 =The rare exception to this is if the subject 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.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as subjects without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may

[redacted]

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 subject 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 16-9 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **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.

16.4.4 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).

[redacted]

16.4.4.1 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).

16.4.4.2 End of treatment phase completion

Subjects **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 subjects 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 subject, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 14 days of the last study treatment.

Subjects may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- 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 subject from trial.

16.4.4.3 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.

Subjects may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision

[redacted]

- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.4.4.4 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 judgment in determining response in these type 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 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.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only subjects with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.4.4.5 Programming rules

The following should be used for programming of efficacy results:

16.4.4.5.1 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.

[redacted]

16.4.4.5.2 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 16.4.3.2.8). 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.

16.4.4.5.3 Incomplete dates for last known date participant 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.

16.4.4.5.4 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)'.

16.4.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

16.4.4.5.6 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.

For survival the following censoring reasons are possible:

- Alive
- Died
- Unknown

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 16-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*

[redacted]

- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.4.3.2.8. 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 subjects 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.

16.4.5 References (available upon request)

Dent S, Zee B, Dancey J, et al (2001) application of a new multinomial phase II stopping rule using response and early progression. J Clin Oncol: 19:785-91.

Eisenhauer EA, Therasse P, BogaertsJ, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Euro JCancer; 45:228-47.

Ellis S, Carroll KJ, Pemberton K, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials; 29:456-65.

EMA Guidance: 2012 Guideline on the evaluation of anticancer medicinal products in man

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

Therasse P, Arbuck SG, Eisenhauer EA, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J Natl Cancer Inst ;, 92; 205-16

16.5 Appendix 5: List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in DDI that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or alpelisib. Please note that all lists in Section 16.5 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 16.5.2. In doubt, please the contact medical monitor with any questions.

[redacted]

16.5.1 Permitted medication to be used with caution

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

Table 16-10 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 : Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsades de Pointes, QT prolongation).
CYP3A4 substrates which are auto-perpetrators: Based on Novartis internal assessment

16.5.2 Prohibited Medication

Strong inducers of CYP3A4

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

Table 16-11 List of prohibited strong inducers of CYP3A

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

[1] Herbal product

Inhibitors of BCRP

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

[redacted]

Table 16-12 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]

1Lee et al 2015

2 Novartis PK Sciences DDI List (January, 2018)

[redacted]