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Clinical Development

BYL719, Alpelisib

Oncology Clinical Protocol CBYL719C2301 / NCT02437318

SOLAR-1: A phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment

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Table of contents

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List of figures

List of tables

[redacted]

[redacted]

List of abbreviations

ADA	American Diabetes Association
ADME	Absorption Distribution Metabolism and Excretion
AE	Adverse Event
AI	Aromatase Inhibitor
AESI	Adverse Events of Special Interest
AKT	Protein Kinase B
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/GPT
ARA	Acid Reducing Agents
aPTT	Activated partial thromboplastin time
Arizona CERT	Arizona Center for Research and Education on Therapeutics
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/GOT
ATC	Anatomical Therapeutic Chemical Classification System
AUC0-6h	Area Under the Curve 0-6h
b.i.d.	bis in diem (twice a day)
BAL	Broncho-alveolar Lavage
[redacted]	[redacted]
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
BIRC	Blinded Independent Review Committee
BOV	Between-Occasion-Variability
[redacted]	[redacted]
BSA	Body Surface Area
BSV	Between-Subject-Variability
BUN	Blood Urea Nitrogen
CABG	coronary artery bypass graft
CAR	Constitutive Androstane Receptor
CDK4/6	Cyclin-Dependent Kinases 4 and 6
CFR	Code of Federal Regulations
CISH	Chromogenic In Situ Hybridization
CK	Creatine Kinase
Cmin	Minimum Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CV	Coefficient of Variation
CYP	Cytochrome P
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DBP	Diastolic Blood Pressure

[redacted]

DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
[redacted]	[redacted]
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DS&E	Drug Safety and Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EM	Erythema Multiforme
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer's core quality of life questionnaire
EOT	End of Treatment
[redacted]	[redacted]
ER	Estrogen Receptor
FAS	Full Analysis Set
eSAE	Electronic Serious Adverse Event
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FISH	Fluorescence In Situ Hybridization
FPG	Fasting Plasma Glucose
FSH	Follicle-stimulating Hormone
GGT	Gamma-glutamyltranspeptidase
GI	Gastrointestinal
GLP	Good Laboratory Practice
[redacted]	[redacted]
HbA1c	Glycosylated Hemoglobulin
HDL	High Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
HFHC	High-fat high-calorie
HIV	Human Immunodeficiency Virus
HLA	Human Leukocytes Antigen
HR	Hormone Receptor
HR.	Hazard Ratio
HR+	Hormone Receptor Positive
i.v.	intravenous(ly)
IB	Investigator Brochure
IC50	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IIT	Investigator Initiated Trial
IN	Investigator Notification
INR	International Normalized Ratio

[redacted]

IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Tests
LLOQ	Lower Limits of Quantitation
LFLC	Low-fat low-calorie
LH-RHa	Luteinizing hormone-releasing hormone agonist
LVEF	Left Ventricular Ejection Fraction
MBC	Metastatic Breast Cancer
MCF7	Michigan Cancer Foundation-7
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDR1	Multi Drug Resistance
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRP2	Multi-drug Resistance Protein-2
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
MUGA	Multiple Gated Acquisition
NCCN	National Comprehensive Cancer Network
NCDS	Novartis Clinical Data Standards
NCI-CTCAE	National Cancer Institute Common Terminology Criteria Adverse Event
NGS	Next Generation Sequencing
NSAI	Non-Steroidal Aromatase Inhibitors
NTCP	Sodium Taurocholate Co-transporting Polypeptide
o.d.	omnia die (once a day)
OAT	Organic Anion Transporter
OATP	Organic Anion-transporting Polypeptide
OCT	Organic Cation Transporter
ORR	Overall Response Rate
OS	Overall Survival
p.o.	per os (by mouth/orally)
PD	Progressive Disease
PET/CT	Positron Emission Tomography/Computed Tomography
PFS	Progression-Free Survival
PgR	Progesterone Receptor
PHI	Protected Health Information
PhRMA	Pharmaceutical Research and Manufacturers in America
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Gene which encodes the p110alpha catalytic subunit of PI3K
PK	Pharmacokinetics
PoC	Proof of Concept
PPS	Per-Protocol Set

[redacted]

PR	Partial Response
PRO	Patient Reported Outcomes
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PTEN	Phosphatase and Tensin Homolog
PXR	Pregnane X receptor
q.d.	Quaque Die (every day)
QOL	Quality of Life
QTcF	Q-T interval in the ECG (corrected according to the formula of Fridericia)
RBC	Red Blood Cells
REB	Research Ethics Board
R Value	ALT/ALP in x ULN
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	Stable Disease
SEC	Specific safety event categories
SERD	Selective Estrogen Receptor Down regulator
SERM	Selective Estrogen Receptor modulator
SISH	Silver in situ Hybridization
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
t.i.d.	Ter in die (3 times a day)
Tc99	Technetium-99
TdP	Torsade de Pointes
TTP	Time to Progression
UGT1A9	UDP-glucuronosyltransferase 1 family, polypeptide A9
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients based on the *PIK3CA* status defined as mutant or non-mutant
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment arms of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No. NCDS)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

[redacted]

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

[redacted]

Protocol summary

Title	SOLAR-1: A phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor (AI) treatment
Brief title	Study assessing the efficacy and safety of alpelisib plus fulvestrant in men and postmenopausal women with advanced breast cancer which progressed on or after AI treatment.
Sponsor and Clinical Phase	Novartis; Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine whether treatment with alpelisib plus fulvestrant prolongs progression-free survival (PFS) compared to fulvestrant and placebo in men and postmenopausal women with hormone receptor positive (HR+), HER2-negative advanced breast cancer, who received prior treatment with an AI either as (neo)adjuvant or for advanced disease. Pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy, in particular fulvestrant. Furthermore promising clinical activity has been observed with single agent alpelisib in heavily pre-treated ER+ Metastatic Breast Cancer (MBC) patients and when alpelisib was given in combination with fulvestrant or AI to HR+ HER2-negative metastatic breast cancer patients.
Primary Objective(s) and Key Secondary Objective	The primary objective is to determine whether treatment with alpelisib in combination with fulvestrant prolongs PFS compared to treatment with placebo in combination with fulvestrant based on local radiological assessment for patients with *PIK3CA* mutant status The key secondary objective is to determine whether treatment with alpelisib in combination with fulvestrant prolongs overall survival (OS) compared to treatment with placebo in combination with fulvestrant for patients with *PIK3CA* mutant status
Secondary Objectives	● To establish proof of concept of treatment benefit with alpelisib in combination with fulvestrant with respect to PFS for patients with *PIK3CA* non-mutant status ● To evaluate the two treatment arms with respect to OS for patients with *PIK3CA* non-mutant status ● To evaluate the two treatment arms and cohorts of interest with respect to overall response rate (ORR), clinical benefit rate. ● To evaluate the two treatment arms and cohorts of interest with respect to time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status ● To evaluate the safety and tolerability of alpelisib in combination with fulvestrant ● To evaluate change in global health status/Quality of Life (QOL) in the two treatment arms and cohorts of interest ● To characterize the pharmacokinetics (PK) of fulvestrant and alpelisib when given in combination with fulvestrant. ● To evaluate the association between *PIK3CA* mutation status as measured in ctDNA at baseline with PFS upon treatment with alpelisib.

[redacted]

Study design	This is a randomized, phase III, double-blind, placebo controlled global trial comparing the combination of fulvestrant + alpelisib to fulvestrant + placebo in men and postmenopausal women with HR+, HER2-negative advanced breast cancer. The study will consist of 35-days screening phase, of a treatment phase, and of a post-treatment phase which includes safety, efficacy, and survival follow-up. After molecular assessment of *PIK3CA* mutation status, patients will be assigned to one of the following cohorts: ● Cohort I; *PIK3CA* mutant: Patients with a confirmed *PIK3CA* mutation as per protocol definition. ● Cohort II; *PIK3CA* non-mutant: Patients without evidence of *PIK3CA* mutation as per protocol definition. In each cohort, patient will be randomly assigned to either fulvestrant+alpelisib or fulvestrant+placebo in a 1:1 ratio. Randomization will be stratified by the following factors: ● Lung and/or liver metastases (yes versus no) ● Previous treatment with any CDK4/6 inhibitor (yes versus no) (note: the total number of patients pre-treated with any CDK4/6 inhibitor will be limited to 30% of the overall study population)
Population	The study will include approximately 560 men and postmenopausal women with HR+, HER2-negative advanced breast cancer which progressed on or after AI treatment. The investigator or designee must ensure that only patients who meet all of the inclusion and none of the exclusion criteria are offered treatment in the study.
Key Inclusion criteria	● Patient is man or postmenopausal woman ● Patient has adequate tumor tissue for the analysis of *PIK3CA* mutational status by a Novartis designated laboratory. One new or recent biopsy (collected at screening if feasible) or archival tumor block or slides (15 slides minimum from a surgical specimen, 20 slides minimum from a biopsy) must be provided. It is recommended to provide a tumor sample collected after the most recent progression or recurrence ● Patient has identified *PIK3CA* status (mutant or non-mutant; determined by a Novartis designated laboratory) ● Patient has advanced (loco regionally recurrent not amenable to curative therapy or metastatic) breast cancer. ● Patients may be: ● relapsed with documented evidence of progression while on (neo) adjuvant endocrine therapy or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease ● relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression while on or after only one line of endocrine 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 therapy ● Patient has recurrence or progression of disease during or after AI therapy (i.e. letrozole, anastrozole, exemestane). ● Patient has a histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ breast cancer by local laboratory ● Patient has HER2-negative breast cancer defined as a negative in situ hybridization test or an 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 ● Patient has either measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria OR if no measurable disease is present, then at least one predominantly lytic bone lesion must be present ● Patient has ECOG performance status 0 or 1 ● Patient has adequate bone marrow function

[redacted]

<table>
<tr><td>Key Exclusion criteria</td><td>● Patient who relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease
● Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment
● Patient has received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant, any PI3K, mTOR or AKT inhibitor
● Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer
● Patient 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) and/or from whom ≥ 25% of the bone marrow was irradiated
● Patients with an established diagnosis of diabetes mellitus type I or not controlled type II
● Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs
● Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate patient participation in the clinical study
● Patient has currently documented pneumonitis
● Patient has active cardiac disease or a history of cardiac dysfunction (more details in Section 5.3)
● Patient has a history of acute pancreatitis within 1 year of screening or a past medical history of chronic pancreatitis</td></tr>
<tr><td>Investigational and reference therapy</td><td>Within each cohort, patients will be randomized 1:1 to receive either alpelisib in combination with Fulvestrant (treatment arm B) or placebo in combination with Fulvestrant (treatment arm A)
For this study, the term "investigational drug" refers to Novartis study drug alpelisib. Fulvestrant is also being used in this study. Study treatment in this study refers to the combination of drugs in each of the study arms and includes alpelisib/placebo and fulvestrant.
Patients will be randomly assigned to one of the below treatment arms in a 1:1 ratio:
● Control arm (Arm A): fulvestrant + alpelisib placebo
OR
● Experimental arm (Arm B): fulvestrant + alpelisib
<table>
<tr><th>Study treatment</th><th>Pharmaceutical form and route of administration</th><th>Frequency and/or Regimen</th></tr>
<tr><td>Fulvestrant</td><td>Two 5ml injections for i.m. administration</td><td>Dosed every 28 days (Cycle n Day 1) with 1 additional dose on Day 15 of Cycle 1</td></tr>
<tr><td>Alpelisib/ Placebo</td><td>Tablet for oral use</td><td>Once daily</td></tr>
</table></td></tr>
<tr><td>Efficacy assessments</td><td>● CT/ MRI every 8 weeks for the first 18 months, then every 12 weeks until 36 months, then change to as clinically indicated thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision
● Brain CT or MRI as clinically indicated if brain lesion at screening
● Whole body scan as clinically indicated
● Bone X-ray, CT or MRI (if bone lesion at screening) every 8 weeks for the first 18 months and then every 12 weeks until 36 months, then change to as clinically indicated
● Skin color photography (if skin lesions at screening) every 8 weeks during the first 18 months and then every 12 weeks until 36 months, then change to as clinically indicated
● CT/ MRI for any disease outside of the chest, abdomen, pelvis (if lesion identified at screening) every 8 weeks for the first 18 months and then every 12 weeks until 36 months, then change to as clinically indicated
● Survival status every 12 weeks (or earlier if required) regardless of treatment discontinuation reason</td></tr>
</table>

[redacted]

Safety assessments	● Physical examination ● ECOG performance status ● Height, weight, and vital signs ● 12 lead ECGs ● ECHO, MUGA scan ● Laboratory assessments including hematology, biochemistry, lipid panel, FPG and HbA1c, fasting lipase, fasting amylase, coagulation (via aPTT, PTT and INR) and urinalysis
Other assessments	**Pharmacokinetic**: blood samples will be obtained from approximately 200 patients (25%) in the study for sparse PK for alpelisib. In all other patients, pre-dose samples will be taken for alpelisib and fulvestrant trough plasma concentrations. **Biomarker**: tumor and blood samples will be collected for biomarker analysis [redacted] All [redacted] assessments will be performed by a Novartis designated laboratory. The assessments on [redacted] samples will include a multiplex approach. **Patient-reported outcomes**: Patient questionnaires (EORTC-QLQ-C30, [redacted]) will be collected to assess health-related quality-of-life, health status, functioning, disease symptoms, side effects, and cancer-related pain. **Healthcare resource utilization**: Potential differences in hospital resource utilization will be explored by assessing the number of patients hospitalized, the total number and length of hospitalizations
Data analysis	The primary efficacy endpoint, PFS, will be determined based on local tumor assessment following RECIST 1.1 guidelines. The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups using a stratified log-rank test at a one-sided 2.0% level of significance in the *PIK3CA* mutant cohort. Interim analyses that allow to stop for futility and efficacy in the *PIK3CA* mutant cohort with the primary endpoint are included. A stratified Cox regression model will be used to estimate the hazard ratio of PFS, along with 95% confidence interval. Subgroup analyses will be performed on each level of stratification factors if the primary analysis is significant. If the primary endpoint PFS is statistically significant in the *PIK3CA* mutant cohort, the key secondary efficacy analysis will be the comparison of the distribution of OS between the two treatment groups using a stratified log-rank test at a one-sided 2.0% level of significance. Interim analyses that allow to stop for efficacy with the key secondary endpoint are included. A stratified Cox regression will be used to estimate the hazard ratio of OS, along with 95% confidence interval. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges.
Key words	HR+, HER2-negative, advanced breast cancer, alpelisib, fulvestrant,PI3K, Phase III, ER+, PgR+, men, postmenopausal, aromatase inhibitor.

Amendment 5 (11-Feb-2020)

Study CBYL719C2301 was initiated in 2015 with first patient screened on 23 July 2015 and completed enrollment on 21 July 2017 with 572 patients randomized (341 in the PIK3CA mutant cohort and 231 in the PIK3CA non-mutant cohort). Results of this trial led to the registration of PIQRAY (Alpelisib, BYL719) in combination with fulvestrant for the treatment of HR-positive, HER-2 negative, PIK3CA-mutated, advanced or metastatic breast

[redacted]

cancer, with approvals already received in some countries including the United States. Patients are still being followed up for survival and long-term safety.

The purpose of this amendment is to provide a protocol update on the following based on the recently released IB Edition 13:
Update on [redacted] and the use of [redacted]
Update on guidance of dose interruption/modifications, management of AEs associated with the use of alpelisib, and guidance for follow-up on toxicities
Added AST/ALT/Total Bilirubin dose modifications in Table 6-3 (based on a feedback from FDA to match PIQRAY USPI). Accordingly, Table 6-4 was replaced with a table on alternative causes of liver diseases; and section on follow-up of potential drug-induced liver injury (DILI) was updated
Minor update for the guidelines of skin rash (based on feedback from KOL Dermatologist)
Added DRESS as one of possible manifestations of severe cutaneous skin reactions
Update of the VES for PRO, ECG, ECHO/MUGA assessments

Amendment 5 Rationale

Safety update
Patients are still being followed up for survival and long-term safety. The Investigator's Brochure (IB) Edition 13, dated 15-Oct-2019, included comprehensive assessments of SOLAR-1 safety data (with cutoff date: 13-May-2019) and all other available safety data which led to further defining alpelisib safety profile and risks associated with alpelisib.

Additionally, this amendment covers the updates:

VES update for PRO assessment
The PRO section of the VES (table 7-1) was reformatted to clarify the PRO schedule during the post-treatment follow-up phase and to align with section 7.2.6

Change to efficacy, ECG, ECHO/MUGA and PRO assessments Since the study met its primary endpoint,the visit schedule for efficacy, ECG, ECHO/MUGA and PRO assessments will be performed at C3D1 and then every 2 cycles until 36 months, then it will change to as clinically indicated to reflect more closely clinical practice.

Update to the treatment blinding
Protocol text regarding timing of unblinding clarified.

Changes to the protocol
The changes are outlined as follows in order of appearance:

- Section 1 : Background: Update on health authority approval and the current status of the study treatment in clinical research
- Section 4.1.4: efficacy follow-up: Update to the frequency of assessments for patients in longer-term efficacy follow-up

[redacted]

- Section 6.1.1.1: Alpelisib/placebo dosing: Clarification on instructions for a missed dose
- Section 6.3: Dose modifications: Updates based on IB-12 and IB-13
- Section 6.3.1: Dose modification and dose delay
    - Table 6-3: Criteria for interruption and re-initiation of alpelisib/placebo treatment: Minor updates on the management of AEs of special interest
- Section 6.3.2: Follow up on toxicities: Updates based on IB-12 and IB-13
- Section 6.3.2.1.1: Management of Pneumonitis/ILD: included ILD as a selected toxicity
- Section 6.3.2.1.2: Guidelines for the treatment of study drug induced skin toxicity: included DRESS as a skin toxicity and guidelines for follow up on skin toxicity further clarified
- Section 6.3.2.1.3: Guidelines for the treatment of alpelisib induced hyperglycemia: Update on guidance for glucose lowering medications after discontinuation of alpelisib
- Section 6.3.2.1.5: Follow up on potential drug-induced liver injury (DILI) cases: Additional information on the diagnosis of DILI and clarification on the approach if DILI is confirmed or unlikely
    - Table 6-4: Alternative causes of liver disease: Table added
- Section 6.3.2.1.6: Guidelines for hypersensitivity: Section added
- [redacted]
- Section 6.5.3: Treatment blinding: Timing of unblinding clarified
- Section 7.1: Study flow and visit schedule: Frequency of assessments reduced for patients in longer-term efficacy follow-up
    - Table 7-1: Visit evaluation schedule: Efficacy assessment schedule updated
- Section 7.1.6: Efficacy follow-up Frequency of assessments changed for patients in longer-term efficacy follow-up
- Section 7.2.1: Efficacy assessment Frequency of assessments changed for patients in longer-term efficacy follow-up
    - Table 7-2: Imaging assessment collection plan Frequency of imaging assessments changed for patients in longer-term efficacy follow-up
- Section 7.2.2.7.1: Electrocardiogram (ECG)
    - Table 7-5: Local ECG collection plan
- Section 7.2.2.7.2: Cardiac imaging – MUGA scan or ECHO
- Section 7.2.6: Patient reported outcomes Frequency of PROs changed for patients in longer-term efficacy follow-up
- Table 7-10: Patient reported outcomes collection plan
- Section 14: Appendix 7: Liver event and Laboratory trigger Definitions and Follow-up Requirements Section/Table added

[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]

Amendment 4 (22-Nov2017)

The first patient was screened on 23 July 2015 and enrollment was completed on 21 July 2017, with a total of 572 patients randomized (341 in the *PIK3CA* mutant cohort and 231 in the *PIK3CA* non-mutant cohort).

The purpose of this amendment is to provide updated guidance on the management of skin and subcutaneous reactions.

Additional change in the protocol amendment:

To correct the sentence in section 8.1.1 regarding the timeline of the safety follow up visit. Since fulvestrant is a marketed product, and is being used according to locally approved labeling, the safety follow-up visit for adverse event monitoring after fulvestrant 5 half-lives (i.e. 40-50 days) is not applicable.

This visit will take place within 30 days following the last dose of study treatment, which is longer than 5 half-lives of alpelisib.

Amendment 4 rationale

Update in Skin Toxicity Management Guidance

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

Changes to the protocol

The changes are outlined as follows in order of appearance:

- Table 6-3 Criteria for interruption and re-initiation of alpelisib/placebo treatment
- Section 6.3.2.1.2 Guidelines for the treatment of study drug induced skin toxicity
- Table 7.1 Visit evaluation schedule
- Section 8.1.1 Safety monitoring and reporting

IRBs/IECs

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

[redacted]

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

Amendment 3 (14-Dec-2016)

The first patient was screened on 23 July 2015 and as of 14 December 2016, 443 patients (214 in the PIK3CA mutant cohort and 229 in the PIK3CA non-mutant cohort) have been randomized in the study CBYL719C2301. Enrollment into the PIK3CA non-mutant cohort ended on 29 September 2016.

No efficacy analyses have been performed in this study as of the date of this amendment.

The purpose of this amendment is to:

- Modify the interim PFS analysis efficacy stopping boundary from Lan-DeMets (O'Brien-Fleming) to Haybittle-Peto boundary in the PIK3CA mutant cohort
- Ensure that the Novartis clinical team will remain blinded to the treatment allocation in both cohorts until the time point when PIK3CA mutant cohort can be unblinded. The responsibility for performing the final PFS analysis (and first interim OS analysis) in the PIK3CA non-mutant cohort is modified from the Novartis Clinical Team to an independent statistical group. The results from this analysis will be provided by the independent statistical group to the DMC for decision making on the outcome of the PIK3CA non-mutant cohort

Additional changes in the protocol amendment

- Add a blood sample collection to [redacted]
- Revision of window regarding whole body bone scan: change from within 28 days to within 42 days prior to randomization
- Table 6-3-"Criteria for interruption and re-initiation of alpelisib/placebo treatment": clarification has been added, to indicate that metformin is a preferred option, but that other insulin sensitizers such as thiazolidinediones or dipeptidyl peptidase-4 Inhibitors can also be used, per investigator judgement
- Clarify that the data from the audit-based BIRC assessment summarized using the method proposed by Amit et al. 2011 is not considered as exploratory

Amendment 3 rationale

Rationale to change the interim PFS analysis efficacy stopping boundary in the PIK3CA mutant cohort

The interim PFS analysis efficacy stopping boundary is changed from Lan-DeMets (O'Brien-Fleming) to a Haybittle-Peto boundary in the PIK3CA mutant cohort. At the interim efficacy analysis for PFS, the observed p-value has to be less than or equal to 0.0001 based on Haybittle-Peto boundary in order to conclude superior efficacy.

[redacted]

The main advantage of the Haybittle–Peto boundary is that very little alpha is spent at the early interim look which allows stopping the trial early only in case of compelling and overwhelming evidence against the null hypothesis. Hence, stopping the trial early for PFS benefit based on a Haybittle-Peto boundary is likely to confirm the robustness of the interim analysis results.

Rationale to modify the responsibility for performing the final PFS analysis in the PIK3CA non-mutant cohort

In the Protocol Amendment 2 the responsibility for performing the final PFS analysis in the PIK3CA non-mutant cohort (and the first IA for OS, if applicable at that time), both of which are secondary objectives, was attributed to the Novartis clinical team. The Novartis clinical team would unblind the treatment allocations in this cohort to perform this analysis.

In order to avoid any potential for impacting the integrity of the trial in relation to the PIK3CA mutant cohort whilst this cohort is still blinded and ongoing, the responsibility for performing the final PFS analysis in the PIK3CA non-mutant cohort (and the first IA for OS) will now belong to an independent statistical group and this analysis will be provided to DMC. The Novartis clinical team will remain blinded to the treatment allocations in both cohorts up until such point the PIK3CA mutant cohort can be unblinded.

The DMC will inform the sponsor only on the outcome of the Proof of Concept result (along with the formal testing outcome if Proof of Concept is met).

Rationale to collect an additional blood sample [redacted]

To further [redacted]

Changes to the protocol

The changes are outlined as follows in order of appearance:

- List of abbreviations is updated
- [redacted]
- Section 6.3.1.2, Table 6-3 has been updated to clarify that metformin is a preferred option, but that other insulin sensitizers such as thiazolidinediones or dipeptidyl peptidase-4 Inhibitors can also be used, per investigator judgement
- Section 7.1 and 7.1.1 have been updated to clarify that the whole body bone scan required at screening can be performed within 42 days prior to randomization
- Table 7-1 has been updated to clarify that the whole body bone scan required at screening can be performed within 42 days prior to randomization [redacted]
- Section 7.2.1.1 and Table 7.2, have been updated to clarify the whole body bone scan required at screening can be performed within 42 days prior to randomization

[redacted]

[redacted]

- Section 10.4.4: has been updated to clarify that a sample based BIRC audit strategy will be used to assess PFS by BIRC.

[redacted]

- Section 10.7.1: has been updated to correct typographical errors to clarify that at the time of the futility analysis, the PIK3CA mutant cohort may be stopped for futility if one or both of the criteria are met.
- Sections 10.7.1 and 10.7.2: have been updated to modify the interim PFS analysis efficacy stopping boundary from Lan-DeMets (O'Brien-Fleming) to a Haybittle-Peto boundary in the PIK3CA mutant cohort. Table 10-1 is updated accordingly.
- Section 10.7.1: PFS futility boundary based on gamma-family beta spending function has been modified due to the slight change in power resulting from change in efficacy stopping boundary from a Lan-DeMets (O'Brien-Fleming) to a Haybittle-Peto boundary whilst maintaining the same number of PFS events as the original design.
- Section 10.7.2 has been updated to clarify that the responsibility for performing the final PFS analysis in the PIK3CA mutant cohort (and the first IA for OS, if applicable at that time), belongs to the Novartis clinical team
- Section 10.7.3 has been updated to clarify that the responsibility for performing the final PFS analysis in the PIK3CA non-mutant cohort (and the first IA for OS, if applicable at that time), belongs to an independent statistical group and this analysis will be provided to DMC.
- Section 10.8 has been updated to amend the interim PFS analysis efficacy stopping boundary to a Haybittle-Peto boundary and update the statistical power for the primary endpoint in the PIK3CA mutant cohort.
- Section 14.6.1 has been updated to amend Table 14-11 with the revised interim futility stopping probabilities.
- In addition to above, changes to typographical errors where applicable have been made

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.

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]

Amendment 2 (30-Aug-2016)

The first patient was screened on 23 July 2015 and as of 19 August 2016, 317 patients have been randomized in the study CBYL719C2301.

The purpose of this amendment is to:

- Modify the patient population to be enrolled in the study. Patients who relapsed more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease will no longer be enrolled in the study
- Modify the criteria to define futility at the interim analysis in the *PIK3CA* mutant cohort
- Update inclusion criteria and provide more detailed treatment guidance for AE of hyperglycemia and update on AE management for skin toxicity following an advisory-board meeting recommendation
- Update the general administration guidelines for alpelisib/placebo based on a food effect and ARA DDI study: alpelisib must be taken with a meal regardless of composition or overall calorie intake. A staggered approach for co-administration of alpelisib with acid reducing agents is no longer required
- Change the approach for Blinded Independent Review Committee (BIRC) assessment of PFS from a full read to an audit (sample) based approach. As PFS in the *PIK3CA* non-mutant cohort is a secondary endpoint, no BIRC assessment will be made for these patients.

[redacted]

- Update the estimated timing of interim and final PFS and OS analyses taking into account current and expected enrolment rates.

Additional Changes in the protocol amendment:

- The protocol appendix 2 has been updated to reflect the new Novartis guidance on the implementation of RECIST 1.1
- Clarify dose adjustment recommendation in case of isolated AST/ALT grade 3 increase, for patients with a baseline AST/ALT between 3 and 5 x ULN
- Exclude female patients with a QTcF>460 msec for alignment to the standard language
- Add a recommendation to ensure that the central *PIK3CA* testing result is available before conducting other screening assessments, when possible
- Removal of the requirement for a central radiology assessment by medical oncologist: medical oncologist review has been replaced by a standard blinded independent review committee (BIRC) assessment
- Clarify possibility to perform unscheduled laboratory assessments locally if medically indicated
- Update section 11.5 "Publication of study protocols and results"

Amendment 2 Rationale

Rationale to modify patient population and exclude patients sensitive to prior endocrine therapy

[redacted]

The original protocol allows for patients with documented evidence of progression more than 12 months from completion of (neo-) adjuvant endocrine therapy with no treatment for metastatic disease to participate in the study. The number of patients in this category was assumed to be around 15% of the total study population. Based on Howell 2004 and Robertson 2014, the median PFS for fulvestrant of this group was considered to be 18 months (Section 10.8). Based on the expected median PFS, a low number of events at interim analysis is anticipated to occur in this subgroup. Due to potential difficulties in the interpretation of the results for this subgroup, it was decided to exclude endocrine sensitive patients from the study. Thus, the proposed patient population will become more homogenous, focusing on patients that are refractory to prior hormonal therapy. Accordingly, Section 5.2, Inclusion criterion 9 and Section 10.8, sample size assumptions, have been modified. The endocrine sensitive patients enrolled before the current protocol amendment will be included in the full analysis set. The initial assumption for the non-mutant cohort (i.e. 15% of patients being sensitive to prior endocrine therapy) is not impacted as enrollment in this cohort is expected to be completed at the time of the implementation of the current protocol amendment.

Rationale to modify futility criteria in *PIK3CA* mutant cohort

In light of the emerging changing treatment landscape, the futility criteria for the *PIK3CA* mutant cohort have been modified.

In addition to the stopping boundary for futility based on a beta-spending function defined in Section 10.7.1, the DMC will now be asked to consider the conditional probability of observing a clinically relevant PFS result of a HR≤0.6 at the final PFS analysis of this cohort, given the data observed at the time of the interim analysis. The *PIK3CA* mutant cohort sample size and futility analysis timing remain unchanged.

Update of Inclusion Criteria and detailed guidance for AE management of hyperglycemia and updated AE management for skin toxicity

In 2016, a program-wide assessment of available data on alpelisib-induced hyperglycemia and skin toxicity was conducted and results were shared and discussed by an advisory board consisting of oncologists, endocrinologists and a dermatopathologist. The inclusion/exclusion criteria as well as management guidelines were reviewed and more detailed guidance for the management of alpelisib induced hyperglycemia and skin toxicity has been developed. The inclusion criteria have been modified to exclude patients with HbA1c ≥ 6.5%, as patients with fasting plasma glucose ≥ 126 mg/dl (eligible by protocol) and HbA1c ≥6.5% are considered to be diabetic according to American Diabetes Association (ADA) guidelines. In addition, patients with baseline FPG ≥100 mg/dl(5.6 mmol/L) and/or HbA1c ≥5.7% should be instructed on lifestyle changes at screening and a consultation with a diabetologist is highly recommended.

For skin toxicity of any grade, treatment with topical steroids 3-4 times daily is recommended. Oral anti-histamines are indicated in case of skin toxicity accompanied with burning, stinging or pruritus or prophylactic in case of hypersensitivity in patients' medical history, e.g. seasonal allergy, allergic asthma, drug-induced exanthema in the past. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity.

Table 6.3, Criteria for interruption and re-initiation of alpelisib/placebo treatment, has been updated to provide more detailed guidance than the previous version of the protocol.

[redacted]

Update of general administration guidelines for alpelisib/placebo

The impact of food on the absorption of alpelisib was investigated in a clinical trial in healthy volunteers (Study CBYL719A2103) after a single 300 mg oral dose of alpelisib. Compared to the fasted state a high-fat high-calorie (HFHC) meal increased – on average – AUCinf by 73% and Cmax by 84%, and a low-fat low-calorie (LFLC) meal increased AUCinf by 77% and Cmax by 145%, confirming a positive food effect on absorption of alpelisib. No significant difference was found for AUCinf between LFLC and HFLC meals. Overall, data from study CBYL719A2103 confirmed that alpelisib must continue to be given with a meal. However as neither composition nor overall calorie intake have shown an effect, the light meal restriction can be lifted, allowing also some further flexibility with regards to alpelisib intake during the day if dose administration has been forgotten in the morning.

Co-administration of an acid-reducing agent (ARA) was investigated in the same clinical trial. The co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced the bioavailability of alpelisib and decreased overall exposure of alpelisib. In the presence of a LFLC meal, AUCinf was decreased – on average – by 21% and Cmax by 36% with ranitidine. In the absence of food, the effect was more pronounced with a 30% decrease in AUCinf and a 51% decrease in Cmax with ranitidine compared to the fasted state without co-administration of ranitidine. As the study showed a non-clinically relevant 21% decrease in exposure of alpelisib in combination with ranitidine when given with a LFLC meal, ARAs can be administered concomitantly and do not have to be administered in a staggered manner. Hence, the restriction about the staggered administration of H2-receptor antagonists as well as the avoidance of proton-pump inhibitors has been removed.

For more information, please refer to the [Alpelisib (BYL719) Investigators Brochure Edition 9].

Rationale to change the approach for Blinded Independent Review Committee (BIRC) assessment:

For studies with local PFS as the primary endpoint, central PFS has generally been used as a secondary analysis in support of the treatment effect observed in the primary efficacy analysis. Although, 100% central review of scans has been performed in many studies, there is a growing body of evidence that an audit based approach for central evaluation is sufficient (Zhang et al, 2012, FDA ODAC 2012). Therefore, the study is being amended to change the central assessment of PFS from a full read to an audit based approach. Consequently, blinded independent review committee (BIRC) based PFS will no longer be a secondary endpoint but will be considered supportive of the primary endpoint analysis in the *PIK3CA* mutant cohort only. As PFS in the *PIK3CA* non-mutant cohort is a secondary endpoint, no BIRC assessment will be made for these patients.

Changes to the protocol

The changes are outlined as follows in order of appearance:

- List of abbreviations and Glossary of terms are updated
- Protocol summary has been revised to reflect changes made in other protocol sections

[redacted]

- Section 3, Table 3-1 - secondary [redacted] objectives and endpoints have been updated to remove the PFS assessed by BIRC as secondary objective [redacted]
- Section 4.1.1 recommendation has been added to ensure that the central *PIK3CA* testing result is available before conducting other screening assessments, when possible
- [redacted]
- Section 5.2 has been updated to include only patients resistant to prior endocrine therapy and patients with HbA1c ≤ 6.4%
- Section 5.2 has been updated to exclude female patients with a QTcF>460 msec
- Section 5.2 has been updated to exclude patients who relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease
- Section 6.1.1.1 on alpelisib/placebo dosing instructions and recommendations have been updated based on the results of a food effect and ARA DDI study for alpelisib
- Section 6.3.1.2, Table 6-3 has been updated to provide more guidance for hyperglycemia and skin toxicity management and to update guidance on AST/ALT increase and in case of acute pancreatitis
- Section 6.3.2.1.3 has been updated per update of Table 6-3
- Section 6.4.1.4 has been updated to reflect the changes with respect to the co-administration of acid reducing agents, lifting the restriction for the use of proton-pump-inhibitors and staggered dosing of other gastric protection agents
- [redacted]
- [redacted]
- Section 7.2.1.1 has been updated to reflect the addition of the audit based strategy for the BIRC assessment in the *PIK3CA* mutant cohort
- [redacted]
- Section 7.2.1.3 has been added to describe the audit-based central assessment in the *PIK3CA* mutant cohort
- Section 7.2.3.3 has been updated based on the results of a food effect and ARA DDI study for alpelisib
- Section 7.2.2.5 has been updated to allow possibility to perform unscheduled laboratory assessments locally if medically indicated
- Section 10.4.4 has been updated to describe the supportive analysis of PFS using an audit based BIRC assessment in the *PIK3CA* mutant cohort
- Section 10.5.1 has been updated to describe the amended interim analysis timings for OS in the *PIK3CA* mutant cohort

[redacted]

- Section 10.5.2.2 has been updated to describe the amended interim analysis timings for OS in the *PIK3CA* non-mutant cohort
- Section 10.5.2.6 has been removed to reflect the removal as a secondary endpoint of PFS as assessed by the BIRC, for both cohorts
- [redacted]
- Section 10.7.1 has been updated to describe:
  - the amended interim analysis timings for PFS and revised operating characteristics in the *PIK3CA* mutant cohort
  - The revised interim futility criteria for PFS in the *PIK3CA* mutant cohort
- Section 10.7.2 has been updated to describe the amended interim analysis timings for OS and revised operating characteristics in the *PIK3CA* mutant cohort
- Section 10.7.3 has been updated to describe the amended interim analysis timings for OS and revised operating characteristics in the *PIK3CA* non-mutant cohort
- Section 10.8 has been updated to amend the power calculation in the *PIK3CA* mutant cohort resulting from the addition of the revised futility criteria
- Section 10.8 has been updated to add revised assumptions regarding the patient population, expected *PIK3CA* mutation rate and revised current and expected accrual rates
- Section 10.8 has been updated to add a sample size calculation for the audit size of sample-based BIRC assessment of PFS in the *PIK3CA* mutant cohort
- Section 10.9 has been updated to add amended interim and final analysis timings for OS in the *PIK3CA* mutant cohort as a result of the revised assumptions in Section 10.8
- Section 10.9.1 has been updated to add amended interim and final analysis timings for OS in the *PIK3CA* non-mutant cohort aligning these timings with the revised interim analysis timings for OS in the *PIK3CA* mutant cohort as described in Section 10.9
- Section 11.5 has been modified to reflect update in publication of study protocol and results
- Section 14.3 Appendix 3 has been updated to reflect the new Novartis guidance on the implementation of RECIST 1.1
- Section 14.6 Appendix 6 has been updated to provide the statistical methodology and operating characteristics for the revised interim futility criteria for PFS in the *PIK3CA* mutant cohort
- In addition to above, changes to typographical errors where applicable have been made

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.

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.

[redacted]

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

Amendment 1

Amendment rationale

The first patient was screened on 23 July 2015 and as of 10 February 2016, 92 patients have been randomized in the study CBYL719C2301.

The main purpose of this protocol amendment is to modify the study design for the *PIK3CA* non-mutant cohort from pivotal to a proof-of-concept. The *PIK3CA* mutant cohort will remain unchanged. Consequently the primary and key secondary objectives of the study will be to compare the two treatment groups, based on PFS and OS respectively, for patients in the *PIK3CA* mutant cohort. Comparison of PFS and OS for patients in the *PIK3CA* non-mutant cohort will be part of the secondary objectives.

The additional purposes of this amendment are:

- To update inclusion/exclusion criteria, monitoring and guidance for hyperglycemia and skin toxicity management following recent overall safety assessment of alpelisib across the development program
- To update inclusion/exclusion criteria and to add management guidelines for acute pancreatitis; as a life-threatening case of acute pancreatitis has been reported in this study
- To add collection of a post-dose ECG assessment around the expected Tmax (2h) for all patients
- To extend the time window by one week for providing the tumor sample for molecular testing from day -28 to day -35 of the screening period; this will allow more time for re-sending of tumor material/re-biopsy if necessary, or perform a new tumor biopsy
- To clarify that a [redacted] is recommended, when feasible, over archival sample for [redacted] to minimize [redacted] at time of study entry
- To add the collection of an additional whole blood sample to be used as non-tumor control for those patients where a newly obtained tumor biopsy is collected at progression
- To update the language of some protocol sections as part of a general update implemented across the development program (e.g. safety language for liver toxicity, pancreatitis and QT prolongation; language for Adverse Events reporting)

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

Rationale to modify the study design for *PIK3CA* non-mutant cohort from a pivotal to a proof-of-concept:

PIK3CA mutations have been established to be associated with a higher sensitivity to alpelisib both *in vivo* and *in vitro* (Fritsch 2014). In accordance with pre-clinical data, more mature clinical data from study [CBYL719X2101] demonstrate that patients with HR+ HER2-negative

[redacted]

PIK3CA mutant mBC may derive a greater benefit from alpelisib either as monotherapy or in combination with fulvestrant as opposed to patients with *PIK3CA* non-mutant tumors (Janku 2014; Novartis internal data). In addition, this finding has been suggested for the combination of alpelisib with letrozole or exemestane in a more recently reported study (Dickler 2015). Furthermore, a large phase III study assessing the safety and efficacy of the pan-PI3K inhibitor buparlisib in combination with fulvestrant showed a trend towards better efficacy in patients carrying *PIK3CA* mutant tumors assessed by ctDNA compared to patients with *PIK3CA* non-mutant tumor (Baselga 2015). These data are considered hypothesis generating and at this time, the relatively limited activity of pan-PI3K inhibitor and alpelisib in patients with *PIK3CA* non-mutant HR+ HER2-negative mBC is not considered conclusive.

Therefore, the primary and key secondary objectives of this study are amended to determine whether treatment with alpelisib in combination with fulvestrant prolongs PFS and OS respectively, compared to treatment with placebo in combination with fulvestrant for patients with *PIK3CA* mutant status only.

[redacted] Analysis of PFS for the PIK3CA non-mutant cohort will be conducted as a secondary endpoint and will be carried out once 102 PFS events in that cohort have been reported. Considering that analysis for the PIK3CA non-mutant cohort will be conducted independently of the primary analysis in the PIK3CA mutant cohort, an alpha of 0.5% will be assigned to this comparison. The primary efficacy analysis of PFS based on the population of patients with PIK3CA mutation status will be performed at a 2.0% level of significance. This approach guarantees the protection of the overall type I error ($\alpha = 2.5\%$).

The updated design will allow a reasonable estimate of the effect of the combination of alpelisib and fulvestrant in the *PIK3CA* non-mutant cohort with a decrease in the number of patients to be randomized (220 instead of 478). An interim futility analysis based on PFS in the non-mutant cohort will no longer be conducted due to the reduced sample size; the planned OS analyses have been updated accordingly.

Rationale for updating the inclusion/exclusion criteria and management of hyperglycemia

An overall assessment of occurrence and risk factors for alpelisib induced hyperglycemia has recently been conducted across the development program in more than 1000 patients treated with alpelisib at different dose levels, tumor types and regimens. A higher risk of developing grade 3/4 hyperglycemia was observed in patients with HbA1c between 6.5 and 8.0% (Novartis Internal Data). In addition, and according to the American Diabetes Association (ADA) guidelines with regards to glycemic targets in patients with diabetes mellitus, a value of HbA1c >6.5% represents a status of not-optimally controlled diabetes. The equivalent FPG values for an HbA1c of 6.5% are around 140 mg/dl. Therefore, in an attempt to reduce the risk of alpelisib-induced hyperglycemia and in alignment with ADA guidelines, the inclusion criterion #12 for FPG and HbA1c has been modified as follows: FPG $\leq$ 140 mg/dl and HbA1c $\leq$ 6.5%.

Further recommendations for management of hyperglycemia have also been added in the additional follow-up for selected toxicities section.

[redacted]

Rationale for update on skin toxicity management

A second on-target effect of alpelisib treatment is skin toxicity. As for hyperglycemia, an overall assessment of skin toxicity occurrence and possible preventive actions has also been conducted recently across the alpelisib development program. Although some improvement in the severity of rash has been reported with the prophylactic use of non-sedating oral anti-histamines (Dickler 2015, Mayer 2015), no conclusive data are available with the combination of alpelisib at 300 mg/day and fulvestrant 500 mg. Nevertheless, the study is amended to recommend the use of prophylactic oral non-sedating anti-histamines (e.g. cetirizine or equivalent), as per the discretion of the investigator.

Skin toxicity also typically occurs within the first few weeks of treatment. Therefore, the visit on day 8 at cycle 1 is amended to include a clinical assessment of the skin for rash or other toxicities.

Rationale for updating the inclusion and exclusion criteria, and the management of pancreatitis

One case of life threatening acute pancreatitis has recently been reported in the study CBYL719A2301 (SOLAR-1), where postmenopausal women with advanced breast cancer are randomized to receive BYL719 (300 mg, once daily) and fulvestrant or BYL719 and placebo. No preclinical evidence for this risk has been observed. An overall assessment of the risk of alpelisib to induce acute pancreatitis has been conducted at the end of November 2015 across the development program (details reported in the IN PHHO2015IL018569). The key findings of such evaluation indicate that asymptomatic elevations of pancreatic enzymes may occur in some patients treated with alpelisib. Clinical data suggest that a small percentage (< 1%) of patients treated with alpelisib may develop acute clinical pancreatitis (Tenner et al 2013).

Therefore, in the current protocol and across the alpelisib development program, the following changes have been implemented to allow for diagnosis of acute pancreatitis based on the American College of Gastroenterology Guidelines (Tenner et al 2013): modification of inclusion criteria; now including fasting amylase and lipase added to the panel of investigations at screening; frequent monitoring of amylase and lipase; detailed dose modification guidelines in case of increase of amylase and/or lipase or clinical signs of pancreatitis included.

Rationale for the modification of the potassium inclusion criterion

A concentration-effect-analysis for BYL719 (single agent) showed a limited but positive trend of increase in QT. While no clinical significant QT prolongation (> 10 ms) is expected at a 300 mg dose, potassium levels should be within normal range at study entry to limit the risk of cardiac adverse events, as hypokalemia has been shown to increase QT prolongation and hyperkalemia can lead to faster repolarization of the cardiac action potential. During study conduct, any potassium related adverse event will be monitored.

Rationale for ECG PK:

Based on a concentration-effect-analysis for alpelisib single agent and in combination with fulvestrant (based on [CBYL719X2101]), no clinically significant QT prolongation (> 10ms) is expected. Following FDA consultation, to gather additional data, a post-dose ECG

[redacted]

assessment, around the expected Tmax (2h), was added for all patients. The expected Tmax (2h) is matched to the C1 D15 PK sample for the sparse population (approximately 200 patients overall).

Rationale for the update of the management of liver toxicity

Management of liver toxicity has been incorporated as guidance for Investigators and criteria for alpelisib dose modification have been updated to better characterize liver toxicities and provide more details on their management and follow up.

Changes to the protocol

The changes are outlined as follows in order of appearance:

- List of abbreviations and Glossary of terms are updated
- Protocol summary has been revised to reflect changes made in other protocol sections
- Section 2 Rationale has been updated to reflect the change in study design for *PIK3CA* non-mutant cohort
- Table 3-1 Objectives and Related Endpoints have been updated to reflect the change in study design for *PIK3CA* non-mutant cohort(errors have also been corrected)
- Section 4.1 Description of study design has been updated to reflect the change in study design for *PIK3CA* non-mutant cohort
- Section 4.1.1 Screening phase has been extended to 35 days prior to randomization/C1D1 to increase flexibility for sites to send a second biopsy sample in case the first screening biopsy sample does not yield a *PIK3CA* result
- Section 4.2 Timing of interim analysis and design adaptions has been modified to reflect change in study design change for the *PIK3CA* non-mutant cohort
- Section 4.3 Definition of end of the study has been modified to reflect the change of study design for the *PIK3CA* non-mutant cohort
- Section 5.2 Inclusion criteria and Section 5.3 Exclusion criteria have been updated to reflect the redefined patient population, to provide further clarity, and to reflect the new standard language
- Section 6.1.1.1.2 has been revised to include dosing of amylase and lipase
- Section 6.3.1.2 has been revised to provide more clarity for treatment dosing (recommendation for dose reduction or interruption, and to clarify that treatment must be discontinued per Table 6-3)
- Table 6-3. Criteria for alpelisib/placebo dose modifications has been revised to introduce new guidance to investigators to better characterized liver and pancreatic toxicities and to reflect the new standard language
- Section 6.3.2 Standard protocol language for the management of liver toxicity and amylase/lipase elevation has been incorporated as guidance for Investigators. In addition, the management of skin toxicity is revised following recent overall safety assessment of alpelisib
- Section 6.4.3 Prohibited concomitant therapy has been revised to provide further guidance with regards to administration of QT prolonging drugs

[redacted]

- Section 6.5.2 Treatment assignment or randomization has been updated in accordance with study design modification of the *PIK3CA* non-mutant cohort
- Table 7-1 Visit evaluation schedule has been modified:
  - to extend the screening phase to 35 days prior to randomization/C1D1
  - to reflect the addition of ECG reading at C1D15 for all patients
  - to add a physical examination at C1D8
  - to add FPG assessment at C1D8
  - to add fasting amylase and lipase at C1D8 and revise the assessment schedule of those 2 parameters to monthly monitoring instead of every second cycle
  - [redacted]
- Section 7.1.1 Screening has been updated to extend period of screening for molecular testing
- Section 7.1.1.3 has been updated to reflect collection of amylase
- Section 7.2.2.1 Physical examination has been updated to include physical examination at C1D8 and has been clarified to allow flexibility of when the exam can be done prior to randomization
- Section 7.2.2.5 Laboratory evaluations have been updated to reflect collection of fasting amylase and to recommend local assessment of FPG at C1D8 and C1D15
- Table 7-4 Central clinical laboratory parameters collection plan has been modified to incorporate new lab parameters for chemistry (creatine kinase, lactate dehydrogenase) and coagulation (activated partial thromboplastin time), and to add fasting amylase as additional test.
- Sections 7.2.2.5.2; 7.2.2.5.3 and 7.2.2.5.4 have been updated to reflect collection of new lab parameters as per Table 7-4, and to update FPG assessment schedule
- Section 7.2.2.7.1 Electrocardiogram added at C1D15 for all patients and clarification provided for triplicate ECG required at screening – As a consequence, Table 7-5 has been updated accordingly
- Section 7.2.3.3 Pharmacokinetic blood sample collection plan has been clarified with recommendation for unscheduled PK
  - [redacted]
- Section 7.2.4.1.1 Assessments in tumor tissues has been clarified to recommend provision of newly obtained tumor biopsy if possible
  - [redacted]
- Section 8. Safety monitoring and reporting has been updated to reflect implementation of new SAE reporting instruction

[redacted]

- Section 10. Statistical methods and data analysis: updates to reflect changes to study design (from a pivotal to proof-of-concept design for *PIK3CA* non-mutant cohort)
- Section 10.1.2 Definition of the Safety Set updated to reflect standard text per new protocol template
- Section 10.1.3 Situations where Per Protocol Set may be used is updated to reflect changes to study design objectives
- Section 10.4 Primary objective amended to be PFS in *PIK3CA* mutant cohort
- Section 10.4.2 Statistical hypothesis, model, and method of analysis amended for PFS in *PIK3CA* non-mutant cohort
- Section 10.4.4. Clarification on situation where subgroup analysis of primary endpoint will be conducted
- Section 10.5.1 Key secondary objective amended to be OS in *PIK3CA* mutant cohort only.
- Section 10.5.2 Secondary objectives of PFS and OS in *PIK3CA* non-mutant cohorts added.
- Section 10.5.3.1 Clarification on reporting of safety data added
- Section 10.5.3.2 : Language for Adverse Event (AE) reporting has been updated to reflect new protocol template
- Section 10.7 Changes to the Interim Analysis scheme reflecting changes to study design (from a pivotal to proof-of-concept design for *PIK3CA* non-mutant cohort)
- Section 10.8 Specification of the new sample size derivation for PFS in the *PIK3CA* non-mutant cohort.
- Section 10.9 Changes to the timing and assessment of statistical power for Overall Survival in the *PIK3CA* non-mutant cohort
- [redacted]
- Section 14.6 Appendix 6 – Statistical methodology has been added

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 underlined for insertions.

IRB/IEC

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]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Hormone receptor-positive breast cancer

Breast cancer (BC) is the most common cancer in women, with about 900,000 new cases annually. It is estimated that worldwide over 508,000 women died in 2011 due to breast cancer (Global Health Estimates, WHO 2013). Breast cancer in men is a more rare disease and makes up < 1% of all cases of breast cancers, but its treatment is based on the guidelines for female breast cancer (Foerster et al 2014, Agrawal et al 2007, Patten et al 2013, Giordano et al 2002).Subtypes of breast cancer are distinguished by expression of estrogen receptors (ER), progesterone receptors (PgR) and human epidermal growth factor receptor-2 (HER2), as well as by distinct gene expression profiles (Perou et al 2000; Sotiriou and Pusztai 2009). Within these subtypes 60-70% of breast tumors are HR+HER2-negative. Expression of the ER and/or PgR is one of the most important prognostic factors in invasive breast cancer. Estrogen deprivation therapy is the core treatment modality in patients with HR+ advanced breast cancer. Endocrine therapy options for postmenopausal women with ER+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer (MBC)) include selective ER modulators (SERM; tamoxifen), ER antagonists (fulvestrant), selective nonsteroidal AIs (NSAI; anastrozole and letrozole) and steroidal AIs (exemestane). Blocking estrogen signaling with tamoxifen has been the main approach in treatment for ER+ breast cancer for over 35 years. In postmenopausal women, AIs reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens in non-ovarian tissues; synthesis in these tissues is the primary source of estrogens in postmenopausal women. AIs are generally used as the first line of therapy for women with HR+ breast cancer (Beslija et al 2009; NCCN 2.2015). The combination of targeted and endocrine therapies has also been evaluated: everolimus, an mTOR inhibitor, combined with exemestane showed synergistic inhibition of the tumor proliferation and is approved for postmenopausal women with advanced HR+, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole (Baselga et al 2012, Yardley et al 2014); recently, palbociclib, a Cyclin-Dependent Kinases 4 and 6 inhibitor (CDK4/6i), has been approved in United States in combination with letrozole for the treatment of postmenopausal women with ER+, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease based on the results of the phase 2 Paloma-1 study. The addition of palbociclib to letrozole significantly prolonged PFS as compared to letrozole alone (median PFS 20.2 months versus 10.2 months (HR 0.49; 95% CI:0.32, 0.75; p=0.0004) (Finn et al 2015).

1.1.2 The PI3K pathway

The phosphatidylinositol-3-kinase (PI3K) signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso et al 2001). PI3K signaling also serves a central role in the pathogenesis of numerous forms of neoplasia. Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors and in many tumor types (Liu et al 2009). Resistance to a variety of

[redacted]

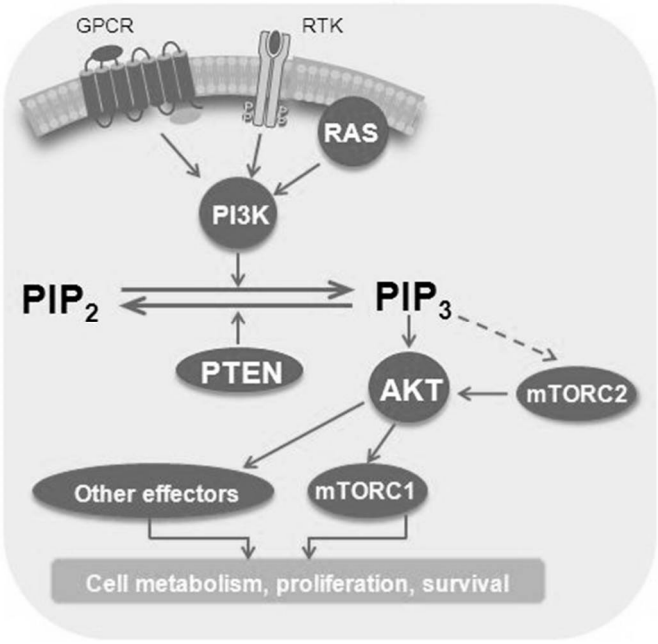
therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey et al 2006).

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

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

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

Figure 1-1 Schematic representation of the PI3K pathway



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

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gene were reported to occur in the mutational hotspots from exons 7, 9 and 20 which affect the C2, helical and kinase domains of PI3Kα respectively (Mankoo et al 2009).

1.1.3 PI3K pathway in HR+ breast cancer

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

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

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

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

Furthermore, pre-clinical data have shown that the ER pathway interacts with the PI3K pathway. Extensive crosstalk has been shown between ER and growth factor pathway (Miller et al 2011a; Osborne and Schiff 2011).

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

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

The FERGIE phase II trial was the first randomized Phase II trial investigating the combination of the pan-PI3K inhibitor pictilisib with fulvestrant 500 mg vs matching placebo with fulvestrant in patients with ER+, HER2-negative, AI-resistant advanced or metastatic breast cancer either PI3K mutant or not. One hundred sixty eight patients were randomized. The observed mPFS in the combination arm was 6.2 months vs. 3.8 months in the placebo arm (HR 0.77; 95% CI 0.50-1.19). For patients with *PIK3CA* mutation mPFS was 6.2 months in the combination compared to 5.1 months in the placebo arm (HR 0.92; 95% CI 0.48-1.76), (Krop et al 2014). Exploratory post-hoc subgroup analysis suggested a statistically significant improvement in mPFS in patients with ER+ and PgR+ tumors treated with pictilisib plus fulvestrant 7.2 vs 3.7 months (HR 0.46; 95% CI, 0.27 to 0.78). Multivariate analysis suggests

[redacted]

that this treatment effect in patients with ER+/PgR+ tumors is maintained after adjusting for possible baseline imbalances.

In the pictilisib arm an increased number of GI toxicities (mainly diarrhea, nausea, vomiting and stomatitis), rash and fatigue were observed. All hyperglycemia grades (considered also as a potential pharmacodynamic marker for PI3K pathway inhibition) were observed only in 17% of patients treated with pictilisib.

Taken together, these observations suggest that the combination of an endocrine treatment, like fulvestrant, a selective ER downregulator, and PI3K-inhibitors could be an interesting therapeutic option for patients with HR+ breast cancer.

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

1.2.1 Overview of fulvestrant

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

Fulvestrant is approved for the treatment of HR+ metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy (USA, Europe). However, also in postmenopausal women without symptomatic visceral disease also after recurrence or progression to an AI, current clinical practice and treatment guidelines include fulvestrant as treatment option (NCCN 2.2015).

Fulvestrant 250 mg monthly and exemestane were compared in the EFECT study, a double blind placebo controlled phase III trial in 693 postmenopausal women with HR+ breast cancer after recurrence or progression on a NSAI (Chia et al 2008). No difference in PFS (median 3.7 months in both arms), response rate (7.4% vs. 6.7%, respectively) or clinical benefit rate (32.2% vs. 31.5%) were observed. A recently completed phase III trial (SOFeA study) compared fulvestrant (induction with 500 mg and then 250 mg monthly), to exemestane, and to the combination of fulvestrant and anastrozole in ER+ breast cancer patients, following progression on non-steroidal AI (Johnston et al 2013). There was no evidence of difference in median PFS 4.8 months (95%CI 3.6-5.5); 3.4 months (95%CI 3.0-4.6) and 4.4 months (95%CI 3.4-5.4) respectively for the fulvestrant, exemestane and fulvestrant plus anastrozole arms.

In postmenopausal patients who experienced progression after prior endocrine therapy (either AI or tamoxifen), fulvestrant 500 mg emerged as the optimal dose based on the results of the CONFIRM study, which showed that the higher dose (500 mg monthly) significantly prolonged PFS compared to the 250 mg dose (mPFS 6.5 vs. 5.5 months; HR= 0.80; p = 0.006) (Di Leo et al 2010). More specifically, in that trial, subgroup analysis showed that PFS was prolonged in patients who had recurred or relapsed during anti-estrogen therapy (median PFS 8.6 vs. 5.8 months; HR 0.76; p = 0.013) or during AI therapy although not reaching statistical significance for the latter (median PFS 5.4 vs. 4.1 months; HR 0.85; p = 0.195) (Summary of Product

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Characteristics (SmPC) Faslodex®). Median OS (not a predefined endpoint) was 26.4 months for fulvestrant 500 mg and 22.3 months for 250 mg (HR 0.81; p = 0.02, at 75% maturity), irrespective of type of prior endocrine treatment (Di Leo et al 2013).

Recently, data have been presented for the phase II randomized study (FIRST) of fulvestrant 500 mg compared to anastrozole as a first-line therapy in postmenopausal women with HR+ advanced breast cancer who received no prior endocrine therapy for advanced disease (Robertson et al 2014). Among the 205 patients randomized, 75% of them were naïve from any endocrine treatment and 25% had received tamoxifen as adjuvant treatment. The observed clinical benefit rate (primary endpoint of the study) was 72.5% for fulvestrant vs 67% for anastrozole (HR 1.30; p = 0.386). No significant difference was observed in ORR (36% vs 35.5%). The median Time to Progression (TTP) was significantly longer for fulvestrant than anastrozole (23.4 vs 13.1 months, HR 0.66; p = 0.01). Median OS was 54.1 months for fulvestrant and 48.4 months for anastrozole (HR 0.7; p=0.041). OS was not a predefined endpoint of FIRST in the initial protocol; OS analysis was performed at 66.8% maturity. Incidence of Serious Adverse Events were similar between the arms (23.8% fulvestrant vs 21.4% anastrozole).

Fulvestrant at the dose of 250 mg did not show superior efficacy compared to tamoxifen in the same first-line setting of HR+ metastatic breast cancer where median TTP of 8.2 months was observed with fulvestrant and 8.3 months with tamoxifen (HR 1.10; p = 0.39) (Howell et al 2004). The difference in these TTPs for fulvestrant may be attributed to the higher dose of 500 mg since findings from clinical, biological studies and PK modeling suggested that fulvestrant at an increased dose could further increase the clinical efficacy (Robertson et al 2004). A caveat may be found in the small sample size of FIRST study (n= 102 for fulvestrant arm). FALCON (ClinicalTrials.gov identifier: NCT01602380), a randomized phase III study comparing fulvestrant 500 mg with anastrozole as first-line treatment for postmenopausal women with HR+ MBC, completed enrollment in September 2014; results are still pending.

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

1.2.1.1 Clinical pharmacokinetics of fulvestrant

The recommended dose (intramuscular injection) is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose. Fulvestrant is slowly absorbed reaching maximum plasma concentrations after about 5 days. Steady-state is achieved within the first month of dosing. At steady-state there is more than a 2-fold difference between mean Cmax and Cmin. After intramuscular administration, the exposure is approximately dose-proportional in the dose range of 50 to 500 mg. Fulvestrant is subject to extensive and rapid distribution. Fulvestrant is eliminated mainly by metabolism. The major route of excretion is

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via the feces with less than 1% being excreted in the urine. Fulvestrant has a high clearance, suggesting that it is a drug with a high extraction ratio. The terminal half-life after intramuscular administration is governed by the absorption rate and was estimated to be 40-50 days. An in vitro inhibition study showed no relevant inhibition of CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. The lack of inhibition of CYP3A4 was confirmed in an in vivo interaction study with midazolam. Studies using human liver preparations and recombinant human enzymes indicate that CYP3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant; however, non-P450 routes appear to be more predominant *in vivo* as interaction studies with rifampicin (CYP3A4 inducer) and ketoconazole (CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics. The relative contribution of P-450 and non-P-450 routes *in vivo* is unknown [Faslodex® Prescribing Information].The potential for interaction with fulvestrant therefore appears to be low.

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

1.2.2 Overview of alpelisib

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

Alpelisib has demonstrated anti-tumor activity in preclinical *in vitro* and *in vivo* tumor models. *In vitro*, alpelisib has been shown to preferentially inhibit the proliferation of cell lines harboring *PIK3CA* mutations (Fritsch et al 2014). *In vivo*, alpelisib has demonstrated dose-dependent tumor growth inhibition in various subcutaneous tumor transplant models. Both *in vitro* and *in vivo* tumor models (other than breast cancer) provided evidence that PTEN driven model might display a lesser sensitivity to alpelisib, in particular if the PTEN alteration is concomitant with *PIK3CA* mutation. This feature, however might not be relevant in HR+ breast cancer patients considering how rarely overlap between these alterations has been seen (see Section 1.1.3). Alpelisib is currently being investigated in Phase I dose escalation trials and in Phase Ib combination trials. Doses up to 450 mg once daily (q.d.) have been administered to patients suffering from cancer. The Maximum Tolerated Dose (MTD) of single-agent oral alpelisib has been declared at 400 mg q.d. and the recommended phase II single agent dose declared at 350 mg.

For further details on clinical and non-clinical experience, please refer to the latest version of [Alpelisib (BYL719) Investigators Brochure].

1.2.2.1 Non-clinical experience

1.2.2.1.1 Pharmacodynamics of alpelisib

In biochemical assays, alpelisib inhibits specifically p110α (IC50 = 4.6 nM,) more potently than the p110δ and γ isoforms. Alpelisib is equipotent against the most common somatic mutations of p110α (H1047R, E545K) compared to wild type p110α. The alpelisib biological activity

[redacted]

correlates with inhibition of various PI3K/AKT downstream signaling pathway components commonly used as indicators of pharmacodynamics. Please refer to the [Alpelisib (BYL719) Investigators Brochure] for further details.

In vivo, alpelisib shows dose and time-dependent inhibition of the PI3K/AKT pathway in relevant tumor xenograft models (p110α-mechanistic model and p110α-mutant xenograft models) in nude mice and rats. *In vivo* analyses of tumor tissues, upon acute dose or after repeated dosing, show a good correlation between compound exposure and PI3K pathway blockade (Fritsch et al 2014).

Finally, in breast cancer xenograft models, treatment with alpelisib led to significant decrease in AKT phosphorylation, further supporting the observation of effective inhibition of PI3K signaling (see Section 1.1.2).

1.2.2.1.2 Nonclinical PK and metabolism of alpelisib

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

In vitro metabolism and transport

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

[redacted]

Disposition of alpelisib

Elimination of alpelisib in vivo - at the current stage of knowledge - appears to be a three-parted pathway consisting of CYP450-mediated oxidative metabolism, hydrolysis to BZG791 (enzymatic or chemical, currently unknown) and biliary elimination. Recent results from human ADME trial [CBYL719X2107] have shown that the contribution of oxidative metabolism to the overall clearance of alpelisib can be considered minor, in line with in vitro metabolism results. The main circulating metabolite in human plasma was BZG791 which represented on average 21.4% of the Area Under the Curve 0-6h (AUC0-6h) (proportionately higher than in rat and dog). Other circulating metabolites (oxidative metabolite M3 and N-glucoronide M12) were considered minor, as they represented only 0.03% and 1.89% of total radioactivity in the plasma of one out of four subjects but were below the limit of quantification in the other subjects. Alpelisib and identified metabolites represented on average 94% of the plasma AUC0-6h. In terms of excretion the bulk of the dose was excreted in feces (78.8% of the dose) and urine

[redacted]

(13.1 % of the dose) with only ~2% of unchanged alpelisib in urine indicating the renal clearance is negligible. In excreta (urine and feces combined), alpelisib represented 37.8% of the administered dose, BZG791 represented 39.1%. Biliary excretion has been also previously been demonstrated in a rat excretion study showing that 25% of the dose of [14C]-alpelisib was excreted in feces with 40% of the dose being found unchanged in bile. As alpelisib is a substrate for human BCRP in vitro there is strong evidence for a hepatobiliary excretion, which is also supported by rat and human sandwich-cultured hepatocyte experiments.

1.2.2.1.3 Safety pharmacology and toxicology of alpelisib

PI3 kinase is involved in various cellular processes such as proliferation, metastasis, or energy metabolism. Therefore, it is not unexpected to observe toxic effects when cellular test systems or animals are exposed to an inhibitor of this pathway.

In accordance with current guidance, repeated-dose toxicity studies were conducted up to 13 weeks of duration, using a daily oral treatment in rats and dogs. In the 4- and 13-week studies, reversibility of toxicity findings was assessed for a 4-week treatment-free recovery period (8 weeks in the 13-week rat study). This package was complemented by *in vitro* and *in vivo* safety pharmacology studies to investigate effects on respiratory, neuronal and cardiovascular functions, an ICH-compliant genotoxicity battery and the evaluation of a phototoxic potential *in vitro*. In addition, for exploratory studies, such as insulin/glucose tolerance tests, mice were used.

Alpelisib was relatively well tolerated in the 4- and 13-week repeated-dose toxicity studies at exposure levels at which tumor growth control was achieved in mouse or rat tumor models. Alpelisib affected rapidly dividing tissues which only resulted in pharmacologically relevant observations in the animals exposed to an alpelisib dose close to or at MTD. The most frequently affected organs were the bone marrow and lymphoid tissue (spleen, thymus), the epithelia of the alimentary tract, while other tissues like the vagina and uterus in rats, or prostate in dogs were also affected at higher doses. Bone/cartilage and tooth-forming structures were only affected in rats. In dogs, epithelial effects were seen in the cornea; however, the dose-dependency of this cornea observation was not evident. No other ophthalmologic abnormalities, associated with alpelisib treatment, were observed in rats or in dogs.

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

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

In conclusion, the majority of the observed toxicological effects of alpelisib were related to the pharmacological activity of alpelisib as a p110α specific inhibitor of PI3K pathway, such as an influence on insulin (and potentially glucose) homeostasis and the risk of increased blood

[redacted]

pressure. The pharmacologically relevant toxicity was mainly observed at dosages close to or at MTD with the bone marrow and lymphoid tissue, pancreas, and some reproductive organs of both genders being the main target organs of the toxic effects (refer to the [Alpelisib (BYL719) Investigators Brochure] for further details).

1.2.2.1.4 Genotoxicity status of alpelisib and metabolites

In an *in vitro* genotoxicity package consisting of a 2-strain miniscreen Ames and a TK6 micronucleus screen, as well as International Conference on Harmonization (ICH) S2 guidance-compliant GLP tests for Salmonella reverse mutations in five strains, and chromosome aberrations in primary human lymphocytes, no evidence of a potential to induce reverse gene mutations or numerical or structural chromosome aberrations was seen for alpelisib. No elevated micronucleus frequencies were found in peripheral blood reticulocytes sampled in week 4 of the 13-week rat study. In addition, metabolite BZG791 was tested in a Salmonella reverse mutation and a micronucleus test *in vitro* and found to be free of a genotoxic potential.

1.2.2.2 Clinical experience

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

Alpelisib has been investigated both as a single agent and as combination therapy in 25 clinical studies and as of 13-May-2019, 17 studies have been completed and 9 studies are ongoing. The safety profile of alpelisib is well characterized and manageable with generally reversible AEs. The alpelisib Investigator's Brochure (IB) provides a more detailed review of the preclinical and clinical information.

The most common adverse events observed with treatment of alpelisib alone or in various combinations are hyperglycemia, rash or GI disorder (nausea, vomiting, diarrhea).

In summary, the current data indicate a favorable clinical safety profile for alpelisib.

The trial [CBYL719X2101] was a Phase IA, multicenter, open-label, dose-escalation study with a dose expansion arm of single-agent alpelisib in patients with *PIK3CA*-altered advanced solid tumors, *PIK3CA*-altered or wildtype ER+ breast cancer. Alpelisib was administered orally as a tablet using doses ranging from 30 to 450 mg q.d., and 120 to 200 mg b.i.d. The trial enrolled 132 patients with advanced solid tumors and the single agent MTD has been declared at 400 mg q.d., and RP2D at 350 mg q.d. The most frequent observed AEs were hyperglycemia (47%), nausea (46%), diarrhea (38%), decreased appetite (37%), fatigue (29%) and vomiting (27%). The most common drug-related Grade 3 or 4 adverse event was hyperglycemia (24%). Other Grade 3 or 4 AEs occurred in three patients, in all cases maculopapular rash. Among the 131 evaluable patients, confirmed partial response (PR) was observed in 7 patients (5.3%), with 8 (6.0%) that achieved an unconfirmed PR. Stable disease (SD) was observed in 68 patients (52%) with a disease control rate (CR/PR/SD) of 53%. All tumor responses were observed at alpelisib doses of 270 mg or higher (Juric 2014, Juric manuscript in preparation).

[redacted]

Overall, 20 patients with ER+, *PIK3CA*-altered, metastatic breast cancer received alpelisib as part of the Phase I study (Juric et al 2012). Sixteen out of 20 patients had received some form of chemotherapy and most patients had received multiple prior lines of therapy, including AIs, tamoxifen and fulvestrant. Hyperglycemia was observed in 13/20 patients (65%), with Grade 3 or 4 in 25% of patients. Rash was observed in 11/20 patients (55%), with Grade 3 or 4 in 15% of patients. GI events and fatigue/asthenia were also among the most commonly reported AE. Overall the safety profile of alpelisib in patients with advanced breast cancer was comparable to that seen in patients with other solid tumors. Eighteen of the 20 patients received potentially effective doses of ≥270 mg/day. Among 18 patients evaluable for radiologic response, 6 patients achieved tumor shrinkage >20%, with 2 patients demonstrating a PR (1 confirmed, 1 unconfirmed). Among the 11 patients who received study treatment for ≥16 weeks, 2 patients had PR and 9 had stable SD. Median PFS for the 20 breast cancer patients was 166 days (5.5 months; 95% CI: 110–286 days), compared with 107 days (3.5 months; 95% CI: 63–148 days) for 56 patients with other advanced solid tumors.

For further details on clinical experience, please refer to the latest version of [Alpelisib (BYL719) Investigators Brochure].

In vivo metabolism and transport

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

1.2.2.3 Clinical pharmacokinetics

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

A high-fat high-calorie meal (985 calories with 58.1 g of fat) increased alpelisib AUC by 73% and Cmax by 84%, and a low-fat low-calorie meal (334 calories with 8.7 g of fat) increased

[redacted]

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

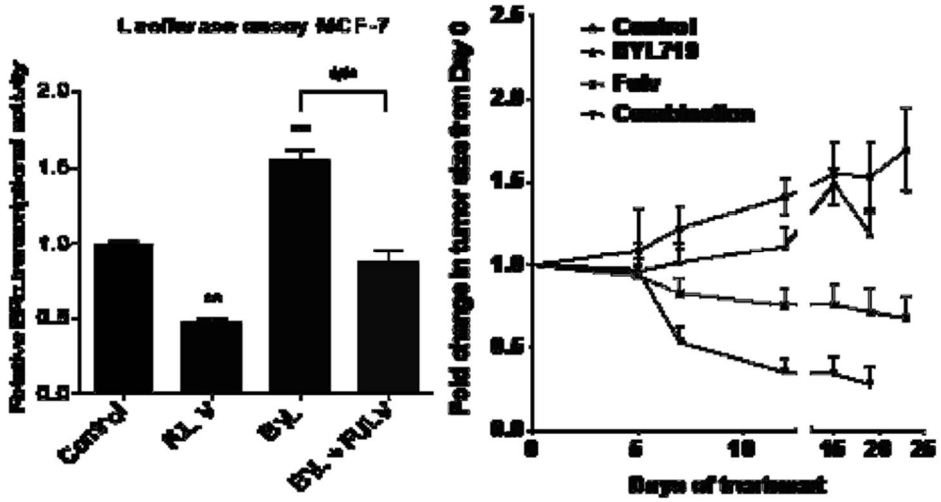
1.2.3 Overview of the combination of alpelisib and endocrine treatments

1.2.3.1 Preclinical experience

Pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy. *In vitro* combination of letrozole or fulvestrant with alpelisib in a *PIK3CA* mutant cell line of ER+ breast cancer (MCF7) displays synergy (O'Brien et al 2014) in line with the concept of synthetic lethality seen previously when PI3K was inhibited in an estrogen deprived cell line (Crowder et al 2009).

In addition it has been recently demonstrated that PI3Kα inhibition through alpelisib induces a transcriptome switch toward a more luminal (ER-driven) phenotype (Bosh et al 2013). The trend towards the more luminal signature is related to an increase in ER transcriptional (left panel of Figure 1-2) and adding a selective ER down regulator (SERD) like fulvestrant to alpelisib prevents the increase in ERα transcriptional activity effectively shutting down both ER and PI3K pathways. This can explain the tumor regression observed by the combination of fulvestrant and alpelisib and position fulvestrant as a preferred partner to alpelisib in HR+ breast cancer *in vivo* models (Figure 1-2, right panel) (Baselga in press; Bosh et al 2013).

Figure 1-2 Effect of alpelisib and fulvestrant alone or in combination on ER transcriptional activity and tumor growth in MCF7 *PIK3CA* mutant ER+ breast cancer model

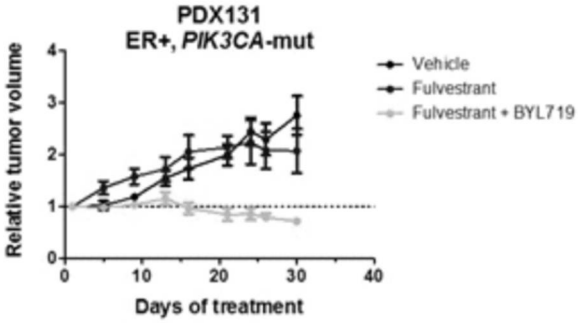


Although initial analysis demonstrated an increased sensitivity in cells carrying a *PIK3CA* mutation, further investigation using patient derived xenografts reveal a potential for the

[redacted]

combination in models presenting no mutations as well. This is illustrated in [redacted] where both [redacted] derive a [redacted] form the [redacted]

[redacted]



1.2.3.2 Clinical experience with alpelisib and aromatase inhibitors in MBC

An investigator initiated trial (IIT), phase Ib (n=26), is currently ongoing, assessing the combination of alpelisib + letrozole in previously treated HR+ HER2-negative metastatic breast cancer patients. All the patients were pretreated with AI, with 24 and 8 of them that received endocrine therapy and chemotherapy in metastatic setting, respectively. The RP2D of alpelisib in combination with letrozole was established at 300 mg q.d. Favorable safety profile was reported. Most common Grade 3 AEs at 300 mg were hyperglycemia, diarrhea (12% each), and transaminitis (6%). Overall, 5 PRs (19%) have been reported, with SD in 12 (46%). Six out 9 patients on treatment for ≥ 6 months had a *PIK3CA* mutant breast cancer, however so far the clinical activity was not restricted to patients with *PIK3CA* mutant tumors only (Mayer et al 2014).

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

[CLEE011X2107] is a phase Ib/II study investigating in three arms the combination of LEE011 (CDK4/6 inhibitor) and letrozole, alpelisib and letrozole, and LEE011 plus alpelisib and letrozole in adult patients with advanced HR+ HER2-negative MBC. Data from 17 patients have been reported, 7 of whom received alpelisib 300 mg q.d. (starting dose) + letrozole 2.5 mg. In alpelisib plus letrozole arm 2 DLTs (Grade 2 hyperglycemia) were observed and the most common of all grade AEs were hyperglycemia (57%), nausea (43%), decreased appetite (43%) and diarrhea (43%) (Munster et al 2014).

[CBYL719A2201] is a phase II randomized, double-blind, placebo-controlled, study of letrozole with or without alpelisib or buparlisib (pan-PI3K inhibitor), for the neoadjuvant

[redacted]

treatment of postmenopausal women with HR+ HER2-negative early BC. Patients are randomized in a 1:1:1 ratio within two cohorts (*PIK3CA* mutant tumors, and *PIK3CA* non-mutant). The primary objective of this study is pCR rate in each cohort. The alpelisib dose being used in this study is also 300 mg q.d.

1.2.3.3 Experience with alpelisib and fulvestrant in MBC

The combination of alpelisib with fulvestrant 500 mg q28 days was investigated as part of [CBYL719X2101] study in heavily pre-treated patients with HR+ metastatic breast cancer (median number of prior therapies = 5 [1-16] in two groups: *PIK3CA* mutant and non- mutant patients. Eighty-four patients have been enrolled (50 with *PIK3CA* mutant tumors, 31 wild-type, 3 unknown) and updated data have been recently presented (Janku et al 2014). Overall, for all dose levels, the most common all-grade AEs were diarrhea (57% of patients), hyperglycemia (45%), decreased appetite and nausea (37% each). The most frequent Grade 3 or 4 AEs were hyperglycemia (18%) and maculopapular rash (13%) (see Table 1-2). The MTD for alpelisib was declared at 400 mg, with DLTs in 4 patients (diarrhea, vomiting, decreased appetite, abdominal distension and fatigue). Also alpelisib doses of 350 mg and 300 mg q.d. were investigated and 300 mg q.d. emerged as the recommended dose in this combination for the following reasons:

- Similar level of pharmacodynamic and clinical activity were observed among the dose levels explored (300, 350 and 400 mg);
- Among the patients starting alpelisib treatment at 400 mg, 70% and 13% experienced AEs leading to dose reduction or drug discontinuation, respectively, compared to 33% and 0% respectively, among those patients treated at 300 mg
- Despite different dose levels and dose linearity shown in the single agent arm of [CBYL719X2101] study, exposure of alpelisib in the combination arm with fulvestrant was similar between 300 mg and 400 mg.

In fact, for comparison with the single agent arm, full PK profiles of alpelisib were collected on Day 1 and Day 8 of Cycle 1 and on Day 1 of Cycle 2. While median values were within the ranges observed for the 300 to 400 mg single agent cohorts, median Cmax was lower in combination with fulvestrant (~30%). Exposure (AUC0-24) at steady state was comparable at 300 mg (30500 vs. 33200 ng*h/ml) and 350 mg (30600 vs. 29500 ng*h/ml) but lower for the 400 mg cohort (28900 vs. 39600 ng*h/ml). Median Tmax remained largely unchanged (ranging between 1.8 and 3.1 hours) but median terminal T1/2 was also slightly increased (approximately 9-10 hours compared to 7 to 8 hours for single agent) at 400 mg.

Preliminary clinical efficacy of alpelisib + fulvestrant was demonstrated across all dose levels. Best overall response achieved was confirmed PR for 12 (24%) patients and SD for 28 (56%) patients with *PIK3CA* mutant tumors vs PR for 0 (0%) patient and SD for 14 (45%) patients with *PIK3CA* non-mutant tumors. Disease control rate was 80% (95% CI: 66.3–90.0) and 45% (95% CI: 27.3–64.0) in the *PIK3CA* mutant and *PIK3CA* non-mutant groups, respectively. Estimated median PFS was longer in the *PIK3CA* mutant group vs *PIK3CA* non-mutant group (8.3 months vs 4.7 months) (Janku et al 2014).

[redacted]

Table 1-2 Study [CBYL719X2101]: AEs (greater than or equal to10%) suspected to be related to study treatment

Drug related Adverse Event n (%)	Grade	Alpelisib Dose 300 mg/day n=9	350 mg/day n=8	400 mg/day n=66	All Patients (N=84)*
Diarrhea	All	5 (55.6)	5 (62.5)	36 (54.5)	48 (57.1)*
	3/4	0	0	2 (3.0)	2 (2.4)
Hyperglycemia	All	4 (44.4)	5 (62.5)	29 (43.9)	38 (45.2)
	3/4	0	2 (25.0)	13 (19.7)	15 (17.9)
Decreased appetite	All	1 (11.1)	4 (50.0)	26 (39.4)	31 (36.9)
	3/4	0	0	1 (1.5)	1 (1.2)
Nausea	All	4 (44.4)	5 (62.5)	22 (33.3)	31 (36.9)
	3/4	0	0	0	0
Fatigue	All	3 (33.3)	6 (75.0)	15 (22.7)	26 (31.0)*
	3/4	0	0	3 (4.5)	3 (3.6)
Stomatitis	All	2 (22.2)	3 (37.5)	18 (27.3)	23 (27.4)
	3/4	0	0	1 (1.5)	1 (1.2)
Vomiting	All	3 (33.3)	1 (12.5)	17 (25.8)	21 (25.0)
	3/4	0	0	1 (1.5)	1 (1.2)
Rash	All	3 (33.3)	4 (50.0)	8 (12.1)	15 (17.9)
	3/4	0	1 (12.5)	5 (7.6)	6 (7.1)
Rash (maculopapular)	All	0	2 (25.0)	13 (19.7)	15 (17.9)
	3/4	0	2 (25.0)	9 (13.6)	11 (13.1)
Dysgeusia	All	3 (33.3)	1 (12.5)	10 (15.2)	14 (16.7)
	3/4	0	0	0	0
Asthenia	All	1 (11.1)	3 (37.5)	7 (10.6)	11 (13.1)
	3/4	0	0	0	0
Dry skin	All	1 (11.1)	2 (25.0)	7 (10.6)	10 (11.9)
	3/4	0	0	0	0
Pruritus	All	1 (11.1)	3 (37.5)	6 (9.1)	10 (11.9)
	3/4	0	0	2 (3.0)	2 (2.4)

1.2.4 Potential for drug interactions

1.2.4.1 Potential overlapping toxicities

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

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

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

1.2.4.2 Potential for drug-drug interactions with fulvestrant

The potential for a drug-drug interaction between fulvestrant and co-administered drugs is considered low. There are no known drug interactions with fulvestrant. In vitro studies showed no relevant inhibition of the major CYP enzymes, including CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. The lack of inhibition of CYP3A4 was confirmed in an in vivo interaction study with midazolam. In addition, interaction studies with rifampicin (strong CYP3A4 inducer) and

[redacted]

ketoconazole (strong CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics. Therefore, a DDI involving fulvestrant and alpelisib are unlikely to occur [Faslodex® Prescribing Information].

However, due to the slightly reduced exposure of alpelisib observed in [CBYL719X2101] in combination with fulvestrant compared to single agent (see Section 1.2.3.3), pharmacokinetics of alpelisib in combination with fulvestrant will be explored in this study in a larger population using a population PK approach to assess whether fulvestrant affects the pharmacokinetics of alpelisib. The effect of alpelisib on fulvestrant will also be assessed by comparative trough analysis in the treatment arms.

2 Rationale

2.1 Study rationale and purpose

The purpose of this study is to determine whether treatment with alpelisib plus fulvestrant prolongs PFS compared to fulvestrant and placebo in men and postmenopausal women with HR+, HER2-negative advanced breast cancer which progressed on or after AI treatment.

As described in Section 1.2.3.1, promising pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy, in particular fulvestrant (O'Brien et al 2014). Furthermore clinical activity has been observed with single agent alpelisib in heavily pre-treated ER+ breast cancer patients and when alpelisib was given in combination with fulvestrant AI to HR+ HER2-negative metastatic breast cancer patients (Janku et al 2014; Mayer et al 2014).

Rationale for enrolling all patients (*PIK3CA* mutant and non-mutant)

Up to 45% of HR+ breast cancers present with a mutation in the *PIK3CA* gene, and thus these tumors may be particularly suited to treatment with the alpha specific PI3K inhibitor alpelisib. More specifically, about 30% of patients' tumors display a *PIK3CA* mutation identified as one of the most frequently reported hotspots. While *PIK3CA* mutant cell lines display an increased sensitivity to alpelisib treatment (Fritsch et al 2014), sensitivity to alpelisib in combination with fulvestrant was observed in both *PIK3CA* mutant and wild-type ER+ *in vivo* models (see Figure 1-3, Section 1.2.3.1). Indeed, HR+ breast cancer – particularly if previously treated with endocrine agents - may display a dependency on the PI3K pathway that is independent of a *PIK3CA* mutation and hence confer a level of sensitivity to alpelisib in non-*PIK3CA* mutant breast cancer tumors as well.

In addition, although preliminary phase I data suggest a better outcome (i.e. response rate, clinical benefit rate, PFS) in *PIK3CA* mutant breast tumors when treated with alpelisib (either in monotherapy or combination with an endocrine agent), some patients without identified mutations benefitted as well (Mayer et al 2014; Dickler et al 2014, Janku et al 2014). Overall the current pre-clinical and clinical findings show an increased efficacy of the combination of alpelisib and fulvestrant in *PIK3CA* mutant HR+ BC patients, while suggesting that this combination may also have some activity in *PIK3CA* non-mutant HR+ BC patients.

To assess the treatment effect of alpelisib specifically in *PIK3CA* mutant and non-mutant patients, two cohorts are considered:

[redacted]

- One pivotal cohort aiming at confirming the activity of the combination of alpelisib and fulvestrant in *PIK3CA* mutant HR+ BC patients
- One "proof-of concept" cohort aiming at further evaluating the anti-tumor activity of the combination of alpelisib and fulvestrant in *PIK3CA* non-mutant HR+ BC patients

Within each of these cohorts patients will be randomized and treated in a 1:1 fashion between alpelisib plus fulvestrant and placebo plus fulvestrant.

2.2 Rationale for the study design

This study is a multicenter, randomized, double-blind, placebo controlled phase III trial. Patients will be randomized to receive alpelisib in combination with fulvestrant or placebo in combination with fulvestrant. After molecular assessment of *PIK3CA* mutation status, patients will be assigned to one of the following two cohorts:

- Cohort I; *PIK3CA* mutant: Patients with a confirmed *PIK3CA* mutation as per protocol definition
- Cohort II; *PIK3CA* non-mutant: Patients without evidence of *PIK3CA* mutation as per protocol definition.

PIK3CA mutant status will be defined as follows: *PIK3CA* mutation will be identified by analyzing the *PIK3CA* gene for hotspots known to impact the PI3K function in exons 7, 9 and 20 (see Section 7.2.4.1). [redacted]

PIK3CA non-mutant status will be defined as follows: all analysis for *PIK3CA* mutation are interpretable and do not show evidence of a mutation in the *PIK3CA* gene for the defined hotspots on Exons 7, 9 and 20.

If the analysis for *PIK3CA* gene was not fully interpretable, i.e. at least one hot-spot is providing a non-interpretable read out, the patient is not eligible for the trial.

To avoid any bias, sites will be kept blinded to *PIK3CA* mutation status provided by the Novartis designated laboratory.

Based on Novartis Internal Data obtained on a similar population, frequency of *PIK3CA* mutation status as defined above in HR+ breast cancer is expected to be approximately 30% for this study.

Randomization will be stratified by the following factors (see Section 4.1 for further details):

1. Lung and/or liver metastases (yes versus no)
2. Previous treatment with any CDK4/6 inhibitor (yes versus no).

It is well known that visceral involvement is a prognostic factor in the clinical outcome of breast cancer patients. Patients with visceral involvement like lung and/or liver metastases have a shorter PFS compared to patients with no visceral involvement (Clark et al 1987).

Currently no data are available if and how pretreatment with a CDK4/6 inhibitors may impact the outcome of any subsequent treatment with fulvestrant and/or PI3K inhibitors, or may have any prognostic value. However, recently the CDK4/6 inhibitor palbociclib in combination with

[redacted]

letrozole showed a strong PFS advantage over single agent letrozole (that led to palbociclib approval in USA). Therefore, CDK4/6 inhibitor pretreatment may have an important impact on any subsequent treatment and may lead to different outcome compared to what currently estimated according to published data (based on CDK4/6 inhibitors naïve patients). Stratification of randomization based on previous CDK4/6 inhibitors treatment in the current study will prevent imbalance between the two treatment arms in each cohort.

To avoid any unforeseen impact on the overall study results, for the reasons stated above and the lack of data, the total number of patients pre-treated with any CDK4/6 inhibitor will be limited to 30% of the overall study population.

2.3 Rationale for dose and regimen selection

In study [CBYL719X2101] single agent MTD has been declared at 400 mg q.d., and RP2D at 350 mg q.d.

As described in Section 1.2.3.3, the recommended dose for alpelisib in combination with fulvestrant in the same clinical trial was 300 mg q.d. Pharmacokinetic data and longitudinal tumor size measurements from [CBYL719X2101] were used for population pharmacokinetic (PopPK) and pharmacodynamic modelling of tumor growth to describe the time course of tumor response (anti-tumor efficacy) in relation to drug systemic exposure and simulate the anti-tumor activity of different doses and regimens of alpelisib for the single agent arm (De Buck et al 2014). The pharmacodynamic model consisted of a sigmoid Emax tumor growth model with a zero order rate tumor growth constant (Kgrowth), a first order tumor death rate constant (Kdeg), the maximum pharmacodynamic effect (Emax) and IC50 as the plasma drug concentration at 50% of the maximal inhibitory effect. The IC50 for tumor growth inhibition was estimated to be 101 ng/ml (95% CI:40.6-179), corresponding to a free drug estimate of about 10 ng/ml (fraction unbound 0.108) which is in close agreement to the *in vitro*-based inhibitory potential against the kinase activity of recombinant PI3Kα (IC50 of ~4.6 ng/ml) and in Rat1-myr-p110α cells (IC50 = 74 nM or 32.7 ng/ml; free drug IC50 of ~18 ng/ml, free fraction in cellular assay ~0.55) (Fritsch et al 2014). The calculated IC80 by the Hill equation was 404 ng/ml. In [CBYL719X2101] median trough levels (Cmin) at steady state were found to be > 101 ng/ml at doses greater than 180 mg QD (Novartis Internal Data). Based on this model simulation were conducted showing that the minimum dose to achieve tumor regression was between 135 and 136 mg QD, therefore doses of 250 mg and 200 mg (in case dose reductions are required per protocol) can be considered as effective doses.

In addition, alpelisib 300 mg q.d. was also the selected starting dose or emerged to be the best tolerated dose in combination with AIs (Mayer et al 2014; Dickler et al 2014; Munster et al 2014; CBYL719A2201 study) (see Section 1.2.3.2 and Section 1.2.3.3).

Therefore, in this clinical trial alpelisib will be given at the dose of 300 mg q.d. together with fulvestrant administered as per the product labeling (Faslodex® EU SmPC and US PI): 500 mg given intra-muscularly (i.m.) at Day 1, 15 of Cycle (month) 1 and Day 1 of every cycle (month) thereafter. In this study, a cycle is defined as 28 days ± 3 days.

2.4 Rationale for choice of combination drugs

The rationale to combine alpelisib with fulvestrant is based on the following:

[redacted]

- The demonstrated efficacy of fulvestrant in this patient population (Section 1.2.1)
- Synergism between PI3K inhibition with alpelisib and the effect of fulvestrant seen in preclinical experiments the combination being significantly more effective than each drug taken separately (Section 1.2.3)
- No drug-drug interaction between alpelisib and fulvestrant and same pharmacokinetic results for alpelisib in the combination with fulvestrant compared to single agent alpelisib [CBYL719X2101 study] (Section 1.2.4.2)
- Preliminary preclinical and clinical data suggesting acceptable safety profile of the combination [CBYL719X2101 study] (Section 1.2.3.3)
- Preliminary promising clinical activity [CBYL719X2101 study].

2.5 Rationale for choice of comparators drugs

Patients enrolled in the study will either be in first line or in second line for the treatment of their metastatic disease.

In first line setting, currently approved treatment options include tamoxifen, AI or palbociclib in combination with letrozole.

The recently presented data from the FIRST study, conducted in HR+ HER2-negative advanced breast cancer patients with no prior endocrine therapy or with long DFS after adjuvant endocrine therapy, showed superiority of fulvestrant 500 mg compared to anastrozole (Robertson 2014). Despite methodological limitations linked to indirect comparisons, the benefit brought by fulvestrant over anastrozole appears to be of the same extent than the one brought by the addition of palbociclib to letrozole. FALCON (ClinicalTrials.gov identifier: NCT01602380), a randomized phase III study comparing fulvestrant 500 mg with anastrozole as first-line treatment for postmenopausal women with HR+ MBC, completed enrollment in September 2014; results are still pending.

Taken together, these data support fulvestrant 500 mg as an acceptable therapy in the first-line metastatic setting.

In second line setting, several acceptable options are available (NCCN 2.2015) 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).

In conclusion, fulvestrant at the selected dose of 500 mg given intramuscularly at one month intervals, with an additional 500 mg dose given 2 weeks after the initial dose, is considered an appropriate comparator arm for this study (see also Section 1.2.1).

2.6 Risks and benefits

2.6.1 Potential benefit for participants

Treatment with alpelisib in combination with fulvestrant may result in an improved clinical benefit compared to fulvestrant alone in men and postmenopausal women with HR+, HER2-

[redacted]

negative advanced breast cancer, which progressed on or after AI treatment. All patients enrolled in this trial will receive an active endocrine therapy for their disease (see Section 2.5). Based on preclinical and preliminary clinical data (see Section 1.2.3), treatment with alpelisib in combination with fulvestrant is expected to be well tolerated and it is hypothesized that it will result in delayed disease progression by inhibiting proliferation of endocrine-resistant breast cancer cells.

For further details on clinical safety, please refer to Section 1.2.2 and the latest version of [Alpelisib (BYL719) Investigators Brochure].

2.6.2 Potential risks to clinical trial participants

Patients in this study will be carefully monitored for key toxicities that have been observed with alpelisib (see Section 1.2.2), fulvestrant (see Section 1.2.1) or the combination of both (see Section 1.2.3) with the following assessments (see Section 7): periodic laboratory, renal and liver function, urinalysis and ECG.

Risk will be further minimized by adherence to inclusion/exclusion selection criteria (see Section 5), avoidance of prohibited medication (see Section 6.4.3), close safety monitoring (see Section 8) and dose adjustment guidelines (see Section 6.3 and current fulvestrant prescribing information [Faslodex® prescribing information]. PK sampling will be conducted in patients to assess plasma concentration of the study drug to evaluate any potential drug interaction. An independent data monitoring committee (DMC) (see Section 8.6) will be constituted and will monitor safety, efficacy and available PK data as outlined in the protocol. A Steering Committee (SC) (see Section 8.7) will be established comprising of investigators and Novartis personnel participating in the trial to ensure transparent management of the trial according to the protocol. A Novartis Safety Management Team (SMT) periodically reviews and evaluates all emerging data across the alpelisib program for potential safety signal assessment in a timely manner.

2.6.3 Risks related to study procedures

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

2.6.4 Risk management strategies

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

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

3 Objectives and endpoints

Objectives and related selected endpoints are described in Table 3-1 below. More details are described in Section 10 as referred in the Table 3-1.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
● To determine whether treatment with alpelisib in combination with fulvestrant prolongs PFS compared to treatment with placebo in combination with fulvestrant for patients with *PIK3CA* mutant status	PFS based on local radiology assessments and using RECIST 1.1 criteria in the *PIK3CA* mutant cohort	
Key secondary		Refer to Section 10.5.1
To determine whether treatment with alpelisib in combination with fulvestrant prolongs overall survival (OS) compared to treatment with placebo in combination with fulvestrant for patients with *PIK3CA* mutant status	OS in the *PIK3CA* mutant cohort	
Other secondary		Refer to Section 10.5.2
● To establish proof of concept of treatment benefit with alpelisib in combination with fulvestrant with respect to PFS for patients with PIK3CA non-mutant status	PFS based on local radiology assessments and using RECIST 1.1 criteria in the *PIK3CA* non-mutant cohort	
● To evaluate the two treatment arms with respect to OS for patients with *PIK3CA* non-mutant status	OS in the *PIK3CA* non-mutant cohort	
● To evaluate the two treatment arms and cohorts of interest with respect to overall response rate (ORR), clinical benefit rate.	ORR and CBR in each of the *PIK3CA* mutant and non-mutant cohorts	
● To evaluate the two treatment arms and cohorts of interest with respect to time to deterioration of ECOG performance status.	Time to definitive deterioration of the ECOG performance status of the score from baseline in each of the *PIK3CA* mutant and non-mutant cohorts	
● To evaluate the safety and tolerability of alpelisib in combination with fulvestrant	● Type, frequency and severity of adverse events per CTCAEv4.03 ● Type, frequency and severity of laboratory toxicities per CTCAEv4.03	Refer to Section 10.5.3
● To evaluate change in global health status/QOL in the two treatment arms and cohorts of interest	● Time to 10% deterioration in the global health status/QOL scale score of the EORTC QLQ-C30 ● Change from baseline in the global health status/QOL scale score of the EORTC QLQ-C30 in each of the *PIK3CA* mutant and non-mutant cohorts	Refer to Section 10.5.4

[redacted]

Objective	Endpoint	Analysis
● To characterize the pharmacokinetics (PK) of fulvestrant and alpelisib when given in combination with fulvestrant.	Summary statistics for PK: plasma concentration-time profiles of alpelisib given in combination with fulvestrant and appropriate individual PK parameters based on population PK model Summary statistics of fulvestrant trough plasma concentrations in each treatment arm (alpelisib/placebo)	Refer to Section 10.5.5
● To evaluate the association between *PIK3CA* mutation status as measured in ctDNA at baseline with PFS upon treatment with alpelisib.	PFS based on local radiology assessments and using RECIST 1.1 criteria for each of (i) patients with *PIK3CA* mutant status and (ii) patients with *PIK3CA* non-mutant status as measured in ctDNA at baseline.	
[redacted]		Refer to Section 10.6
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	Refer to Section 10.5.4
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

[redacted]

4 Study design

4.1 Description of study design

This is a randomized, double blind, placebo controlled, international multi-center Phase III trial to determine the efficacy and safety of treatment with fulvestrant + alpelisib versus fulvestrant + placebo in men and postmenopausal women with HR+ HER2-negative advanced breast cancer which progressed on or after AI treatment.

PFS, as assessed by the local radiologists/investigators and using RECIST 1.1 criteria will be the primary endpoint. PFS as assessed through Blinded Independent Review Committee (BIRC) will be used for supportive evidence of the primary efficacy endpoint.

This study will consist of 4 phases: screening (35 days), randomized treatment, post-treatment disease progression follow-up, and post-treatment survival follow-up. Patients will be treated until disease progression, unacceptable toxicity, or discontinuation from the study treatment for any other reason.

In the randomized treatment phase, patients will be randomized 1:1 to receive:

- Control arm (Arm A): fulvestrant (500 mg intramuscular [as two 5 ml injections] on Day 1 and 15 of Cycle 1 and on Day 1 ± 3 days of every Cycle thereafter + Placebo (by mouth once daily, in a 28-day cycle)

  OR
- Experimental arm (Arm B): fulvestrant (500 mg intramuscular [as two 5 ml injections] on Day 1 and 15 of Cycle 1 and on Day 1 ± 3 days of every Cycle thereafter + Alpelisib (300 mg by mouth once daily, in a 28-day cycle)

A total of approximately 560 patients will be enrolled; in which approximately 340 and 220 patients will be enrolled respectively to each of two cohorts: *PIK3CA* mutant and *PIK3CA* non-mutant. Within each of these two cohorts, randomization will be stratified by:

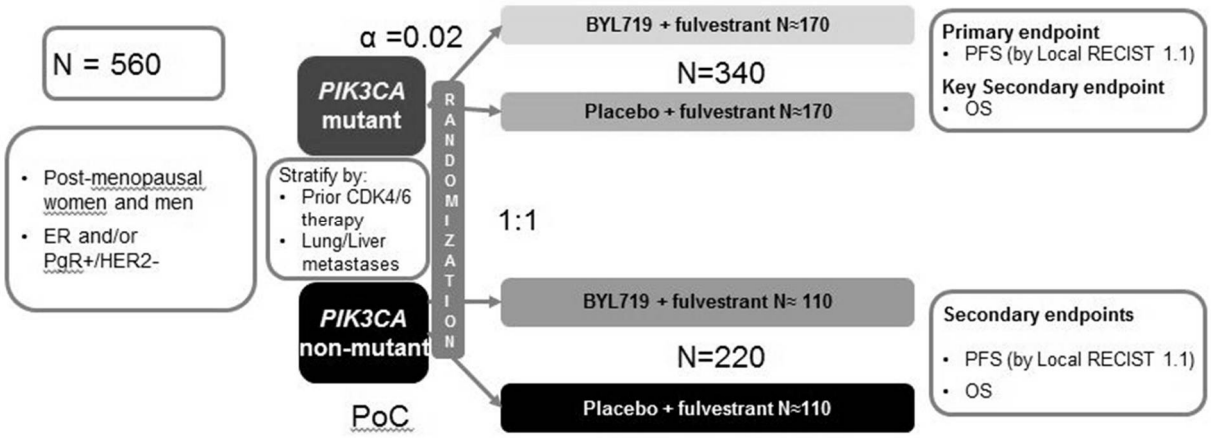
1. Lung and/or liver metastases (yes versus no)
2. Previous treatment with any CDK4/6 inhibitor (yes versus no)

The total number of patients pre-treated with any CDK4/6 inhibitor will be limited to 30% of the total number of patients.

One futility interim analysis is planned for the primary efficacy endpoint (PFS) in the *PIK3CA* mutant cohort at the expected time given in Section 10.8. There is no intention to stop for superiority at this interim analysis. Another interim analysis that allows the study to stop for superior efficacy is planned in the *PIK3CA* mutant cohort, after all patients have been randomized and approximately 75% of the total PFS events have been documented, as per local assessments. If PFS is statistically significant, interim analyses for OS will also be conducted as detailed in Section 10.5.1 and Section 10.7.

[redacted]

Figure 4-1 Study design



An independent data monitoring committee (DMC) will be constituted and will monitor safety and efficacy as outlined in Section 8.6 and Section 10.7. A Study Steering Committee (SSC) will be established comprising investigators participating in the trial to ensure transparent management of the study according to the protocol through recommending and approving modifications as outlined in Section 8.7.

Patients will receive treatment until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Patients will still be followed for efficacy when discontinuing study treatment for any reason other than disease progression or death. Patients will be followed for survival regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up). Treatment crossover from placebo to alpelisib will not be permitted in this study.

This study will use an Interactive Response Technology (IRT) for patient screening, enrollment, randomization, discontinuation, stratification and alpelisib/placebo study medication management. In addition the IRT will manage the limitation of the number of patients with prior CDK4/6 inhibitors treatment up to 30% of the total number of the patients (see Section 2.2). If the study will continue in both cohorts to the final analyses, the maximum total number of CDK4/6 inhibitors pretreated patients will be 168.

4.1.1 Screening phase

At screening, the patient will provide a signed informed consent form prior to any study related activities. Signed informed consent will be obtained as early as Day−35. Collection and shipment of tumor sample (archived tissue or new biopsy) to Novartis designated laboratory should occur as soon as possible as early as Day-35 and no later than Day−21. The tumor sample will serve to establish the *PIK3CA* mutation status for randomization. It is recommended to wait for the central *PIK3CA* testing results before conducting other screening assessments. Additional screening evaluations must be performed within 28 days before treatment start; physical examinations and laboratory assessments will be performed within 14 days before treatment start (see Section 7 for more details).

Patients will be screened in IRT only once patient has provided signed informed consent form.

[redacted]

4.1.2 Treatment phase

Patient eligibility will be checked once all screening procedures are completed. An eligibility review and confirmation will be embedded to the IRT system. Please refer to and comply with detailed guidelines in the IRT manual. Once the *PIK3CA* mutation status is identified by the Novartis designated laboratory, the IRT system will confirm the inclusion of eligible patients and randomize them in a 1:1 ratio to one of the two treatment groups described in Section 4.1.

Sites will be kept blinded to *PIK3CA* mutation status provided by the Novartis designated laboratory.

In order to assess any potential impact of fulvestrant on the pharmacokinetics of alpelisib, sparse and trough PK samples for alpelisib and fulvestrant will be collected in approximately 200 patients from selected centers; trough PK samples will be collected for alpelisib and fulvestrant in all other patients as detailed in Section 7.2.3.

Patients will receive treatment until disease progression (assessed by RECIST 1.1), unacceptable toxicity, death or discontinuation from treatment for any other reason. Efficacy and safety monitoring will continue as per visit schedule (Table 7-1).

All antineoplastic therapies given after the last dose of the study drug unless patient is lost to follow-up, or withdraws consent will be recorded in the electronic Case Report Forms (eCRFs).

4.1.3 Safety follow-up

After discontinuation of study treatment, all patients will be followed for safety, AEs and patient reported outcomes (PROs) which will be collected until 30 days after last study therapy administration, except in case of death, loss to follow-up or withdrawal of consent. For details please refer to Section 7.1.5.

4.1.4 Efficacy follow-up

Patients who discontinue treatment for reasons other than disease progression or withdrawal of consent for efficacy follow-up, will continue to be followed every 8 weeks ± 1 week for efficacy (i.e., tumor assessments and PROs) during the first 18 months and every 12 weeks ± 1 week until 36 months, then change to as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision. All scans will be acquired and analyzed for primary endpoint locally and will be sent to the Contract Research Organization (CRO) designated by Novartis for central imaging interpretation. If a patient starts a new antineoplastic treatment without withdrawing consent, the patient will continue to be followed for efficacy according to above specified protocol schedule until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision. For further details please refer to Table 7-1 and Section 7.1.6.

4.1.5 Survival follow-up

All patients will be followed for survival once they discontinue study treatment and tumor evaluations until the final number of OS events have been reached or the study is stopped for other reasons. Survival follow-up will be done every 12 weeks ± 1 week or earlier if a survival update is required to meet safety or regulatory needs. Survival information can be obtained by

[redacted]

clinical visits or telephone calls (Section 7.1.8) until death, the patient is lost to follow-up, or the patient withdraws consent for survival follow-up.

During the survival follow-up, in addition, subsequent [redacted] will be collected along with the [redacted] on subsequent therapies to assess [redacted]

4.2 Timing of interim analyses and design adaptations

Interim analyses for both the primary endpoint (PFS) and key secondary endpoint (OS) are planned for this study, in the *PIK3CA* mutant cohort. Interim analyses for the secondary endpoint, OS, in the *PIK3CA* non-mutant cohort are also planned.

An interim analysis that allows the cohort to stop for futility (non-binding) is planned after approximately 40% PFS events in the *PIK3CA* mutant cohort have been documented per local assessments. Another interim analysis that allows the cohort to stop for superior efficacy is planned after all patients in the *PIK3CA* mutant cohort have been randomized and approximately 75% PFS events have been documented, as per local assessments.

If PFS is statistically significant in either cohort, interim analyses for OS in that cohort will also be conducted. The interim analyses for OS will allow early stopping of the study for evidence of overwhelming efficacy of the alpelisib combination treatment compared to placebo. A maximum of three analyses are planned for OS in each cohort as detailed in Section 10.5.1 and Section 10.7.

4.3 Definition of end of the study

The end of the study for a given patient is defined as when the patient permanently discontinues study treatment with alpelisib + fulvestrant or placebo + fulvestrant and all the end of trial procedures are completed. The end of the overall study is defined as the time point when data collection will stop in both cohorts and the final analysis of the study will occur.

The primary analysis will occur when approximately the required number of PFS events is reached (refer to Section 10.8). The primary clinical study report (CSR) will be produced once the required number of PFS events is reached.

If the enrollment in the *PIK3CA* mutant cohort is stopped due to futility at the interim analysis or if the primary PFS analysis in the *PIK3CA* mutant cohort does not demonstrate a statistically significant treatment effect, then all subjects in each cohort will be followed for safety until 30 days post last dose and data collection will stop after all patients have discontinued study treatment and completed the safety follow-up period.

In the *PIK3CA* mutant cohort, if the primary endpoint of PFS is statistically significant the study will remain open, then patients still being followed, including patients in the *PIK3CA* non-mutant cohort, continue as per the schedule of assessments.

The study will end once the final OS analysis in the *PIK3CA* mutant cohort is performed approximately when the required number of deaths is observed or when statistical significance is reached for OS analysis (see Section 10) and the final analysis of study data is conducted. All available data from all patients in each cohort up to this cut-off date will be analyzed.

[redacted]

Patients continuing to derive benefit from study treatment in the opinion of the investigator at the end of the study will be able to continue receiving trial therapy on an individual basis (e.g. separate protocol or Novartis providing study treatment to the investigator as per local regulations).

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the assessments described in Section 7 for a discontinued or withdrawn patient should be performed. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The study will include men and postmenopausal women with HR+, HER2-negative advanced (loco regionally recurrent not amenable to curative therapy or metastatic) breast cancer which progressed on or after AI treatment.

Patients with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment will not be included in this study.

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

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

5.2 Inclusion criteria

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

Written informed consent must be obtained prior to any screening procedures

1. Patient is an adult ≥ 18 years old at the time of informed consent and has signed informed consent before any trial related activities and according to local guidelines.
2. Patient has adequate tumor tissue for the analysis of *PIK3CA* mutational status by a Novartis designated laboratory. One new or recent biopsy (collected at screening if feasible) or archival tumor block or slides (15 slides minimum from a surgical specimen, 20 slides minimum from a biopsy) must be provided. It is recommended to provide a tumor sample collected after the most recent progression or recurrence.
3. Patient has identified *PIK3CA* status (mutant or non-mutant; determined by a Novartis designated laboratory).
4. If female, then the patient is postmenopausal. Postmenopausal status is defined either by:
    - Prior bilateral oophorectomy

[redacted]

- 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 (NCCN.2.2015). Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression in this trial.

5. Patient has radiological or objective evidence of recurrence or progression.
6. Patient has a histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ breast cancer by local laboratory.
7. Patient has HER2-negative breast cancer defined as a negative in situ hybridization test or an 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.
8. Patient has either:
   - Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria (a lesion at a previously irradiated site may only be counted as a target lesion if there is clear sign of progression since the irradiation) OR
   - If no measurable disease is present, then at least one predominantly lytic bone lesion must be present (patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation).
9. Patient has advanced (loco regionally recurrent not amenable to curative therapy or metastatic) breast cancer.

   Patients may be:
   - relapsed with documented evidence of progression while on (neo) adjuvant endocrine therapy or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease
   - relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression while on or after only one line of endocrine 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 therapy

Note: i) Patients with newly diagnosed endocrine treatment naïve advanced breast cancer, ii) ii) Patient who relapsed with documented evidence of progression on/or within 12 months from completion of adjuvant endocrine therapy and then subsequently relapsed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an AI) for metastatic disease will NOT be included in the study.

10. Patient has recurrence or progression of disease during or after AI therapy (i.e. letrozole, anastrozole, exemestane). AI therapy does not need to be the latest treatment regimen.
11. Patient has an ECOG performance status 0 or 1

[redacted]

12. Patient has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory for eligibility):
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    - Platelets $\geq 100 \times 10^9$/L
    - Hemoglobin ≥ 9.0 g/dL
    - Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ grade 1 according to NCI-CTCAE version 4.03 if judged clinically not significant by the investigator
    - Potassium within normal limits, or corrected with supplements
    - International Noramlized Ratio (INR) ≤1.5
    - Creatinine Clearance ≥ 35 mL/min using Cockcroft-Gault formula
    - In absence of liver metastases, ALT and AST ≤ 2.5 × ULN. If the patient has liver metastases, ALT and AST ≤ 5 × ULN
    - Total bilirubin < ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
    - Fasting plasma glucose (FPG) ≤ 140 mg/dL (7.7 mmol/L)* and Glycosylated Hemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met)
    - Fasting Serum amylase ≤ 2 × ULN
    - Fasting Serum lipase ≤ ULN

*For patients with FPG ≥ 100 mg/dL and/or HbA1c ≥5.7% (i.e. threshold for pre-diabetes) at screening, -recommend lifestyle changes according to ADA guidelines, i.e. dietary advice (e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrate intake over the course of the day, three small meals and 2 small snacks rather than one large meal) and exercise. A consultation with a diabetologist is highly recommended.

5.3 Exclusion criteria

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

1. Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment.
2. Patient has received prior treatment with chemotherapy (except for neoadjuvant/ adjuvant chemotherapy), fulvestrant, any PI3K, mTOR or AKT inhibitor
3. Patient has a known hypersensitivity to alpelisib or fulvestrant, or to any of the excipients of alpelisib or fulvestrant.
4. Patient with inflammatory breast cancer at screening.
5. Patient is concurrently using other anti-cancer therapy.
6. Patient has had surgery within 14 days prior to starting study drug or has not recovered from major side effects.
7. Patient has not recovered from all toxicities related to prior anticancer therapies to NCI CTCAE version 4.03 Grade ≤1. Exception to this criterion: patients with any grade of alopecia are allowed to enter the study.
8. Patients with Child pugh score B or C.

[redacted]

9. Patient 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) and/or from whom ≥ 25% of the bone marrow was irradiated.
10. Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
11. Patient has central nervous system (CNS) involvement
    If patient is fulfilling the following 3 criteria she/he is eligible for the trial.
    - completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study and
    - Central Nervous System (CNS) tumor is clinically stable at the time of screening and
    - patient is not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases
12. Patients with an established diagnosis of diabetes mellitus type I or not controlled type II (based on FPG and HbA1c, see inclusion criterion 12)
13. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
14. Patient has a known history of Human Immunodeficiency Virus (HIV) infection (testing not mandatory)
15. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate patient participation in the clinical study (e.g. chronic active hepatitis, severe hepatic impairment, etc.)
16. Patient has currently documented pneumonitis (chest CT scan performed at baseline for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).
17. Patient 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 12 months prior to the start of study treatment
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
    - Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by MUGA scan or ECHO
    - History of any cardiac arrhythmias, (e.g. ventricular tachycardia), complete left bundle branch block, high grade AV block (e.g. bifascicular block, Mobitz type II and third degree AV block), supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months.

[redacted]

- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.
- Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
  - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
  - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause TdP that cannot be discontinued or replaced by safe alternative medication
- Bradycardia (heart rate < 50 at rest), by ECG or pulse.
- On screening, inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or corrected QT (QTcF) >450 msec for males and >460 msec for females (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs).

18. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to the start of the treatment:
    - That have a known risk to prolong the QT interval or induce TdP.
    - Herbal preparations/medications
19. Patient 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).

20. Sexually active males unless they are sterilized (at least 6 months prior to screening) or use a condom during intercourse while taking drug and for at least 8 months after stopping alpelisib and/or Fulvestrant medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
21. Participation in a prior investigational study within 30 days prior to the start of study treatment or within 5 half-lives of the investigational product, whichever is longer.
22. Not able to understand and to comply with study instructions and requirements.
23. History of acute pancreatitis within1 year of screening or past medical history of chronic pancreatitis
24. Patient who relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease

[redacted]

6 Treatment

6.1 Study treatment

For this study, the term "investigational drug" refers to Novartis study drug alpelisib. Fulvestrant is also being used in this study. Study treatment in this study refers to the combination of drugs in each of the study arms and includes alpelisib/placebo and fulvestrant. This is a double blind placebo controlled study, the investigator and patient will be blinded (i.e. will not know if the patient is receiving alpelisib or placebo). The storage conditions for the alpelisib/placebo will be described on the medication label.

Novartis Drug Supply Management or its designee will provide alpelisib and placebo as 50 mg and 200 mg tablets as individual patient supply, packaged in bottles. Alpelisib will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area.

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

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

6.1.1 Dosing regimen

All eligible patients will be randomized to receive either:

- Alpelisib 300 mg p.o. + fulvestrant 500 mg i.m. or
- Alpelisib Placebo 300 mg p.o. + fulvestrant 500 mg i.m.

During randomized treatment phase, alpelisib 300 mg or alpelisib matching placebo will be administered orally once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in combination with fulvestrant 500 mg starting on Cycle 1 Day 1 and 15 and Day 1 of every cycle thereafter (+/- 3 days) in a 28 days cycle. Treatment crossover from fulvestrant plus placebo to fulvestrant plus alpelisib will not be permitted in this study.

A complete cycle of treatment is defined as 28 days (± 3 days) of once daily continuous treatment of alpelisib or placebo in combination with fulvestrant.

The last day of a complete treatment cycle is Day 28. Day 1 of the next cycle starts on Day 29.

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

[redacted]

Table 6-1 Alpelisib/placebo and fulvestrant dose and treatment schedule

Study drugs	Pharmaceutical form and route of administration	Dose[2]	Frequency and/or Regimen
Alpelisib/placebo	Film coated tablet for oral use	300 mg (e.g. 2 x 50 mg tablets+1x200 mg tablet[1])	Daily (continuous) starting C1D1
Fulvestrant	Injection for i.m. administration	500 mg	Days 1, 15 on Cycle 1 and Day 1 at each cycle thereafter

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

6.1.1.1 Alpelisib/placebo dosing

Alpelisib at a dose of 300 mg or placebo will be administered orally once daily on a continuous dosing schedule starting on Cycle 1 day 1 in combination with fulvestrant 500 mg intra muscular at day of randomization.

Alpelisib/placebo is dosed on a flat scale of mg/day and not by weight or body surface area. The maximum recommended daily dose of alpelisib/ placebo is 300 mg.

There will be no breaks between dosing cycles.

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

The following general guidelines should be followed for alpelisib/placebo administration:

- Patients should be instructed to take the dose of alpelisib/placebo once daily at approximately the same time each day immediately aftera meal (preferably in the morning after breakfast) except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic at any later point of time.
- Alpelisib/placebo must be taken immediately after a meal or snack. If, for any reason, a breakfast (or other meal) was not consumed, then the patient should take study treatment with a glass of water immediately after a snack. If this happens on days of PK sampling, it should be documented in the CRF.
- If a dose of alpelisib/alpelisib matching-placebo is missed, it can be taken immediately after food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day. On the next day, alpelisib/placebo should be taken at the usual time.
- Alpelisib/placebo should be taken with a glass of water. Patients should swallow the tablet as a whole and not chew or crush them.
- During treatment phase, the patient should record if the dose was taken or not in the alpelisib/placebo patient diary.

[redacted]

- If the patient vomits after taking the alpelisib/alpelisib matching-placebo dose, the patient should not take an additional dose on that day and should resume the usual dosing schedule the next day at the usual time.
- The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the CRF.

6.1.1.1.1 Additional dosing guidelines for pharmacokinetic sampling

On days with pharmacokinetic sampling

- For sparse PK subset: Cycle 1 Days 8 and 15, Cycle 2, 4, 6, 8 Day1
- For trough PK: Cycle 2, 4, 6, 8 Day 1

The following additional guidelines should be followed:

The pre-dose sample should be drawn before alpelisib/placebo dosing. On days and time points when PK, biochemistry, hematology or other blood samples are to be performed, the PK sample must be drawn first. The sampling time of the pre-dose PK sample and the dosing time of alpelisib/placebo must be precisely recorded in the CRF. Furthermore, the dosing time of alpelisib/placebo on the previous day must be precisely recorded in the CRF and in the alpelisib/placebo patient diary. If vomiting occurs, the exact time of the first vomiting episode within the first 4 hours post-dosing on that day must be noted. Time of administration of gastric protection agents on days of PK sampling should be precisely recorded in the CRF.

6.1.1.1.2 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 and/or amylase/lipase and/or c-peptide and/or lipid profile samples as described in Table 7-1 and Section 7.2.2.5.3 the following additional guidelines should be followed:

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/placebo must be taken within 1 hour after the meal in the clinic. If a pharmacokinetic sample is also being drawn, then the sample should be taken before alpelisib/placebo dosing, as described in Section 7.2.3.

6.1.1.2 Fulvestrant dosing

Fulvestrant 500 mg will be given at Cycle 1 Day 1 and 15 after randomization and then at Day 1 of each subsequent cycle during the randomized treatment phase (+/- 3 days). Fulvestrant is administered intramuscularly into the buttocks slowly as two 5mL injections, one in each buttock.

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

[redacted]

6.1.1.2.1 Additional dosing guidelines for pharmacokinetic sampling

On days with fulvestrant pharmacokinetic sampling (Day 15 of Cycles 1, 2, 4, 6, and 8) the following additional guidelines should be followed: the pre-dose sample should be drawn just before fulvestrant dosing. The sampling time of the pre-dose PK sample and the dosing time of fulvestrant must be precisely recorded in the CRF. Furthermore, the dosing date and time of the previous dose of fulvestrant must be precisely recorded in the CRF.

6.1.2 Guidelines for continuation of treatment

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

Patients who permanently discontinue one of the study drugs for any reason other than disease progression may continue the other study drug as part of the trial therapy at the 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.

6.1.3 Ancillary treatments

Not applicable

6.1.4 Rescue medication

Not applicable

6.1.5 Treatment duration

Patients will be treated until disease progression (radiologically documented according to RECIST 1.1) or until discontinuation of study treatment due to any other reason.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

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

6.3.1.1 Fulvestrant

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® SmPC or local Prescribing Information.

[redacted]

6.3.1.2 Alpelisib/placebo

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

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

Table 6-2 Dose reduction sequential steps for alpelisib/placebo

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

Recommendations for dose reduction or dose interruption of alpelisib/placebo in the management of adverse reactions are summarized in Table 6-3. No dose modification for fulvestrant is permitted. Clinical judgment of the treating physician, including confirmation of lab values if deemed necessary, should guide the management plan of each patient based on individual benefit/risk assessment.

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

After treatment is resumed at a lower dose:

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

If a patient requires a dose delay of alpelisib/placebo for > 28 days from the intended day then the patient must be discontinued from alpelisib/placebo, but may continue on fulvestrant. All scheduled assessments will continue to be performed. If fulvestrant is held for more than 35 days since a planned injection, then fulvestrant should be permanently discontinued. The patient may continue on alpelisib/placebo at the discretion of the investigator until study completion, in which case all scheduled assessments will continue to be performed.

[redacted]

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

Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
Investigations (Fasting Plasma Glucose)	
Hyperglycemia (see also Section 6.3.2.1.3) Always consider consultation with a diabetologist and recommend/reinforce on lifestyle changes as per ADA, i.e. exercise and dietary advice (e.g. small frequent meals, low carb, high fiber, low process food intake, three macronutrient balanced meals and 2 optional small snacks rather than one large meal). Note: this table provides dose management recommendations. The preferred option for treating alpelisib-induced hyperglycemia is metformin, given its wide availability and well characterized safety profile. However, in case of intolerance to or unavailability of metformin, investigator's judgment should be exercised and other insulin sensitizers such as SGLT2 inhibitors, thiazolidinediones or dipeptidyl peptidase-4 Inhibitors can be used.	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For patients with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this apply only for values > 140 mg/dL (7.7 mmol/L)	**Maintain dose level**, and remind patient on lifestyle changes*. ● If FPG < 140 mg/dl, consider adding metformin as per guidance below or in cooperation with diabetologist ● If FPG 140-160 mg/dl, start/intensify metformin as per guidance below or in cooperation with diabetologist Metformin 500 mg once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg bid, with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Monitor FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every two weeks until FPG is within baseline values.
Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	**Maintain dose level** and remind patient on lifestyle changes*, exclude confounding factors like e.g. urinary tract infection, consider consultation with a diabetologist and start oral-antidiabetic treatment, e.g. metformin 500 mg bid with breakfast and dinner. If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Titrate to the maximum tolerated dose over a period of 3 weeks. A second oral hypoglycemic agent may be initiated if needed. If FPG is still rising on maximum tolerated dose of metformin or persistently >160mg/dl (>8.9 mmol/L, add an SGLT2 inhibitor if available, e.g. empagliflozin up to 25 mg (max. dose). Alternatively, an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose) can be added. Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1 ● If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib/placebo by 1 dose level ● Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl

Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
Grade 3 (FPG > 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L]	Omit alpelisib/placebo 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. Start metformin and titrate as outlined for Grade 2, add insulin sensitizers (i.e. pioglitazone) or a SGLT2 inhibitor, if available, as outlined for Grade 2. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of alpelisib-induced hyperglycemia given the short half-life of alpelisib. Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1. • If FPG resolves to ≤ 160 mg/dL within 3-5 days, while off study treatment and on metformin, re-start alpelisib/placebo and reduce 1 dose level, continue with anti-diabetic treatment..A second and third oral hypoglycemic agent may be initiated concomitantly, if needed, in consultation with a diabetologist. Check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl • If FPG does not resolve to ≤ 160 mg/dL within 3-5 days while off study treatment and on metformin, consult a diabetologist for management of diabetes is strongly recommended. • If FPG does not resolve to ≤ 160 mg/dL within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue patient from alpelisib/placebo treatment.
Grade 4 (FPG > 500 mg/dL) [≥ 27.8 mmol/L]	**Omit alpelisib/placebo**, 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. • Should consult with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours. • If grade improves then follow specific grade recommendations • If FPG is confirmed at Grade 4 and confounding factors could be excluded, permanently discontinue patient from alpelisib/placebo.

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Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
A diabetologist consultation should always be considered. For all grades : instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study, e.g. controlled carbohydrate intake, high fiber, low processed food intake; three macronutrient balanced meals and 2 small snacks rather than one large meal. * specific recommendations please see Section 6.3.2.1.3.	
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Investigations (Renal)	
Serum creatinine	
< 2 x ULN	Maintain dose level
2 – 3 x ULN	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue patient from alpelisib/placebo
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from alpelisib/placebo
Investigations (Hepatic)	
Isolated total Bilirubin elevation	
Grade 1 (> ULN - 1.5 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 14 days, then maintain dose level • If resolved in > 14 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 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 patient from alpelisib/placebo
Isolated AST or ALT Elevation	
Grade 1 (> ULN – 3.0 x ULN)	Maintain dose level. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 3.0 - 5.0 x ULN) •	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.

[redacted]

Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
Grade 3 (> 5.0 - 20.0 x ULN) •	Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level. •
Grade 4 (> 20.0 x ULN) •	Permanently discontinue.
Combined[a] elevations of AST or ALT and total Bilirubin	Please see specific instructions in Section 6.3.2.1.5
	•
All dose modifications should be based on the worst preceding toxicity. [a] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction * Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.	

[redacted]

Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
Investigations (Cardiac)	
Cardiac – QTc prolongation	
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	First Occurrence: 1. Assess the quality of the ECG recording and the QT value and repeat if needed 2. Interrupt study treatment 3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment. 4. Review concomitant medication use for other causes for QT prolongation (refer to crediblemeds.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation 5. Check study drug dosing schedule and treatment compliance 6. Consider collecting a time-matched PK sample and record time and date of last study drug intake. After confirming ECG reading at site, if QTcF > 500 ms or > 60 ms change from baseline • Interrupt study treatment • Repeat ECG and confirm ECG diagnosis by a cardiologist If QTcF confirmed > 500 ms or > 60 ms change from baseline • Correct electrolytes, eliminate culprit concomitant treatments, and identify clinical conditions that could potentially prolong the QT • Consult with a cardiologist (or qualified specialist) • Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 ms or < 60ms change from baseline. • After resolution to ≤ 480 ms /60 ms change from baseline, consider re-introducing treatment at reduced dose, and increase ECG monitoring • If QTcF remains ≤ 500 ms/60 ms change from baseline after dose reduction, continue planned ECG monitoring during subsequent treatment • If QTcF recurs > 500 ms/60 ms change from baseline after dose reduction, discontinue patientfrom alpelisib/placebo.
Cardiac - Left Ventricular Systolic Dysfunction	
Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	-Maintain dose level, and continue alpelisib with caution -Repeat LVEF within 4 weeks or as clinically appropriate
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	-Omit alpelisib/placebo until resolved* (as defined below), then ↓ 1 dose level -LVEF measurement to be repeated, if not resolved* within 28 days permanently discontinue patientfrom alpelisib/placebo treatment
Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue patientfrom alpelisib/placebo
*the event is considered resolved when the patientis asymptomatic, has a resting ejection fraction ≥ 40% and ≤20% decrease from baseline.	

[redacted]

Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
Other Cardiac Events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from alpelisib/placebo
Investigations (Gastrointestinal)	
Diarrhea (see also Appendix 4)	
Grade 1	Maintain dose level but initiate appropriate medical therapy and monitor as clinically indicated
Grade 2	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
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated
Grade 4	Discontinue patient from treatment. Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.
Investigations (Pancreatic)	
Pancreatitis	
Grade 2 (enzymatic elevation or radiologic findings only)	Omit dose until resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. If toxicity recurs, permanently discontinue patient from alpelisib/placebo

Grade 3
• For patients deriving clinical benefit upon investigator's judgement:
• For other patients:
	• Omit dose until complete resolution of symptoms and lipase resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed.
	  • If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study.
	  • If toxicity reoccurs, permanently discontinue patient from alpelisib/placebo
	• Permanently discontinue patient from alpelisib/placebo

Grade 4	Permanently discontinue patient from alpelisib/placebo
Stomatitis/Oral mucositis (see also Appendix 5)	
Grade 1/Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouth wash.
Intolerable Grade 2 or Grade 3	First occurrence: hold until ≤ Grade 1 and ↓ 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until ≤ Grade 1 and ↓ 1 dose level.
Grade 4	Permanently discontinue patient from alpelisib/placebo.

[redacted]

Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
Skin and subcutaneous tissue disorders	
Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. (see also Section 6.3.2.1.2). Dermatologist consultation is mandated for serious cutaneous reactions (i.e. fulfilling seriousness criteria for AE Reporting) and for severe cutaneous reactions like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	
Rash	
Grade 1 (<10% body surface area (BSA) with active skin toxicity*)	**Maintain dose level** • Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are Triamcinolone, Betamethasone as long as skin toxicity is active, during maximum 28 days 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 3x/day. For patients with symptoms like burning and/or pruritus add non-sedating anti-histamine, such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night
Grade 2 (10-30% BSA with active skin toxicity*)	**Maintain dose level**. • Initiate or intensify topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone as long as skin toxicity is active, up to max. 28 days • Add systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued. For patients with symptoms like burning, stinging and/or pruritus add 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/placebo** dose until rash /skin toxicity is improved to Grade 1 or resolved, recommend documentation by photography and consider performing a skin biopsy. Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone for at least 28 days Add systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued Re-start alpelisib/placebo dose once rash /skin toxicity is no longer active but fading (G1): - at a reduced dose in case of first occurrence, - If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with alpelisib/placebo; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued For patients with symptoms like burning, 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. Antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib/placebo.

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Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Permanently discontinue patient from alpelisib/placebo Consult a dermatologist, ensure documentation by imaging like photographs, and obtain a skin biopsy Treatment may follow guidelines for Grade 3 above with the exception of rechallenge . Additional measures may be taken as per local treatment guidance. •
Any Grade of Stevens-Johnson-Syndrome /Toxic Epidermal Necrolysis/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or other SJS/TEN/DRESS like severe skin reactions	Permanently discontinue patient from alpelisib/placebo Consult a dermatologist, ensure documentation by imaging like photographs, and obtain a skin biopsy Follow local treatment guidelines for SJS/TEN/ DRESS
*"Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.	
Immune system disorders	
Hypersensitivity	
Please see specific instructions in Section 6.3.2.1.6	
Investigations (Pulmonary disorders)	
Pneumonitis	
Please see specific instructions in Section 6.3.2.1.1.	
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation (see also Section 6.3.2.1.4)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥ 3 (> 2.0 x ULN)	Omit dose until resolved to baseline, then • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, then ↓ 1 dose level. Note: • In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase) as specified in Section 6.3.2.1.4.
Note: Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g. abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Investigations (any other)	
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue from alpelisib/placebo 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)

[redacted]

Dose Modifications for alpelisib/placebo as specified below. Fulvestrant may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified in Section 6.3.1	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
For additional details on the safety profile of alpelisib, please refer to the alpelisib Investigator Brochure.	

6.3.2 Follow-up for toxicities

All patients must be followed up for safety (adverse events and serious adverse events) for 30 days following the last dose of study treatment (alpelisib/placebo and/or fulvestrant). Patients 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 which includes all study assessments appropriate to monitor the event. Further guidelines and recommendations for the management of specific study treatment combination-induced toxicities are provided below.

6.3.2.1 Additional follow-up for selected toxicities

6.3.2.1.1 Management of pneumonitis /Interstitial lung disease

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

All patients will be routinely asked about and observed for the occurrence of adverse events including new or changed pulmonary symptoms (consistent with lung abnormalities). Patients who are suspected to have developed pneumonitis should suspend (alpelisib/placebo) immediately (but may continue fulvestrant if clinically indicated) and undergo appropriate imaging (high resolution CT scan) and broncho-alveolar lavage (BAL) and biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out. 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/placebo and promptly initiate appropriate treatment and supportive measures.

~~Alpelisib/placebo should be permanently discontinued in all subjects with confirmed pneumonitis.~~

6.3.2.1.2 Guidelines for the treatment of study drug induced skin toxicity

Skin toxicity is a class-effect adverse event observed with PI3Ki/mTORi 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 comedication 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

[redacted]

Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis or Erythema multiforme or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)is suspected. Workup for skin toxicity events includes skin photography, a complete blood count with differential, and a full chemistry panel. A paired skin biopsy should be obtained (from both affected and an unaffected skin area) for local histopathology assessment to further assess the skin toxicity, especially to confirm suspected diagnosis of any severe cutaneous reactions.

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. In case of Grade 3 skin toxicity, Novartis recommends that photographs are taken and a skin biopsy is performed.

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

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

For any grade of severe cutaneous reactions, alpelisib treatment must be permanently discontinued without any re-challenge.

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

- Mid to high potency topical steroids: triamcinolone 0.01% or fluocinonide 0.05% twice daily for at least 28 days. Recommend spray, lotion, or cream preparation for ease of application on trunk. For scalp involvement, recommend a foam or solution preparation.
- Gamma-aminobutyric acid (GABA) Agonists: Gabapentin 300mg every 8 hours, Pregabalin 50-75 mg every 8 hours (to adjust of renal impairment). Depending on patient'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.

Dry skin has been reported. It is recommended that patients with dry skin use mild and fragrance free soaps and detergents.

Although preclinical experiments demonstrated that patients should avoid sun exposure during treatment with ~~buparlisib or~~ alpelisib, especially when they already have experienced rash or other skin toxicities as the increased blood flow of the skin may worsen skin symptoms. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts and long pants when outdoors.

[redacted]

6.3.2.1.3 Guidelines for the treatment of alpelisib induced hyperglycemia

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

Detailed guidelines for management of alpelisib induced hyperglycemia is provided in Table 6-3 following discussion with an advisory board. This includes early administration of metformin. Metformin may be titrated to a daily dose of 1000 mg BID. Local protocols per standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting plasma glucose may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance. Special attention should be paid to the risk of hypoglycemia in patients interrupting alpelisib treatment and concomitantly receiving insulin and/or sulfonylureas. Due to the short half-life of alpelisib, all glucose lowering medications should be discontinued when alpelisib is stopped.

Consultation with a diabetologist is highly recommended for better assessment and management of alpelisib-induced hyperglycemia.

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

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

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

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

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

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

[redacted]

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

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events.
In general, any increase of serum aminotransferases to > 3 x ULN should be followed by repeat testing within 48 to 72 hours.

If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

Upon presentation:

1. Obtain PK sample,as close as possible to last dose of study drug, to determine exposure to study drug and metabolites
2. Perform comprehensive medical history including cardiac disease, blood transfusions, i.v. drug abuse, travel, work, alcohol intake, and full clinical examination for evidence of acute or chronic liver disease, cardiac disease and infection etc
3. History of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury 4. Exclude other causes of liver disease. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted

   Obtain PK sample,as close as possible to last dose of study drug, to determine exposure to study drug and metabolites

Patient monitoring:

[redacted]

•Repeat liver chemistry tests within 48-72 hours
•Retest frequency can decrease to weekly or less if abnormalities stabilize, drug has been discontinued, and the patient is asymptomatic.

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before the diagnosis of DILI is confirmed (see Table 6-4). Liver biopsy has limited value in the diagnosis of DILI as histopathological findings in DILI can resemble many other liver conditions. However, biopsy can be useful to establish an alternative diagnosis especially if other tests are inconclusive.
If DILI confirmed: permanently discontinue.
If DILI unlikely - interrupt treatment. Treat identified cause according to institutional guidelines. If resolved, reduce by one dose level. Re-administration of study treatment should be considered only if the investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drug/s and dose regimen should be discussed with the Novartis medical safety team.

Table 6-4 Alternative causes of liver disease

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

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

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", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented

[redacted]

6.3.2.1.6 Guidelines for hypersensitivity

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

6.3.3 Anticipated risks and safety concerns of the study drug

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

[redacted]

[redacted]

Medications to be used with caution during combined alpelisib/placebo and fulvestrant

[redacted]

[redacted]

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

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

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

IRT must be notified within 2 days that the patient was not randomized.

6.5.2 Treatment assignment or randomization

Once eligibility criteria have been confirmed, patients will be classified into one of the two cohorts (i.e. *PIK3CA* mutant and *PIK3CA* non-mutant). The *PIK3CA* mutation status provided by the Novartis designated laboratory will not be communicated to the investigators nor the patients at time of the randomization in order to avoid any potential bias.

Patients in each cohort will be randomized to one of the **2** treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1.

Randomization will be stratified by presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor.

In addition the IRT will manage the limitation of the number of patients with prior CDK4/6 inhibitors treatment up to 30% of the total number of the patients. If the study will continue in both cohorts to the final analyses, the maximum total number of CDK4/6 inhibitors pretreated patients will be 168.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient 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 or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion and none of exclusion criteria will be randomized via IRT to one of the treatment arms at Cycle 1 Day 1. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion and none of exclusion criteria. The IRT will assign a randomization number to the patient, which

[redacted]

will be used to link the patient to a cohort and a treatment arm and will specify a unique medication number for the first package of alpelisib/placebo to be dispensed and administered to the patient in combination with fulvestrant at Cycle 1 Day 1. The randomization number will not be communicated to the caller.

6.5.3 Treatment blinding

This is a double blind placebo controlled study. In particular patients, investigators, Blinded Independent Review Committee (BIRC) and the local radiologists will remain blinded from randomization until the preparation of the study closure. Novartis study team will be blinded from the time of randomization until final PFS analysis in each cohort.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible to anyone involved in the conduct of the study. The identity of the treatments will be concealed by the use of investigational drugs (alpelisib or placebo) that are identical in packaging, labeling, schedule of administration and in appearance. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients.

Unblinding will only occur in the case of patient emergencies (Section 8.3), for regulatory reporting purposes and at the conclusion of the study.

In rare cases when unblinding occurs because of emergency patient management, the actual treatment arm will not be communicated to any of the Novartis employees involved in running the trial in order to remain blinded. The patient will be withdrawn from the study treatment.

An independent statistical group external to Novartis, not involved in the trial conduct, will prepare data reports for the DMC. Details will be presented in the DMC charter.

6.6 Study drug preparation and dispensation

Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive alpelisib/placebo on an outpatient basis.

Fulvestrant should be dispensed according to local prescribing information and practice.

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

6.6.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

[redacted]

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

Table 6-5 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Alpelisib or placebo	Tablets in bottles 50 mg 200 mg	Labeled as BYL719 50mg/placebo and BYL719 200mg/placebo Once daily dosing
Fulvestrant	Refer to local product information	Refer to local product information

Fulvestrant packaging and labeling will be according to locally available supplies of fulvestrant and according to local regulations.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [Alpelisib (BYL719) Investigators Brochure]. The receipt of alpelisib/placebo has to be acknowledged in the IRT system.

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

Table 6-6 Supply and storage of study treatments

Study treatments	Supply	Storage
Alpelisib or placebo	Centrally supplied by Novartis	Refer to study drug label
Fulvestrant	Supplied by Novartis	Refer to local product information

Site staff will be responsible for managing adequate re-supplies for fulvestrant. Only alpelisib/placebo re-supplies are managed with the IRT system.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

An alpelisib/placebo patient medication diary will be provided for each patient. Patients or caregivers are required to complete this diary during the entire study and not only when PK sampling occurs.

On PK sampling days, compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of alpelisib in plasma.

[redacted]

6.6.3.2 Study drug accountability

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

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

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

No CRF will be used as a source document.

Allowed visit windows are specified as follows:

- Screening assessments, apart from those listed below, must occur within 28 days of the randomization as per Table 7-1.
- Tumor sample for molecular testing can be sent within 35 days of the randomization.
- Vital signs, ECOG performance status, required labs, physical exam should be performed within 14 days of randomization.
- Randomization and Cycle 1 Day 1 should occur on the same day.
- For all other visits, a general ±3 days window is permitted on assessments to take into account scheduling over public holidays, if not explicitly specified otherwise.
- No time window for sparse PK sampling is allowed (other than specified in Table 7-7), while, other PK samples may be obtained ± 1 day from the scheduled date.
- Radiological and patient reported outcome assessments must be performed as outlined in Table 7-1. A visit window of ± 7 days is allowed（the whole body bone scan should be performed within 42 days or 6 weeks prior to randomization).

[redacted]

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

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening			Cycle 1			Cycle 2		Subsequent cycles	End of study treatment (EoT)	Post treatment Follow-up phase		[redacted] Survival follow-up
Day of cycle			**-35 to -1**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**N/A**	**30 days after last dose for safety**	**Every 8 weeks for efficacy if appli cable**	**Every 12 weeks**
Obtain Informed Consent	D	11.3	x												
[redacted]	[redacted]	[redacted]	[redacted]												
IWRS/IRT Registration	S		x												
Patient History															
Demography	D	7.1.1.3		x											
Inclusion/exclusion criteria	D	5.2/5.3		x											
Eligibility checklist (within IRT)	S	7.1.1.1			x										
Relevant medical history/current medical conditions	D	7.1.1.3		x											
Diagnosis and extent of cancer	D	7.1.1.3		x											
ER/PgR status	D	7.1.1.3		x											
HER2 status	D	7.1.1.3		x											
Prior antineoplastic therapy	D	7.1.1.3		x											

[redacted]

	Category	Protocol Section	Screening			Cycle 1			Cycle 2		Subsequent cycles	End of study treatment (EoT)	Post treatment Follow-up phase		[redacted] Survival follow-up
Day of cycle			**-35 to -1**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**N/A**	**30 days after last dose for safety**	**Every 8 weeks for efficacy if appli cable**	**Every 12 weeks**
Prior/concomitant medications	D	7.1.1.3		x		Continuous up to 30 days after last dose of study treatment									
Procedures and Significant Non-Drug therapies	D	7.1.1.3		x		Continuous up to 30 days after last dose of study treatment									
Antineoplastic therapies since discontinuation of study treatment	D	7.1.6										x	x	x	x
Randomization															
IWRS/IRT Randomization	D	6.5.2				x									
End of phase disposition	D	7.1.1.2 7.1.3		x								x		x	
Physical Examination															
Performance status (ECOG)	D	7.2.2.4			x				x		x	x			
Height	D	7.2.2.3			x										
Weight	D	7.2.2.3			x				x		C3D1 and then as clinically indicated	x			
Vital signs	D	7.2.2.2			x	x		x	x	x	x	x			
Physical examination	S	7.2.2.1			x		x	x	x	x	x	x			
Laboratory Assessments															
Hematology	D	7.2.2.5.1			x			x	x	x	x	x			
Fasting Chemistry (Full)	D	7.2.2.5.2			x				x		x	x			

[redacted]

	Category	Protocol Section	Screening			Cycle 1			Cycle 2		Subsequent cycles	End of study treatment (EoT)	Post treatment Follow-up phase		[redacted] Survival follow-up
Day of cycle			**-35 to -1**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**N/A**	**30 days after last dose for safety**	**Every 8 weeks for efficacy if appli cable**	**Every 12 weeks**
Fasting Chemistry (Partial)	D	7.2.2.5.2						x		x					
Fasting Plasma Glucose	D	7.2.2.5.3			x		x	x	x	x	x	x			
HbA1c	D	7.2.2.5.3			x				C2D1 and then every 3 cycles			x			
Fasting Lipid Panel	D	7.2.2.5.3			x							x			
Cardiac Enzymes	D	7.2.2.7.3			x	As clinically indicated						x			
Coagulation	D	7.2.2.5.4			x				C2D1 and then every 2 cycles			x			
Fasting Lipase, Fasting Amylase	D	7.2.2.5.3			x		x		C2D1 and then every cycles			x			
Urinalysis (macroscopic)	D	7.2.2.5.5			x	As clinically indicated						x			
Imaging/Other Assessments															
Tumor Assessment	D	7.2.1		x		Every 8 weeks during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, and at EOT (If PR/CR is reported, confirmation of response is required; confirmatory assessment should be performed ≥ 4 weeks after response is first documented). **Note**: tumor assessments must be continued even after start of new antineoplastic therapy									
Whole body bone scan	D	7.2.1.1	x (within 42 days prior to randomization)			As clinically indicated									

[redacted]

	Category	Protocol Section	Screening			Cycle 1			Cycle 2		Subsequent cycles	End of study treatment (EoT)	Post treatment Follow-up phase		[redacted] Survival follow-up
Day of cycle			**-35 to -1**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**N/A**	**30 days after last dose for safety**	**Every 8 weeks for efficacy if appli cable**	**Every 12 weeks**
12-Lead ECG	D	7.2.2.7.1		x		X		x			C3D1 and then every 2 cycles until 36 months, then change to as clinically indicated	x			
Cardiac imaging (MUGA or ECHO)	D	7.2.2.7.2		x							C5D1 and then every 4 cycles until 36 months, then change to as clinically indicated	x			
Safety															
Adverse events	D	8.1	x			Continuous, up to 30 days after the last dose of study treatment									
[redacted]															
[redacted]	[redacted]	[redacted]	[redacted]												
[redacted]	[redacted]	[redacted]				[redacted]			[redacted]		[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]										[redacted]			

[redacted]

	Category	Protocol Section	Screening			Cycle 1			Cycle 2		Subsequent cycles	End of study treatment (EoT)	Post treatment Follow-up phase		[redacted] Survival follow-up
Day of cycle			**-35 to -1**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**N/A**	**30 days after last dose for safety**	**Every 8 weeks for efficacy if appli cable**	**Every 12 weeks**
[redacted]															
[redacted]															
[redacted]															
[redacted]															
Patient Reported Outcomes															
EORTC QLQ-C30	D	7.2.6.1		x		Every 8 weeks during the first 18 months and every 12 weeks until 36 months, then align with the efficacy assessments until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, and at EOT									
[redacted]															
[redacted]															

[redacted]

	Category	Protocol Section	Screening			Cycle 1			Cycle 2		Subsequent cycles	End of study treatment (EoT)	Post treatment Follow-up phase		[redacted] Survival follow-up
Day of cycle			**-35 to -1**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**N/A**	**30 days after last dose for safety**	**Every 8 weeks for efficacy if appli cable**	**Every 12 weeks**
[redacted]															
[redacted]	[redacted]	[redacted]				[redacted]									
Study Drug Administration															
Patient Diary	S	6.1.1.1 6.6.3.1				Daily Continuous									
Alpelisib/Placebo	D	6.6				Daily									
Fulvestrant	D	6.6				x		x	x		x				
Blood sample for Alpelisib/Placebo &Fulvestrant trough PK sampling	D	7.2.3				See Table 7-6 for time points of blood collection for Alpelisib/Placebo & Fulvestrant trough PK assessment									
Blood sample for Alpelisib/Placebo & Fulvestrant sparse PK sampling	D	7.2.3				See Table 7-7 for time points of blood collection for Alpelisib/Placebo & Fulvestrant sparse PK assessment									
Survival Follow-up	D	7.1.7													x

[redacted]

7.1.1 Screening

After signing the study ICF, the tumor sample for *PIK3CA* testing should be sent within days -35 to -21 of the screening period. It is recommended to wait for the central *PIK3CA* testing results before conducting other screening assessments. All other screening assessments will be done within 1 to 28 days prior to randomization or within 1 to 14 days prior to randomization for selected assessments (see Table 7-1 for the list of assessments to be performed). **Note**: Any screening assessment that is done outside the screening window (Day -28 to Day -1 or Day -14 to Day -1 as applicable) must be repeated prior to randomization.

Re-screening of patients is only allowed once per patient if the patient was not registered as entering the treatment phase before (i.e. IRT randomization). In this case the Subject No. assigned to the patient initially will be used and the patient will be identified with this number throughout her entire participation to the study.

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

Assessments of PROs should be collected prior to any clinical assessments, drug dosing or diagnostic testing.

Any imaging assessments already completed during the regular work-up of the patient 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.

An additional [redacted] will be proposed to the patient for [redacted]. For details, refer to Table 7-8 and Section 7.2.4.

7.1.1.1 Eligibility screening

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

7.1.1.2 Information to be collected on screening failures

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

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

- Screening phase disposition page of CRF (including reason for not being started on treatment)
- Informed Consent, [redacted]
- Inclusion/Exclusion Criteria
- Demography

[redacted]

- Adverse events (only if the patient experienced a Serious Adverse Event during the screening period after signing the ICF (see Section 8 for Serious Adverse Event reporting details)
- [redacted]
- Withdrawal of informed consent, if applicable
- Death, if applicable

If a screen failure patient experiences an adverse event which does not meet the Serious Adverse Event criteria, details about the adverse event will be recorded only in the investigator's source documents. In case of an Serious Adverse Event, data must be recorded on both the adverse event page in CRF and Serious Adverse Event report must be submitted to Novartis within 24 hours after becoming aware of it.

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

If the patient fails to in continue into the treatment phase, then IRT must be notified within 2 days of the screen fail that the patient was not enrolled in the treatment phase (Section 6.5.1).

7.1.1.3 Patient demographics and other baseline characteristics

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

- Demography (Date of birth and initials (where permitted), sex, race, ethnicity, source of patient referral)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- Medical history (e.g. important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g. all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History CRF should include the toxicity grade.
- ER, PgR and HER2 status
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures CRF page and updated on a continual basis if there are any new changes to the medications.
- Patient-reported outcome questionnaires (EORTC QLQ-C30[redacted]) (see Section 7.2.6).

Furthermore the following assessments will be performed:

- *PIK3CA* mutation status
- Vital signs
- Height, weight
- Physical examination

[redacted]

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

7.1.2 Treatment period

Patients will be treated with fulvestrant + alpelisib or fulvestrant + placebo until disease progression, unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow-up, death, discontinuation from the study treatment due to any other reason or the sponsor terminates the study. For details of assessments, refer to Table 7-1.

7.1.3 Discontinuation of study treatment

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

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

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every **8** weeks during the first 18 months, every 12 weeks until 36 months, then as clinically indicated until documented disease progression, death, lost to follow-up, or withdrawal of consent.

Study treatment must be discontinued under the following circumstances:

- Adverse event or laboratory abnormalities as indicated in Section 6.3.
- Pregnancy
- Lost to follow-up
- Physician decision
- Subject/guardian decision
- Death
- Progressive Disease
- Study terminated by sponsor
- Technical problems
- Use of prohibited treatment and medications refer to Section 6.4.3 and Section 14.2.
- Any other protocol deviation that results in a significant risk to the patient's safety

[redacted]

The appropriate personnel from the site and Novartis will assess whether alpelisib/placebo plus fulvestrant treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue only one of two medications (fulvestrant or alpelisib/placebo) should NOT be considered withdrawn from the study. They should continue taking fulvestrant only or alpelisib/placebo only (as applicable) as per investigators' clinical judgment, and return for the assessments indicated in Table 7-1.

If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.8.

In addition to the general withdrawal criteria, if alpelisib dosing is held for > 28 days from the intended day then alpelisib should be permanently discontinued. If fulvestrant is held for more than 35 days since a planned injection, then fulvestrant should be permanently discontinued.

Patients who completely discontinue study treatment (i.e. fulvestrant and alpelisib/placebo) should be scheduled for an End of Treatment (EOT) visit as soon as possible, and at least within 14 days after the date study treatment is permanently discontinued, at which time all of the assessments listed in Table 7-1 for the EOT visit will be performed.

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

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

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

The investigator must determine the primary reason for a patient's premature withdrawal from the study and must contact IRT to register the patient's treatment discontinuation within 2 days and record this information on the relevant end of phase disposition CRF page.

7.1.3.1 Replacement policy

Not applicable.

7.1.4 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

[redacted]

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient regarding the study related follow-up are not allowed unless safety findings require communication or follow-up.

7.1.5 Follow-up for safety evaluations

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

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

7.1.6 Efficacy follow-up

If a patient did not discontinue study treatment due to documented disease progression, death, lost to follow-up, or withdrawal of consent for efficacy follow-up, tumor and PRO assessments should continue to be performed every 8 weeks during the first 18 month and then every 12 weeks until 36 months, then change to as clinically indicated until documented disease progression, death, lost to follow-up, or withdrawn consent to efficacy follow-up. At that time, the reason for study completion should be recorded on the Study Phase Completion Disposition CRF page. All tumor evaluation images collected during the efficacy follow-up phase will be sent to central vendor for independent review.

7.1.7 Survival follow-up

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

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

[redacted]the disease progression will be determined based on investigator assessment of progression [redacted] For this purpose, [redacted]since discontinuation of treatment eCRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting

[redacted]

in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate Disposition CRF.

7.1.9 End of post-treatment follow-up

Prior to collecting survival follow-up information, the end of post treatment phase disposition CRF page will be completed once a patient has discontinued study treatment, completed safety follow-up, and can no longer perform efficacy assessment.

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

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

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Imaging tumor assessments

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.1 (Appendix 3) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 7-2. Further details regarding BIRC assessment will be provided in the BIRC charter. The central review of the scans will be carried out in a blinded fashion. The local investigator's assessment will be used for treatment decision making.

Imaging data for all patients in each cohort will be centrally collected and checked for quality by an imaging CRO designated by Novartis. The results of the central evaluations in the *PIK3CA* mutant cohort will be used to support the primary objective.

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 CRFs and will be transmitted to the imaging CRO for review by a medical oncologist.

[redacted]

Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days prior to start of study treatment (Day -28 to Day -1 prior to Cycle 1 Day 1). The whole body scan can be performed within 42 days prior to start of study treatment. Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment (42 days for the whole body scan), 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 as baseline images. The following assessments are required at screening/baseline:

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

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

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

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

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

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

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

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

[redacted]

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 7-2 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7-1). Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) after randomization during the first 18 months and every 12 weeks (+/- 7 days) until 36 months, then change to as clinically indicated. The 8-week (or 12 week) interval should be respected regardless of whether study treatment is temporarily withheld or unscheduled assessments are performed.

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

Each lesion that is measured at 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 Positron Emission Tomography/Computed Tomography (PET/CT) may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 3).

All study imaging (including any off-schedule imaging studies) should be submitted to the designated imaging CRO for quality control promptly after acquisition. If an off-schedule imaging assessment is performed to confirm response or if progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

[redacted]

Table 7-2 Imaging assessment collection plan

Procedure	Screening:*** Day-28 to Day -1	Treatment phase	End of treatment	Post-treatment follow-up phase: Efficacy
CT or MRI (Chest, Abdomen, Pelvis)	Mandated	Every 8 weeks after randomization date during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated	Mandated *	Every 8 weeks during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated. if no documentation of progressive disease at end of treatment visit
CT or MRI for any site of disease	Mandated if suspected lesion at screening	If lesion at screening: every 8 weeks after randomization during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated	Mandated if lesion at screening*	If lesion at screening: Every 8 weeks during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated if no documentation of progressive disease at end of treatment visit
Brain CT or MRI (only if existing or suspected brain metastasis)	Mandated at screening only if existing or suspected brain metastasis	If brain lesion at screening: every 8 weeks after randomization during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated r	Mandated only if brain lesion at screening *	If brain lesion at screening: Every 8 weeks during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated if no documentation of progressive disease at end of treatment visit
Whole Body Bone scan**	Mandated, within 42 days (6 weeks) prior to randomization.	As clinically indicated	As clinically indicated	As clinically indicated
Bone X-ray, CT or MRI	Mandated at screening only if skeletal abnormalities identified by bone scan at screening	If bone lesion at screening: every 8 weeks after randomization during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated	Mandated only if bone lesion at screening*	If bone lesion at screening: Every 8 weeks during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated if no documentation of progressive disease at end of treatment visit
Skin color photography	Mandated if skin lesions at screening	If skin lesions at screening every 8 weeks after randomization during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated r	Mandated if skin lesions at screening*	Mandated if skin lesions at screening Every 8 weeks during the first 18 months and every 12 weeks until 36 months, then change to as clinically indicated if no documentation of progressive disease at end of treatment visit

[redacted]

Procedure	Screening:*** Day-28 to Day -1	Treatment phase	End of treatment	Post-treatment follow-up phase: Efficacy
* Mandated for patients who discontinue study treatment before the first scheduled post-screening tumor assessment and for patients whose previous tumor assessment did not demonstrate PD and was done more than 21 days prior to end of treatment visit. In addition, EOT tumor assessment should be done in patients who discontinue due to clinical progression (e.g. investigator decision) to confirm disease progression by RECIST. ** Type of whole body bone scan according to institutional guidelines *** If CT or MRI scan available before signing of ICF but within 28 days of first dose, no need to repeat the procedures Note: All scans will be acquired and analyzed for primary endpoint locally but should also be sent to the CRO designated by Novartis for central imaging interpretation.				

[redacted]

7.2.1.3 Blinded independent review committee (BIRC) assessment

The primary end point of the study is the local investigator assessed PFS in the PIK3CA mutant cohort. The BIRC assessed PFS will serve as a supportive evidence of the primary end point, if the primary endpoint is statistically significant. The BIRC will perform an assessment of PFS data for a randomly selected subgroup of patients in the PIK3CA mutant cohort only. An independent random sampling process will select all scans (and relevant information) from approximately 50% of randomized patients, whose BIRC randomization identity will be unknown to the investigators. The central review of the scans will be carried out in a blinded fashion. The decision regarding patient management will remain with the investigators. If consistency of treatment effect is not established, the BIRC may perform an assessment of PFS data for all patients in the PIK3CA mutant cohort. Further details regarding BIRC assessment will be provided in the BIRC charter. No BIRC assessment will be made in the PIK3CA non-mutant cohort.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, performance status evaluation, ECG, cardiac imaging, laboratory evaluations for hematology and biochemistry including glucose monitoring as well as collecting of the adverse events at every visit. For details on adverse event collection and reporting, refer to Section 8.1.

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

7.2.2.1 Physical examination

A complete physical examination will be performed at screening (day-14 to day -1), at Day 8 and Day 15 of Cycle 1, at Day 1 and Day 15 of Cycle 2, at Day 1 of each cycle at subsequent cycle, and at the EOT visit. The physical examination at screening can be done at Day 1 of Cycle 1 provided that it is done before the randomization of the patient. The physical examination comprises a total body examination that should include: general appearance, skin,

[redacted]

neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site.

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

7.2.2.2 Vital signs

Vital signs (temperature, blood pressure (supine position preferred when ECG is collected) and pulse) will be monitored at screening (Day-14 to Day -1), Day 1 and Day 15 of Cycle 1 and Cycle 2 and then at Day 1 of each cycle and at the EOT visit. Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for five minutes.

7.2.2.3 Height and weight

Height and body weight will be measured. Weight will be measured at the screening (Day-14 to Day -1), at Day 1 of Cycle 2, at Day 1 Cycle 3, and at EOT. Height will be collected at screening only.

7.2.2.4 Performance status

The performance status will be assessed according to the ECOG performance status scale (Oken 1982). ECOG performance status will be assessed at screening (Day-14 to Day -1), Day 1 of Cycle 2 and then at Day 1 of each cycle and at the EOT visit.

Table 7-3 ECOG performance status

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

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses (hematology, fasting biochemistry (full or partial), coagulation, fasting lipase, fasting amylase, fasting lipid panel/glucose/c-peptide, HbA_{1C}, cardiac enzymes and urinalysis) are to be performed by the central laboratory. In case of urgent safety management of hyperglycemia, fasting plasma glucose assessment may be allowed to be done locally according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-4.

[redacted]

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

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.

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

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g. require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 4.0.3. Additional analyses are left to the discretion of the investigator.

Visit windows 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 CRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

[redacted]

Table 7-4 Central clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology, - Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Fasting Chemistry (full)	Calcium, Magnesium, Potassium, Sodium, [redacted] Alkaline phosphatase, ALT (SGPT), AST (SGOT), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, GGT, Total Protein, Albumin, Creatinine, Creatine kinase (CK), Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Lactate dehydrogenase (LDH)
Fasting Chemistry (Partial)	Creatinine, Creatine kinase, ALT, AST, Total Bilirubin
Fasting Lipid panel	Total Cholesterol, LDL, HDL, Triglycerides
Urinalysis	Macroscopic Panel (Dipstick) (WBC, blood, protein and glucose)
Coagulation	International normalized ratio (INR), and Activated partial thromboplastin time (aPTT) or Partial thromboplastin time (PTT)
Cardiac Enzymes	Troponine I or T
Additional tests	Amylase fasting, Lipase fasting, HbA1c, FPG
All laboratory analysis will be performed centrally; however for urgent safety management, laboratory assessments may be allowed to be done locally and entered on an unscheduled local CRF page (laboratory assessment performed locally should be sent to central laboratory as well for central analysis). Note: fasting plasma glucose at Day 8 and Day 15 of Cycle 1 should be performed both locally and centrally for rapid availability for safety evaluation and dose adjustments.	

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the [CBYL719C2301 Laboratory Manual].

7.2.2.5.1 Hematology

Hematology tests are to be performed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-4. The Hematology panel includes hematocrit, hemoglobin, MCH, MCHC, MCV, platelet count, total red blood cells (RBC), total white blood cells (WBC) count, and a WBC differential (absolute values) including neutrophils, lymphocytes, monocytes, eosinophils and basophils.

7.2.2.5.2 Fasting clinical chemistry

Biochemistry tests are to be performed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-4. The full biochemistry panel includes creatinine, creatine kinase, urea or BUN, uric acid, sodium, magnesium, potassium, calcium, direct, indirect and total bilirubin, c-peptide, alkaline phosphatase, Gamma-glutamyltranspeptidase (GGT), AST/SGOT, ALT/SGPT, total protein albumin, lactase dehydrogenase (LDH).

The partial biochemistry panel includes AST/SGOT, ALT/SGPT, total bilirubin, creatine kinase and creatinine.

[redacted]

7.2.2.5.3 Monitoring fasting plasma glucose, [redacted] fasting lipid panel, amylase, lipase and HbA_{1C}

Fasting c-peptide and lipid panel will be assessed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-4. Patients must be fasting overnight for 8 to 12 hours prior to the blood draw. The study personnel will ask the patient whether she/he has been fasting, which will be captured in the CRF as well.

FPG will be taken at screening (Day -14 to Day-1), pre-dose on Day 8 and Day 15 of Cycle 1, Day 1 and 15 of Cycle 2, on Day 1 of each subsequent cycle and at the EOT visit.

[redacted]

Fasting lipid panel (total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides) is to be performed at screening (Day -14 to Day-1), and at EOT.

Fasting amylase is to be performed at screening (Day -14 to Day-1), pre-dose on Day 8 of Cycle 1, on Day 1 of each subsequent cycle thereafter, and at EOT.

Fasting lipase is to be performed at screening (Day -14 to Day-1), pre-dose on Day 8 of Cycle 1, on Day 1 of each subsequent cycle thereafter, and at EOT.

Fasting HbA_{1c} will be measured at screening (Day -14 to Day-1), Day 1 of Cycle 2, every 3 cycles thereafter and at EOT.

7.2.2.5.4 Coagulation

International normalized ratio (INR) and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) will be assessed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-4 at screening (Day -14 to Day-1), Day 1 of Cycle 2, every 2 cycles and at EOT.

7.2.2.5.5 Urinalysis

Urinalysis dipstick analysis (WBC, blood, protein and glucose) will be performed by the central laboratory at screening, EOT and during the treatment phase if clinically indicated.

7.2.2.6 Radiological examinations

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

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed after the patient has been resting for 5-10 min prior to each time point indicated in Table 7-5. At screening, triplicate ECGs should be taken approximately 2 minutes apart. The combined QTcF values will be averaged to provide a single

[redacted]

baseline value for each patient. This averaged value will be documented in the ECG section of the CRF.

The interpretation of the tracing must be made by a qualified physician and documented in the ECG section of the CRF. Each ECG tracing should be labeled with the study number, patient initials (if permitted by local regulations), Subject No, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the adverse events CRF page.

Table 7-5 Local ECG collection plan

Cycle	Patients	Day	Time	ECG Type
Screening	All	Day -28 to -1	Anytime	Triplicate 12 Lead
Cycle 1	All	Day 1	Pre-dose[1]	12 Lead
Cycle 1	All[1]	Day 15	2h Post-dose ± 30 min[1]	12 Lead
Every 2 cycles until 36 months, then change to as clinically indicated	All	Day 1	Pre-dose[1]	12 Lead
EOT	All	N/A	Anytime	12 Lead
Unscheduled sample[2]			Anytime	12 Lead

[1] ECG assessments are to be done **prior** to PK sampling
[2] If an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the time and date of the last study drug intake to determine the drug exposure

7.2.2.7.2 Cardiac imaging - MUGA scan or ECHO

The left ventricular heart function will be evaluated by ECHO or MUGA at Screening to confirm eligibility, at C5D1, every 4 cycles until 36 months, then change to as clinically indicated, 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.

7.2.2.7.3 Cardiac enzymes

Cardiac enzymes (Cardiac troponine I or T) will be assessed by the central laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-4 at screening (Day -14 to Day-1), during the treatment phase if clinically indicated and at EOT.

7.2.3 Pharmacokinetics

Pharmacokinetic blood samples will be obtained from approximately 200 patients in the study for sparse PK for alpelisib. In all other patients, pre-dose samples will be taken for alpelisib and fulvestrant trough plasma concentrations.

[redacted]

7.2.3.1 Alpelisib/placebo pharmacokinetic blood sampling schedules

Mandatory blood samples for sparse PK assessments of alpelisib will be collected in approximately 200 patients enrolled in the study. Measurement of alpelisib will be performed only in patients randomized to the alpelisib arms arm (i.e., 100 patients assuming a 1:1 ratio). PK will be assessed via a sparse strategy. Five samples will be collected at Cycle 1 Day 15 (post-dose after alpelisib/placebo is started) during absorption, distribution and elimination phase of the PK (Table 7-7). Additionally trough levels will be collected on C1D8 and on separate days later in the trial to capture information on alpelisib clearance.

In all other patients only pre-dose levels will be collected on selected days (Table 7-6)

Population parameters will be determined and factors potentially influencing parameter variability will be investigated by through a prospectively defined covariate analysis. A detailed description of the planned analyses is given in Section 10.5.5.

7.2.3.2 Fulvestrant pharmacokinetic blood sampling schedules

The fulvestrant plasma concentration will be collected in order to assess the impact of alpelisib on fulvestrant exposure in approximately 200 patients (same population as for alpelisib sparse PK assessment). Fulvestrant is administered once monthly after the first cycle and steady state is fully reached after 6 administrations. Pre-dose plasma concentrations will be collected during this period and two cycles after (Table 7-6) in order to assess the time course to reach steady-state.

In trough patients a single fulvestrant pre-dose sample will be taken at steady state at Cycle 6 Day 1 (Table 7-6).

7.2.3.3 Pharmacokinetic blood sample collection and handling

Exact dates and clock times of drug administrations and actual blood draws will be collected on the appropriate Pharmacokinetic Blood Collection CRF pages. The time of the food intake prior to PK sampling, where post dose timepoints are collected, should be recorded in the appropriate alpelisib/placebo CRF page. On days of PK collection and on the day of previous administration the exact time of alpelisib/placebo or fulvestrant dosing, date sample taken and actual time of sampling must be entered on the CRF. Any sampling problem (e.g. study drug was administered before a presample dose) must be noted in the comments section of the CRF.

To ensure compliance with sampling procedures on the days of PK collection, patients will take their alpelisib/placebo doses at the clinic under the supervision of the investigator or his/her designee. Patients who forget to postpone their dose until they arrive at the site on pre-dose sampling days, instead take their medication at home will not participate in PK analysis for that day; they should not have blood samples collected. PK assessment for these patients should be postponed to the next day if possible. Dosing information before alpelisib/placebo PK sampling may be recorded, if feasible, at every PK visit for PK analysis. Any sampling problems must be noted on the CRF and on appropriate source documentation.

If vomiting occurs within 4 hrs following study-drug administration of alpelisib/placebo on Cycle 1 Day 15, where post-dose time points are collected, the time (using the 24 hrs clock) of vomiting should be recorded in a separate section of the CRF and on the transmittal forms,

[redacted]

which accompany the sample. No additional study medication should be taken in an effort to replace the material that has been vomited. If gastric protection agents were taken, this should be recorded in a separate section of the CRF and on the transmittal forms, which accompany the sample.

If the patient experiences an AE related to one or both drugs that fits the criteria of a SAE, or discontinues one or both drugs due to related toxicities, an unscheduled PK blood sample must be obtained whenever possible and as soon as possible after the last dose of alpelisib and/or fulvestrant (preferably within 2 weeks after the last dose). Note: if only one drug is discontinued, only the sample for that drug has to be taken.

The date and time of the last dose is to be recorded in the CRF.

Whenever an ECG with a QTcF change from baseline > 60 msec or a new absolute QTcF ≥ 501 msec result is obtained for patients treated with the drugs combination, a blood sample to assess concentrations of alpelisib and fulvestrant should be obtained and the time of sample collection noted.

7.2.3.3.1 General instructions for blood collection and processing

On days and time points when PK, biochemistry, hematology or other blood samples are to be performed, the PK sample must be drawn first. Complete instructions for sample processing, handling and shipment will be provided in the [CBYL719C2301 Laboratory Manual].

No time window for sparse PK sampling is allowed (other than specified in Table 7-7), while, other PK samples may be obtained ± 1 day from the scheduled date.

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein in accordance with the assessment schedule and institutional guidelines. At the specified time points, one or two 2 mL blood draws will be collected into tubes containing K3-EDTA (alpelisib) and Li-Heparin (fulvestrant) and gently inverted several times to thoroughly mix the anticoagulant. Tubes will be centrifuged to separate plasma and plasma will be immediately split and transferred into separate pre-labeled tubes for each analyte, i.e. alpelisib and fulvestrant as well as primary and backup samples. Plasma samples will be stored frozen in an upright position until shipment to the bioanalytical lab for analysis.

[redacted]This could include [redacted] In addition [redacted]

Refer to the [BYL719C2301 Laboratory Manual] for detailed instructions for the collection, handling and shipment of PK samples.

[redacted]

Table 7-6 Pharmacokinetic blood collection log for trough sampling

Cycle	Day	Scheduled Time Point	Alpelisib/Placebo			Fulvestrant		
			Dose Ref. ID§	PK Sample No	Blood Volume (mL)	Dose Ref. ID§	PK Sample No	Blood Volume (mL)
2	1	Pre-dose*	101 1011	101	2			
4	1	Pre-dose*	102 1021	102	2			
6	1	Pre-dose*	103 1031	103	2	201 2011	201	2
8	1	Pre-dose*	104 1041	104	2			
Anytime		Unscheduled		1001+	2		2001+	2
* Take sample immediately prior to study treatment dose; at days of PK evaluation oral treatment doses should be taken at the clinical site								
+ Refer to Lab manual for naming conventions								
§ Four digit dose reference ID for pre-dose and 24h post dose samples ending on 1 refers to the dose taken before the PK sample (last dose information)								

Table 7-7 Pharmacokinetic blood collection log for sparse sampling

Cycle	Day	Scheduled Time Point	Alpelisib/Placebo			Fulvestrant		
			Dose Ref. ID§	PK Sample No	Blood Volume (mL)	Dose Ref. ID§	PK Sample No	Blood Volume (mL)
1	8	Pre-dose*	301 3011	301	2			
1	15	Pre-dose*	302 3021	302	2	401 4011	401	2
1	15	1 h post dose ± 10 min	302	303	2			
1	15	2 h post dose ± 30 min	302	304	2			
1	15	4 h post dose ± 30 min	302	305	2			
1	15	6 h post dose ± 30 min	302	306	2			
1	15	8 h post dose ± 30 min	302	307	2			
2	1	Pre-dose*	303 3031	308	2	402 4021	402	2
4	1	Pre-dose*	304 3041	309	2	403 4031	403	2
6	1	Pre-dose*	305 3051	310	2	404 4041	404	2
8	1	Pre-dose*	306 3061	311	2	405 4051	405	2
Anytime		Unscheduled		3001+	2		4001+	2
* Take sample immediately prior to study treatment dose; at days of PK evaluation oral treatment doses should be taken at the clinical site								
+ Refer to Lab manual for naming conventions								
§ Four digit dose reference ID for pre-dose and 24h post dose samples ending on 1 refers to the dose taken before the PK sample (last dose information)								

7.2.3.4 Analytical method

Plasma concentrations of alpelisib and fulvestrant will be measured by a designated CRO using validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) assays. The lower limits of quantitation (LLOQ) are currently 5.0 ng/mL for alpelisib and 1.0 ng/mL for

[redacted]

fulvestrant. Values below the assay LLOQ will be reported as 0 ng/mL. All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.6 Patient reported outcomes

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0) [redacted] will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms, treatment-related side effects, global health status, and cancer-related pain. The EORTC QLQ-C30 [redacted] recognized reliable and valid measures (Aaronson 1993, Rabin 2001, Cleeland 1994) frequently used in clinical trials of patients with advanced or metastatic breast cancer.

All patient reported outcome (PRO) measures (e.g. EORTC QLQ-C30 [redacted]) will be administered before any study drug administrations at the visits indicated in Table 7-1 and Table 7-10. Collection of PRO measures have a ± 7 day window unless otherwise indicated.

All PRO data will be collected using an electronic tablet device and should be provided in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient's perspective. Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all patients, including from those who discontinue prior to the study evaluation completion visit, however, if patients refuse to complete questionnaires, this should be documented in study source records. Patient's refusal to complete study questionnaires are not protocol deviations.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, must be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential adverse events or Serious Adverse Events. This review should be documented in study source records.

If an adverse event or Serious Adverse Event is confirmed then the physician should record the event as instructed in Section 8 of this protocol. Investigators should not encourage the patients to change responses reported in questionnaires.

[redacted]

Table 7-10 Patient reported outcomes collection plan

Patient Questionnaires	Cycle	Day	Time
EORTC QLQ-C30 [redacted]	Screening	-28 to 1 day before randomization	Prior to any clinical assessments, drug dosing or diagnostic testing.
	Subsequent cycles	Every 8 weeks after randomization during the first 18 months and every 12 weeks until 36 months, then align with the efficacy assessments until progression	
	End of treatment	Day of end of treatment assessment	
	Efficacy follow-up	Continue collection every 8 weeks after randomization during the first 18 months and every 12 weeks until 36 months, then align with the efficacy assessments only in case end of treatment occurs for reasons other than death, lost to follow-up, withdrawal of consent, or disease progression	

7.2.6.1 EORTC QLQ-C30

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

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

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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

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

Adverse events that begin or worsen after informed consent should be recorded in the adverse events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

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

[redacted]

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

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

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

If the event worsens the event should be reported a second time in the CRF 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 CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

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

[redacted]

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

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

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

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

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

[redacted]

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a Serious Adverse Event given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every Serious Adverse Event, regardless of suspected causality, occurring after the patient has provided main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode 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 should be reported separately as a new event.

Any Serious Adverse Events experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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

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

If the Serious Adverse Event is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis DS&E department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this Serious Adverse Event has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics

[redacted]

committees (ECs) in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, she/he must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when she/he is unavailable. The protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

Study treatment must be discontinued once emergency unblinding has occurred.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis DS&E. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any Serious Adverse Event experienced during pregnancy must be reported on the Serious Adverse Event Report Form.

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

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [Investigator Brochure]. Additional safety information collected between IB updates will be communicated

[redacted]

in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

A DMC will be established to assess the safety and efficacy of alpelisib in an unblinded manner. The DMC will be responsible for reviewing the safety and efficacy results in each cohort from the futility interim, efficacy interim and final analyses for PFS, the interim analysis for OS as well as overseeing the safety data accruing in the trial at regular intervals of approximately every six months, provided that sufficient patients have been randomized. Also, if requested by the DMC Chair, additional safety reviews may be performed.

The DMC will consist of at least two oncologists and one biostatistician and will be formed prior to the randomization of the first patient. Detailed recruitment status and interim safety reports will be provided to the DMC on a regular basis. Recruitment will not be interrupted. Details will be provided in the DMC charter.

8.7 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e., not being members of the DMC, and Novartis representatives from the Clinical Trial Team.

The SC will be an advisory board ensuring 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 SC will be defined in a SC charter. The SC will not have access to unblinded trial data.

9 Data collection and management

9.1 Data confidentiality

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

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

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

[redacted]

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

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or EC standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

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

9.3 Data collection

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

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

[redacted]

Safety laboratory assessments, pharmacokinetic (PK) [redacted] samples drawn during the course of the study will be collected from the investigator sites and sent to the Novartis designated central laboratory for processing.

Imaging data used for tumor assessments will be collected at the sites, transmitted to a designated CRO for centralized analysis, quality control, as well as further processing and data reconciliation. It will be prospectively reviewed by a BIRC.

PRO data must be recorded by patients onto the electronic tablet device maintained at the study site. The device will be programmed to ensure that all relevant observations are recorded.

9.4 Database management and quality control

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

Samples and/or data (e.g. blood, PK [redacted] samples; imaging and IRT data) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

PRO data collected using an electronic tablet device will be documented into a separate study-specific database supplied and managed by a designated vendor. The PRO database will be accessible to study sites and Novartis personnel (or a designated CRO) for data management. All PRO data will be sent electronically to Novartis personnel (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an IRT. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

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

[redacted]

10 Statistical methods and data analysis

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

10.1 Analysis sets

10.1.1 Full Analysis Set

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

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the clinical study protocol. All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the data handling plan and statistical analysis plan. Sensitivity analyses of the primary endpoint of PFS for the *PIK3CA* mutant cohort may be performed using PPS of that cohort when the primary endpoint is statistically significant.

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

The PK Analysis Set (PAS) will consist of all patients who receive at least one dose of study treatment (alpelisib/placebo or fulvestrant) and have at least one evaluable concentration measurement.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be listed and summarized in each of the *PIK3CA* mutant and non-mutant cohorts by treatment arm using the FAS. Categorical data, such as gender, race will be presented by contingency type tables. Descriptive summary statistics (e.g. frequency, mean, median, range and standard deviation) will be used to present numeric data.

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

Duration of study treatment exposure, cumulative dose and dose intensity, the number of patients with dose changes/interruptions along with reasons for the dose change/interruption will be presented in each of the *PIK3CA* mutant and non-mutant cohorts by treatment arm. The safety set will be used for the tables and listings.

Concomitant medications taken concurrently with the study drugs will be listed and summarized by Anatomical Therapeutic Chemical Classification System (ATC) term, preferred term by means of frequency counts and percentages, in each of the *PIK3CA* mutant and non-mutant cohorts by treatment arm. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term in each cohort by treatment arm. These summaries will include therapy starting on or after the start of study treatment (defined as Cycle 1 Day 1) or therapy starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed. The safety set will be used for the tables and listings.

10.4 Primary objective

The primary objective of the study is to determine whether treatment with alpelisib in combination with fulvestrant prolongs PFS compared to treatment with placebo in men and postmenopausal women with HR+, HER2-negative advanced breast cancer which progressed on or after AI treatment for patients with *PIK3CA* mutant status.

10.4.1 Variable

The primary efficacy endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. If a patient has not had an event, PFS will be censored at the date of the last adequate tumor evaluation (see RECIST 1.1 in Appendix 3 for further details). Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The primary analysis for PFS will be performed based on local radiology assessment according to RECIST 1.1.

10.4.2 Statistical hypothesis, model, and method of analysis

The overall Type I error for the trial is one-sided 2.5%. The primary efficacy analysis of PFS based on the population of patients with PIK3CA mutant status will be performed at a one-sided 2.0% level of significance. A secondary efficacy analysis of PFS based on the population of patients with PIK3CA non-mutant status will be performed at a one-sided 0.5% level of significance (see Section 10.5.2.1). This approach guarantees the protection of the overall type I error at 2.5% (based on a Bonferroni adjustment).

The primary efficacy analysis will be the comparison of PFS between the two treatment arms using a stratified log-rank test at one-sided 2.0% level of significance for the *PIK3CA* mutant cohort.

[redacted]

Assuming proportional hazards model for PFS, the following statistical hypotheses will be tested at the one-sided 2.0% level of significance:

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

where θ_1 is the log-hazard ratio (alpelisib + fulvestrant treatment arm vs. placebo+fulvestrant treatment arm) of PFS.

The primary efficacy endpoint PFS will be analyzed at the interim looks and final look of a group sequential design based on the FAS population according to the treatment arm patients were randomized to and the strata they were assigned to at randomization. PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented by treatment arm.

Under the proportional hazards assumption, a test based on the stratified log-rank test provides an asymptotically equivalent result as that of the stratified Cox regression model. In addition, the log-rank test is more powerful for detecting differences that exhibit proportional hazard form. A stratified Cox regression model will be used to estimate the hazard ratio of PFS, along with 95% confidence interval (using the same strata information as above).

10.4.3 Handling of missing values/censoring/discontinuations

PFS times will be censored if no PFS event is observed before the cut-off date. The censoring date will be the date of last adequate tumor assessment before the cut-off date. If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used (see RECIST 1.1. Appendix 3). It is not intended to censor patients for new anticancer therapy prior to documented disease progression in the primary analysis.

10.4.4 Supportive and sensitivity analyses

The following analyses of PFS will be performed in the *PIK3CA* mutant cohort to support the primary PFS analysis, where the primary endpoint is statistically significant.

A sensitivity analysis to support the primary PFS analysis will be conducted where patient's PFS times are censored at the onset of new anticancer therapy.

Subgroup analyses of PFS may be performed in the *PIK3CA* mutant cohort (if the primary endpoint is statistically significant) based on each level of the stratification factors and other prognostic baseline demographic or disease characteristic factors listed below:

- Age
- Race
- ECOG performance status at baseline
- Measurable vs. non-measurable lesions at baseline
- Previous treatment with endocrine therapy for metastatic disease

Additional baseline disease characteristic factors that are deemed relevant may be specified in the SAP. The analyses for the subgroups will include hazard ratios (together with associated two-sided 95% confidence intervals) from un-stratified Cox proportional hazards models.

[redacted]

In addition, the analysis of PFS using stratified Cox proportional hazards model may be repeated using the PPS in the cohort where the primary endpoint is statistically significant.

PFS events will be described according to the type of events (death, documented progression) by treatment arm in the FAS. Censoring reasons will be described by treatment arm. A sensitivity analysis to support the primary PFS analysis will be conducted where patient's PFS times are censored at the onset of new anticancer therapy.

PFS assessed by BIRC will serve as supportive evidence of the primary endpoint. A sample based BIRC audit strategy will be used to assess PFS by BIRC. Two methods will be used to summarize the data from the sample-based BIRC assessment in the PIK3CA mutant cohort. The NCI (National Cancer Institute) method (Dodd et al 2011), uses an auxiliary variable estimator of the log-hazard ratio that combines information from patient-level investigator assessment from all patients in the PIK3CA mutant cohort and the BIRC assessment of these patients randomly selected for central review. This estimate and its one-sided 95% CI will be provided. Details of the audit sample size calculation for the BIRC assessment are provided in Section 10.8. The NCI method will be used for audit sample size determination and summary of treatment effect (HR, 95% confidence intervals) based on the supportive BIRC assessment.

The data from the BIRC assessment generated following the sampling scheme as above will also be summarized using the method proposed by Amit et al 2011, referred to as the PhRMA (Pharmaceutical Research and Manufacturers in America) method. With this approach, the differential discordance (DD) of the early discrepancy rate (EDR) and late discrepancy rate (LDR) between the two arms will be estimated as the rate on the alpelisib+fulvestrant arm minus the rate on the placebo+fulvestrant arm. The EDR and LDR results will also be summarized by treatment arm. Further definitions and details will be provided in the statistical analysis plan.

10.5 Secondary objectives

All secondary efficacy analyses will be reported for each cohort by treatment arm where appropriate. Analyses will be based on the FAS unless otherwise specified.

10.5.1 Key secondary objective(s)

The key secondary objective of the study is to determine whether treatment with alpelisib in combination with fulvestrant prolongs OS compared to treatment with placebo for the cohort of patients with *PIK3CA* mutant status.

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

In the *PIK3CA* mutant cohort, a hierarchical testing procedure will be adopted and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant.

Assuming proportional hazards model for OS, the following statistical hypothesis for OS will be tested using a stratified log-rank test (according to randomization stratification factors) at the one-sided 2.0% level of significance :

$H_{02}: \theta_2 \geq 0$ vs. $H_{a2}: \theta_2 < 0$

[redacted]

where θ_2 is the log-hazard ratio (alpelisib-fulvestrant treatment arm vs. placebo-fulvestrant treatment arm) of OS.

The analysis for OS will be based on the FAS population according to the treatment arm patients were randomized to and the strata they were assigned to at randomization.

The final OS analysis will not be performed at the time point of the final PFS analysis in the *PIK3CA* mutant cohort, but after additional follow-up. Therefore, a three-look group sequential design is considered for OS.

OS will be hierarchically tested for the PIK3CA mutant cohort in the following way:

- The first potential timepoint for OS analysis will be at the time of the PFS efficacy interim analysis after approximately 37% of the expected deaths are observed, at which point approximately 66 deaths are expected. If PFS is not statistically significant at this stage, then OS will not be tested, in which case the next potential timepoint for OS analysis will be at the time of the final PFS analysis after approximately 57% of the expected deaths are observed, at which point approximately 101 deaths are expected to have been recorded in the clinical database.
- If OS is not statistically significant at the first interim analysis, the 2nd OS analysis will be planned after approximately 85% of the expected deaths are observed, at which point approximately 151 deaths have been recorded in the clinical database.
- If OS is not statistically significant at this stage, a final analysis is planned at the time approximately 178 deaths have been recorded.
- If PFS is not statistically significant at the final analysis for PFS, then OS will not be tested.

The type I error probability will be controlled by using a separate Lan-DeMets (O'Brien-Fleming) alpha spending function independent of the Haybittle-Peto boundary used for the primary efficacy analysis of PFS at a 2.0% level of significance for the *PIK3CA* mutant cohort. This guarantees the protection of the overall type I error ($\alpha = 2.5\%$) across all hypotheses and the repeated testing of the OS hypotheses at the interim and the final analyses (Glimm 2010). This includes hypotheses associated with the secondary endpoints PFS and OS in the *PIK3CA* non-mutant cohort (PFS in the non-mutant cohort will be tested at a 0.5% level of significance if PoC is established).

OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals will be presented by treatment arm. Stratified Cox regression will be used to estimate the HR of OS, along with 95% confidence interval.

10.5.2 Other secondary efficacy objectives

Analyses will be based on the FAS.

10.5.2.1 PFS in patients with *PIK3CA* non-mutant status measured in tissue

PFS in the *PIK3CA* non-mutant cohort will be analyzed at a single look based on the FAS population according to the treatment arm patients were randomized to and the strata they were assigned to at randomization.

[redacted]

PFS treatment effect in this cohort will be considered to be clinically relevant via a Bayesian decision rule if:

- The estimated HR (stratified according to presence of lung and/or liver metastasis and previous treatment with CDK4/6 inhibitor) ≤ 0.60

and

- The posterior probability (HR < 1) ≥ 90%

The posterior probability in the second criterion will be derived from the Bayesian posterior distribution of the HR. Assuming a non-informative prior distribution, the distribution of the HR will be updated with all available data from the patients included in the FAS in this cohort. The cumulative posterior distribution will be used to derive the probability that the true HR is less than 1.

If both these criteria are met then the comparison of PFS between the two treatment arms in this cohort using a stratified log-rank test at a one-sided 0.5% level of significance, will be made. Assuming proportional hazards model for PFS, the following statistical hypotheses will be tested at the one-sided 0.5% level of significance:

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

where θ_1 is the log-hazard ratio (alpelisib + fulvestrant treatment arm vs. placebo+fulvestrant treatment arm) of PFS.

The median PFS along with 95% confidence intervals will be presented by treatment arm.

10.5.2.2 OS in patients with *PIK3CA* non-mutant status measured in tissue

OS analyses will be performed only if the secondary efficacy endpoint, PFS, in this cohort meets the PoC criteria given in Section 10.5.2.1 and is statistically significant. A hierarchical testing procedure will be adopted. Assuming proportional hazards model for OS, the following statistical hypotheses will be tested at the one-sided 0.5% level of significance:

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

where θ_1 is the log-hazard ratio (alpelisib + fulvestrant treatment arm vs. placebo+fulvestrant treatment arm) of OS.

The analysis for OS will be based on the FAS population according to the treatment arm patients were randomized to and the strata they were assigned to at randomization.

The final OS analysis will not be performed at the time point of the final PFS analysis in the *PIK3CA* non-mutant cohort, but after additional follow-up. Therefore, a three-look group sequential design is considered for OS.

If PFS in the non-mutant cohort meets the PoC criteria and is statistically significant at a one-sided 0.5% level of significance, OS will be hierarchically tested in the following way:

- The first timepoint for OS analysis will be at the time of the final analysis for PFS (provided PFS is statistically significant) when approximately 29% of the expected deaths are observed, at which point approximately 36 deaths in the *PIK3CA* non-mutant cohort have been recorded (after approximately 18 months from the first patient to be randomized in this cohort).

[redacted]

- If OS is not statistically significant at the first interim analysis, the 2nd OS analysis will be planned after approximately 87% of the expected deaths are observed, at which point approximately 109 deaths are expected to have been recorded in the clinical database.
- If OS is not statistically significant at the second interim analysis, a final analysis is planned after approximately 125 deaths are expected to have been recorded in the clinical database.
- If PFS is not statistically significant, then OS will not be tested.

OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals will be presented by treatment arm. Stratified Cox regression will be used to estimate the HR of OS, along with 95% confidence interval.

10.5.2.3 Overall Response Rate (ORR)

ORR is defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST 1.1. It will be calculated along with the exact binomial two-sided 95% confidence interval (Clopper 1934) by treatment arm for the *PIK3CA* mutant and non-mutant cohorts. In addition, ORR analyses based on blinded independent central review will be performed, if relevant.

10.5.2.4 Clinical benefit rate

Clinical benefit rate is defined as the proportion of patients with a best overall response of CR or PR or SD or Non-CR/Non-PD lasting more than 24 weeks based on local investigator assessment. It will be calculated along with the exact binomial two-sided 95% confidence interval (Clopper 1934) by treatment arm for the *PIK3CA* mutant and non-mutant cohorts. In addition, clinical benefit rate analyses based on blinded independent central review will be performed, if relevant.

10.5.2.5 PFS in patients with *PIK3CA* mutant status measured in ctDNA

An analysis of PFS based on local radiology assessments and using RECIST 1.1 criteria for each of (i) patients with *PIK3CA* mutant status and (ii) patients with *PIK3CA* non-mutant status as measured in ctDNA at baseline will be conducted using the same analytical conventions as the primary analysis.

10.5.2.6 ECOG Performance Status

ECOG performance status will be used to assess physical health of patients. An analysis of the time to definitive deterioration of the ECOG performance status by one category of the score from baseline will be performed using Kaplan-Meier method. A deterioration is considered definitive if no improvements in the ECOG performance status is observed at a subsequent time of measurement during the treatment period following the time point where the deterioration is observed.

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For primary safety analyses, the safety set will be used. All listings and tables will be presented by treatment arm for the *PIK3CA* mutant and non-mutant cohorts individually as well as combined.

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

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

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

10.5.3.2 Adverse events (AEs)

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

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 v4.03 grades), type of adverse event, relation to study treatment by treatment arm. Deaths reportable as Serious Adverse Events and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment arm.

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.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

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

[redacted]

- Number and percentage of patients with worst post-baseline CTC grade (regardless of the baseline status)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.
- listing of all notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities)

In addition to the above mentioned tables and listings, [redacted], for example [redacted] be specified in the statistical analysis plan.

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

10.5.3.4 Other safety data

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

Descriptive summary statistics will be provided for:

- ECGs: changes from baseline results
- Cardiac imaging: change from baseline to worst post-baseline in LVEF values
- Vital signs: number and percentage of patients with at least one post-baseline vital sign abnormality

Listings with flagged notable values and any other information collected will be provided as appropriate.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

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

10.5.4 Patient-reported outcomes

The EORTC QLQ-C30 questionnaire [redacted] will be used to collect patient's QoL data. [redacted] The global health status/QoL scale score of the QLQ-C30 is identified as the primary patient-reported outcome variable of interest. Physical functioning, emotional functioning and social functioning scale scores of the QLQ-C30, [redacted]

[redacted]

[redacted]

Scoring of PRO data and methods for handling of missing items or missing assessments will be performed according to the scoring manual and user guide for each respective patient questionnaire (Fayers et al 2001; Oemar and Janssen 2013; Cleeland et al2009). No imputation procedures will be applied for missing items or missing assessments. [redacted]

The number of patients completing each questionnaire and the number of missing or incomplete assessments will be summarized by treatment group for each scheduled assessment time points for each cohort. No formal statistical tests will be performed and hence no multiplicity adjustment will be applied. The FAS will be used for analyzing PRO data.

Descriptive statistics will be used to summarize [redacted] QLQ-C30, [redacted] at each scheduled assessment time point for each cohort. Additionally, change from baseline [redacted] will be summarized. [redacted] Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

In addition, a repeated measurement analysis model may be used to compare the two treatment groups with respect to changes in the domain scores (global health status/QoL scale score, physical functioning, emotional functioning and social functioning scale scores of the QLQ-C30) [redacted] longitudinally over time. [redacted]

Time to definitive 10% deterioration in the global health status/QoL, physical functioning, emotional functioning, and social functioning scales will be assessed in each cohort. The time to definitive 10% deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% relative to baseline worsening of the corresponding scale score or death due to any cause. If a patient has not had an event, time to deterioration will be censored at the date of the last adequate PRO evaluation. The distribution will be presented descriptively using Kaplan-Meier curves. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to definitive 10% deterioration along with two-sided 95% confidence interval. Additionally, time to definitive deterioration with different cutoff definitions (e.g. 5%, 15%) may be specified in the statistical analysis plan as deemed appropriate. A stratified Cox regression will be used to estimate the hazard ratio, along with two-sided 95% confidence interval.

[redacted]

10.5.5 Pharmacokinetics

10.5.5.1 Trough concentrations

Pre-dose (Cmin) plasma concentrations of alpelisib and fulvestrant will be reported in summary statistics presenting n (number of values to be reported), arithmetic mean, geometric mean, median, standard deviation, coefficient of variation CV (%), Geometric mean CV (%), minimum and maximum using the PAS. Figures of geometric mean and arithmetic mean (+/- standard deviation) of alpelisib and fulvestrant trough concentrations over time will also be presented for the PAS.

The fulvestrant pre-dose plasma concentration will be compared between both arms with or without concomitant alpelisib administration. The time-course of pre-dose plasma concentrations to reach steady state will be assessed using a descriptive approach.

A [redacted] will be used to [redacted] A [redacted] will be used to [redacted] (such as selected [redacted]

10.5.5.2.1 Individual Bayesian estimates

The listing of empirical Bayes estimates of the individual PK parameters will be provided for the patients treated with alpelisib and included in the PAS of this study using a population PK model. The individual concentration vs. time profile at steady state will be simulated. For each of the concentration vs. time profile, the Cmax, AUCtau and t1/2,eff will be determined. Concentrations and appropriate individual PK parameters of alpelisib will be reported in summary statistics presenting n (number of values to be reported), m (number of non-zero

[redacted]

values to be reported) arithmetic mean, geometric mean, median, SD, coefficient of variation CV (%), Geometric mean CV (%), minimum and maximum.

Geometric mean and the geometric CV (%) will be derived from non-zero concentrations. Concentrations below the limit of quantitation will not be imputed and will be treated as zero in summary statistics.

Further [redacted] might be performed to investigate any [redacted]

10.5.5.3 Data handling principles

Detailed data handling methods will be addressed in the statistical analysis plan.

[redacted]

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

10.7.1 Primary endpoint: Progression-free survival in the *PIK3CA* mutant cohort

Two interim analyses are planned after approximately 97 and 185 of the 243 targeted PFS events (40% and 76% information fractions respectively) have been documented. These analyses are expected to take place around 19 and 25 months from the date of first patient randomized in the study. Approximately 243 patients are expected to be randomized when the 97th PFS event occurs at the time of the first interim analysis if H_0 is true (HR.=1). The primary intent of the first interim analysis is to allow the cohort to stop early for lack of efficacy (futility). There is no intent to carry out an analysis to declare superior efficacy at the time of the first interim analysis. The second interim analysis will allow the study to stop early for outstanding efficacy. The second interim analysis will only be carried out after all patients have been randomized in the *PIK3CA* mutant cohort and approximately 76% of the 243 targeted PFS events have been observed.

The assessment of futility will be guided based on two criteria,

A user-defined gamma spending function (γ=5) will be used as a beta-spending function to determine the non-binding futility boundary. One important feature of the design is that the efficacy stopping boundaries will not be affected by the presence of non-binding futility stopping boundaries.

Based on the choice of α-spending and β-spending function described above, the futility boundary in terms of p-value scale (or Z-statistic scale) at the interim is calculated as p =0.128 (or Z=1.134). The observed (i.e. nominal) p-value has to be greater than 0.128 to conclude futility according to this criterion at the time of the first interim analysis.

In addition to the stopping boundary based on the β-spending function described above, DMC will be instructed to include in their recommendation whether the conditional probability of observing a clinically relevant PFS treatment effect at the final PFS analysis is less than 0.20, i.e.:

$$\text{Conditional probability } (HR_{final} \leq 0.6 \mid HR_{interim}) < 0.20$$

This criterion uses the observed interim data and an assumption regarding the distribution of future unobserved data at the final analysis, conditioned under the alternative hypothesis (HR.=0.6). The futility boundary for this criterion in terms of p-value scale at the interim is calculated as p=0.068. Thus the observed (i.e. nominal) p-value has to be greater than the p-value scale futility boundary = 0.068 to conclude futility according to this criterion.

Details of the methodology as well as the operating characteristics for the futility criterion based on conditional probability is described in Appendix 6.

[redacted]

Therefore at the time of the futility analysis, the PIK3CA mutant cohort may be stopped for futility if one or both of the criteria are met.

In addition, the predictive probability of success based on the final planned number of PFS events will be calculated given the interim data, and provided to the DMC at the time of the futility interim analysis as supportive information.

A Haybittle-Peto stopping boundary (as implemented in East 6.3) will be used for interim and final PFS analyses. At the second interim analysis, the observed p-value has to be less than or equal to 0.0001 (or Z=3.719) in order to conclude superior efficacy. If the study continues to final analysis, the p-value that will be used to declare statistical significance at the final analysis will be 0.0199 (Z=2.054).

Since the observed number of events at the interim analyses may not be exactly equal to the planned number of events, the efficacy and futility boundaries will need to be re-calculated (or updated) based on the actual number of observed events using the pre-specified Haybittle-Peto boundary and β-spending function. Therefore, the observed p-values at the interim analyses will be compared with the updated boundaries.

If the study continues to final analysis, the p-value that will be used to declare statistical significance at the final analysis will be based on the actual number of PFS events documented at the cut-off date for the final analysis and the alpha already spent at the interim analysis. Therefore, if the interim analyses were carried out after exactly 40% and 76% of the planned number of events, and the cohort continued until the final analysis, the observed p-value will have to be less than 0.0199 to declare statistical significance. If the number of events in the final analysis deviates from the expected number, the final analysis criteria will be determined so that the significance level is maintained at 0.02 in this cohort.

Statistical properties of the group sequential design in this cohort are summarized in Table 10-1 below.

Table 10-1 Simulated probabilities to stop for futility or efficacy at the interim or final analysis in the *PIK3CA* mutant cohort

Scenario	Look	# PFS events	Cumulative probabilities (%)		Incremental probabilities (%)	
			Stop for efficacy	Stop for futility	Stop for efficacy	Stop for futility
Under H_0 (HR=1)	Interim 1	97	0	92.98	0	92.98
	Interim 2	185	0.02	-	0.02	-
	Final	243	0.98	-	0.96	-
Under H_a (HR=0.6)	Interim 1	97	0.34	15.31	0.34	15.31
	Interim 2	185	38.50	-	38.50	-
	Final	243	83.95	-	45.45	-
Note: The study will not stop for outstanding efficacy at the first (futility) interim analysis. Operating characteristics performed in SAS v9.4 with 10,000 simulations and random seed = 111064						

Interim PFS analysis in the *PIK3CA* mutant cohort will be performed by an independent statistician (not involved with the conduct of the study). Further details will be described in the DMC Charter. The results of the interim analyses will be provided to the DMC by the independent statistician.

[redacted]

10.7.2 Key secondary endpoint: Overall survival in the *PIK3CA* mutant cohort

OS will be compared between the two treatment groups, provided the primary endpoint PFS is statistically significant favouring alpelisib, in the *PIK3CA* mutant cohort. A hierarchical testing procedure will be adopted in this study and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant. A maximum of three analyses are planned for OS:

- at the time of the interim efficacy or final analysis for PFS (provided PFS is statistically significant) when approximately 37% or 57% respectively of the expected deaths are observed, at which point 66 or 101 deaths respectively have been recorded (after approximately 25 or 32 months respectively from the first patient to be randomized in this cohort);
- at the time when approximately 85% of the expected deaths in the *PIK3CA* mutant cohort are observed, at which point approximately 151 deaths in the *PIK3CA* mutant cohort have been recorded (after approximately 45 months from the first patient to be randomized);
- a final analysis for OS when approximately 178 deaths in the *PIK3CA* mutant cohort have been recorded (approximately 54 months from date of first patient to be randomized).

In the *PIK3CA* mutant cohort, an α-spending function according to Lan-DeMets (O'Brien-Fleming) independent of the Haybittle-Peto boundary used for the primary efficacy analysis, along with the testing strategy outlined below will be used to maintain the overall type I error probability (Lan and DeMets 1983). This guarantees the protection of the 2.5% overall level of significance across all hypotheses and the repeated testing of the OS hypotheses at interim and the final analysis (Glimm 2010). This includes hypotheses associated with the secondary endpoints PFS and OS in the *PIK3CA* non-mutant cohort (PFS in the non-mutant cohort will be tested at a 0.5% level of significance if PoC is established).

The trial allows for the stopping of the *PIK3CA* mutant cohort for a superior OS result, provided the primary endpoint PFS has already been shown to be statistically significant favouring the alpelisib arm in that cohort. Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

Given the hierarchical testing strategy of PFS and OS, the design concerning OS analyses will have the following characteristics based on simulations in East 6.3. The probabilities shown in Table 10-2 are conditional probabilities (conditional on PFS being statistically significant) not marginal probabilities.

At the final PFS analysis in the *PIK3CA* mutant cohort:

- The cumulative probability to show efficacy on OS (alternative hypothesis H_a is true) by the final analysis is 71.57%; while the cumulative type I error (rejecting the null hypothesis H_0 if H_0 is true) is 1.91%.
- The cumulative probability to detect efficacy on OS if the alternative hypothesis H_a is true is 19.14% at the first interim analysis, 56.60% at the second interim analysis and 71.57% at the final PFS analysis.

Statistical properties the *PIK3CA* mutant cohort are summarized in Table 10-2 below.

[redacted]

Table 10-2 Simulated probabilities to stop for efficacy at 1st interim, 2nd interim, or final OS analysis in the *PIK3CA* mutant cohort

Scenario	Look	# deaths	Simulated cumulative probabilities (%)*	Simulated incremental probabilities (%) *
			Stop for efficacy	Stop for efficacy
Scenario 1: The first IA for OS is performed at the time of the PFS IA for efficacy				
Under H_0 (HR.=1)	1st Interim	66	0.01	0.01
	2nd Interim	151	1.11	1.09
	Final OS	178	1.89	0.79
Under H_a (HR.=0.67)	1st Interim	66	1.94	1.94
	2nd Interim	151	57.01	55.07
	Final OS	178	71.62	14.61
Scenario 2: The first IA for OS is performed at the time of the final PFS analysis				
Under H_0 (HR.=1)	1st Interim	101	0.17	0.17
	2nd Interim	151	1.12	0.95
	Final OS	178	1.91	0.79
Under H_a (HR.=0.67)	1st Interim	101	19.14	19.14
	2nd Interim	151	56.60	37.46
	Final OS	178	71.57	14.97

Note: Simulations are performed in East 6.3 with number of simulations = 10,000 and randomization seed =37059.

* Probabilities are reported as if OS was tested alone, regardless the testing strategy with PFS. The true probabilities should take into account the probability of PFS at each look. Simulated probabilities shown based on the alpha allocated for testing (p=0.02).

At the time of final PFS analysis in this cohort, both PFS and interim OS analysis will be performed by the Sponsor's clinical team. Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

10.7.3 Secondary endpoint: Overall survival in the *PIK3CA* non-mutant cohort:

OS will be compared between the two treatment groups, provided PFS is statistically significant favouring alpelisib, in the *PIK3CA* non-mutant cohort. A hierarchical testing procedure will be adopted in this study and the OS analyses will be performed only if PFS is statistically significant. A maximum of three analyses are planned for OS:

- at the time of the final analysis for PFS (provided PFS is statistically significant) when approximately 29% of the expected deaths are observed, at which point approximately 36 deaths in the *PIK3CA* non-mutant cohort have been recorded (after approximately 18 months from the first patient to be randomized in this cohort);
- at the time when approximately 87% of the expected deaths are observed, at which point approximately 109 deaths in the *PIK3CA* non-mutant cohort have been recorded (after approximately 45 months from the first patient to be randomized in this cohort);

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- a final analysis for OS when approximately 125 deaths in the *PIK3CA* non-mutant cohort have been recorded (approximately 54 months from date of first patient to be randomized in this cohort).

An α-spending function according to Lan-DeMets (O'Brien-Fleming will be used to maintain the overall type I error probability (Lan and DeMets 1983). The exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

Given the hierarchical testing strategy of PFS and OS, the design concerning OS analyses will have the following characteristics based on simulations in East 6.3. The probabilities shown in Table 10-3 are conditional probabilities (conditional on PFS being statistically significant) not marginal probabilities.

Table 10-3 Simulated probabilities to stop for efficacy at 1st interim, 2nd interim, or final OS analysis in the *PIK3CA* non-mutant cohort

Scenario	Look	# deaths	Simulated cumulative probabilities (%)*	Simulated incremental probabilities (%)*
			Stop for efficacy	Stop for efficacy
Under H0 (HR.=1)	1st Interim	36	<0.001	<0.001
	2nd Interim	109	0.31	0.31
	Final OS	125	0.59	0.28
Under Ha (HR.=0.67)	1st Interim	36	0.001	0.001
	2nd Interim	109	24.59	24.58
	Final OS	125	36.74	12.15

Note: Simulations are performed in East 6.3 with number of simulations = 10,000 and randomization seed =60030. 1st Interim analysis will be conducted at the time of final analysis for PFS
* Probabilities are reported as if OS was tested alone, regardless the testing strategy with PFS. The true probabilities should take into account the probability of PFS at each look. Simulated probabilities shown based on the alpha allocated for testing (p=0.005).

At the time of final PFS analysis in this cohort, both PFS and interim OS analysis will be performed by the independent statistical group for the DMC. The Novartis Clinical team will remain blinded to study treatment allocations up until such point the PIK3CA mutant cohort can be unblinded. Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

10.8 Sample size calculation

The median TTP for fulvestrant in first line post-menopausal advanced breast cancer patients with endocrine sensitive disease is estimated to be between 8 months (Howell et al 2004) and 23 months in FIRST trial (Robertson et al 2014). For sample size calculation, it is assumed that approximately 8% patients in the PIK3CA mutant cohort and 15% of patients in the PIK3CA non-mutant cohort will comprise these patients with an expected median PFS for fulvestrant of 18 months.

Two main studies have been reported assessing fulvestrant in relapsed advanced breast cancer: SoFEA trial with a median PFS of 4.8 months (Johnston et al 2013) and CONFIRM trial with

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a median PFS of 6.5 months (Di Leo et al 2010). However, in the SoFEA study after a first induction with fulvestrant at 500 mg, the dose of fulvestrant continued at 250 mg; in CONFIRM fulvestrant was given at 500 mg throughout. Approximately 92% patients in the PIK3CA mutant cohort and 85% of patients in the PIK3CA non-mutant cohort enrolled in the current study will have similar clinical features to the population treated in CONFIRM trial, therefore for sample size calculation, the median PFS for fulvestrant in this group is assumed to be 6.5 months.

For the overall population in the PIK3CA mutant cohort, the median PFS in the control arm (fulvestrant + placebo) is estimated via simulation to be around 7.0 months.

For the overall population in the PIK3CA non-mutant cohort, the median PFS in the control arm (fulvestrant + placebo) is estimated via simulation to be around 7.4 months.

It is expected that treatment with alpelisib + fulvestrant in both cohorts will result in a 40% reduction in the hazard rate (corresponding to an increase in median PFS from 7.0 months to 11.67 months in the PIK3CA mutant cohort and from 7.4 months to 12.33 months in the PIK3CA non-mutant cohort, under the exponential model assumption).

Patients with *PIK3CA* mutant status:

If the true hazard ratio is 0.6 (under alternative hypothesis), a total of 243 PFS events are required to have 83.80% power at an one-sided overall 2.0% level of significance to reject the null hypothesis (HR.=1) using a log-rank test for a 3-look group sequential design using a Haybittle-Peto boundary to determine the efficacy boundary along with (i) a gamma spending function ($\gamma = 5$) and (ii) a conditional probability function to determine the non-binding futility boundaries. Assuming that 40% of the patients will have a *PIK3CA* mutant status, an enrollment rate of 12 patients during the first 6 months (5 with *PIK3CA* mutant status), 35 patients up to 12 months (14 with *PIK3CA* mutant status) and 59 patients afterwards (24 with *PIK3CA* mutant status) and 10% patients will be lost to follow-up for PFS final analysis, a total of 340 patients will need to be randomized in this cohort to the two treatment arms in a 1:1 ratio. Given the above assumptions, it is estimated that the 243rd PFS event will be observed at approximately 32 months from the date of first patient randomized in the cohort.

The estimated timelines for interim and final PFS analyses are provided in Table 10-4.

Table 10-4 Estimated timelines for interim and final PFS analyses in the *PIK3CA* mutant cohort

Look	Months after randomization of the first patient	Number of PFS events	Number of patients expected to be randomized (HR.=1).
Interim 1 (futility)	19	97	271
Interim 2 (efficacy)	25	185	340
Final	32	243	340

Patients with *PIK3CA* non-mutant status:

The proof of concept criteria require:

(a) an estimate for PFS HR reaching a critical value i.e. HR $\leq$ 0.60

[redacted]

(b) strong evidence that the treatment results in a HR that is better than the value of no interest. i.e. Posterior Probability (HR < 1) ≥ 90%

Based on the dual criteria a minimum of 102 PFS events are required (please refer to Section 14.6). Assuming an enrollment rate of 12 patients during the first 6 months (7 with *PIK3CA* non-mutant status), 35 patients up to 12 months (21 with *PIK3CA* non-mutant status) and 59 patients afterwards (35 with *PIK3CA* non-mutant status) and 10% patients will be lost to follow-up, 220 patients will be randomized (110 per arm), in order to observe the required 102 PFS events in approximately 18 months (if the observed HR is 0.60 and the median PFS for the control arm is 7.4 months).

The primary analysis to estimate the HR will be performed after approximately 102 PFS events have been observed. If the true HR is 1, the probability (obtained by simulation) to obtain a positive conclusion is 0.005; if the true HR is 0.50, the probability to meet efficacy criteria is 0.813. If the true HR is 0.60 (reflecting the minimum clinically relevant difference), the probability to meet efficacy criteria is 0.491. Simulation results are provided in Table 10-5.

Table 10-5 Operating characteristics for PoC criteria in *PIK3CA* non-mutant cohort

True HR	True Median PFS alpelisib (months)	Probability to PoC	Expected duration of cohort (months)
0.3	24.67	0.999	21.0
0.4	18.50	0.975	19.7
0.5	14.80	0.813	18.7
0.6	**12.33**	**0.491**	**18.0**
0.7	10.57	0.220	17.4
0.8	9.25	0.076	16.9
0.9	8.22	0.020	16.5
1.0	7.4	0.005	16.0
Assumes: (1) HR.=0.6, (2) true median PFS for fulvestrant = 7.4 months, (3) protocol planned accrual rates, (4) Analysis after 102 PFS events have been observed			

Audit size for BIRC assessed PFS in the PIK3CA mutant cohort

The audit size of the sample-based BIRC assessment will be 50% of all randomized patients in the PIK3CA mutant cohort. Based on the audit size calculation approach proposed by Dodd, et al (2011), assuming investigator and BIRC assessments are similar and the estimated log of investigator-based HR is -0.51 (i.e. HR.=0.60), the audit size of 50% will ensure that the upper bound of a one-sided 95% CI for BIRC-based log-hazard ratio has 94% probability of being below 0 (i.e. HR. < 1) if the correlation between investigator assessment and BIRC assessment is 0.65 (the estimated correlation based on data from the Bolero-2 [CRAD001Y2301] study in metastatic breast cancer).

10.9 Power for analysis of key secondary variable

For first line patients no phase III data are available with single agent fulvestrant. Data from phase III studies have been reported with letrozole showing a median OS of 34 months (Mouridsen et al 2003) and with anastrozole showing a median OS of 38 months (Bergh et al

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2012). OS data with fulvestrant alone in first line setting have been recently presented within the phase II study FIRST. In that study the median OS for fulvestrant was 54 months (Robertson et al 2014). Therefore, for sample size calculation, median OS for fulvestrant alone in the current study for patients with progression more than 12 months from completion of (neo)adjuvant endocrine therapy is assumed to exceed 50 months.

Median OS for fulvestrant in relapsed post-menopausal advanced breast cancer patients is estimated to be between 19 months (SoFEA trial, Johnston et al 2013) and 26 months (CONFIRM trial, Di Leo et al 2013). For sample size calculation, the median OS for fulvestrant in second line is thus assumed to be 26 months.

Based on the expected split of the patient population as mentioned in Section 10.8, the median OS of control arm is estimated via simulation to be approximately 30 months. It is hypothesized that adding alpelisib to fulvestrant will result in a 33% reduction in the hazard rate for OS (corresponding to an increase in median survival to 44.8 months).

Patients with *PIK3CA* mutant status:

OS will be compared between the two treatment groups, provided that the primary endpoint PFS is statistically significant in this cohort of patients. If the true hazard ratio is 0.67 (under alternative hypothesis), a total of 178 deaths are needed to be observed to have 72% power at an one-sided overall 2.0% level of significance to reject the null hypothesis (HR.=1) using a log-rank test and a 3-look group sequential design. Based on the same number of patients that are planned to be enrolled in this study to detect the primary endpoint and assuming 5% dropout rate by the time of the OS final analysis, it is estimated that these 178 deaths will be observed at approximately 54 months from the date of first patient to be randomized in this cohort.

The estimated timelines for interim and final OS analyses are provided in Table 10-6.

Table 10-6 Estimated timelines for interim and final OS analyses in the *PIK3CA* mutant cohort

Look	Months after randomization of the first patient	Number of OS events
1st OS Interim at time of interim PFS analysis	25	66
1st OS Interim at time of final PFS analysis	32	101
2nd Interim	45	151
Final	54	178

10.9.1 Patients with *PIK3CA* non-mutant status (secondary endpoint):

OS will be compared between the two treatment groups, provided that the secondary endpoint PFS is statistically significant in this cohort of patients. The final analysis of OS for the *PIK3CA* non-mutant cohort will be performed at approximately 54 months from the date of first patient to be randomized in the *PIK3CA* non-mutant cohort. Based on the same number of patients that are planned to be enrolled in the *PIK3CA* non-mutant cohort to detect the primary endpoint and assuming 5% dropout rate by the time of the OS final analysis, it is estimated that approximately 125 deaths will be observed. If the true hazard ratio is 0.67 (under alternative hypothesis), a

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total of 125 deaths will allow 36.1% power at a one-sided overall 0.5% level of significance to reject the null hypothesis (HR.=1) using a log-rank test and a 3-look group sequential design.

The power calculations were conducted with software package East 6.3.

The estimated timelines for interim and final OS analyses are provided in Table 10-7.

Table 10-7 Estimated timelines for interim and final OS analyses in the *PIK3CA* non-mutant cohort

Look	Months after randomization of the first patient	Number of OS events
1st Interim	18	36
2nd Interim	45	109
Final	54	125

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, she/he should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

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

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

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11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

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

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

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

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

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

11.6 Study documentation, record keeping and retention of documents

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

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

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

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

11.7 Confidentiality of study documents and patient records

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

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11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

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

12.1 Amendments to the protocol

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

[redacted]

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14 Appendices

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14.2 Appendix 2 – Patient Patient reported outcomes

Figure 14-1 EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

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ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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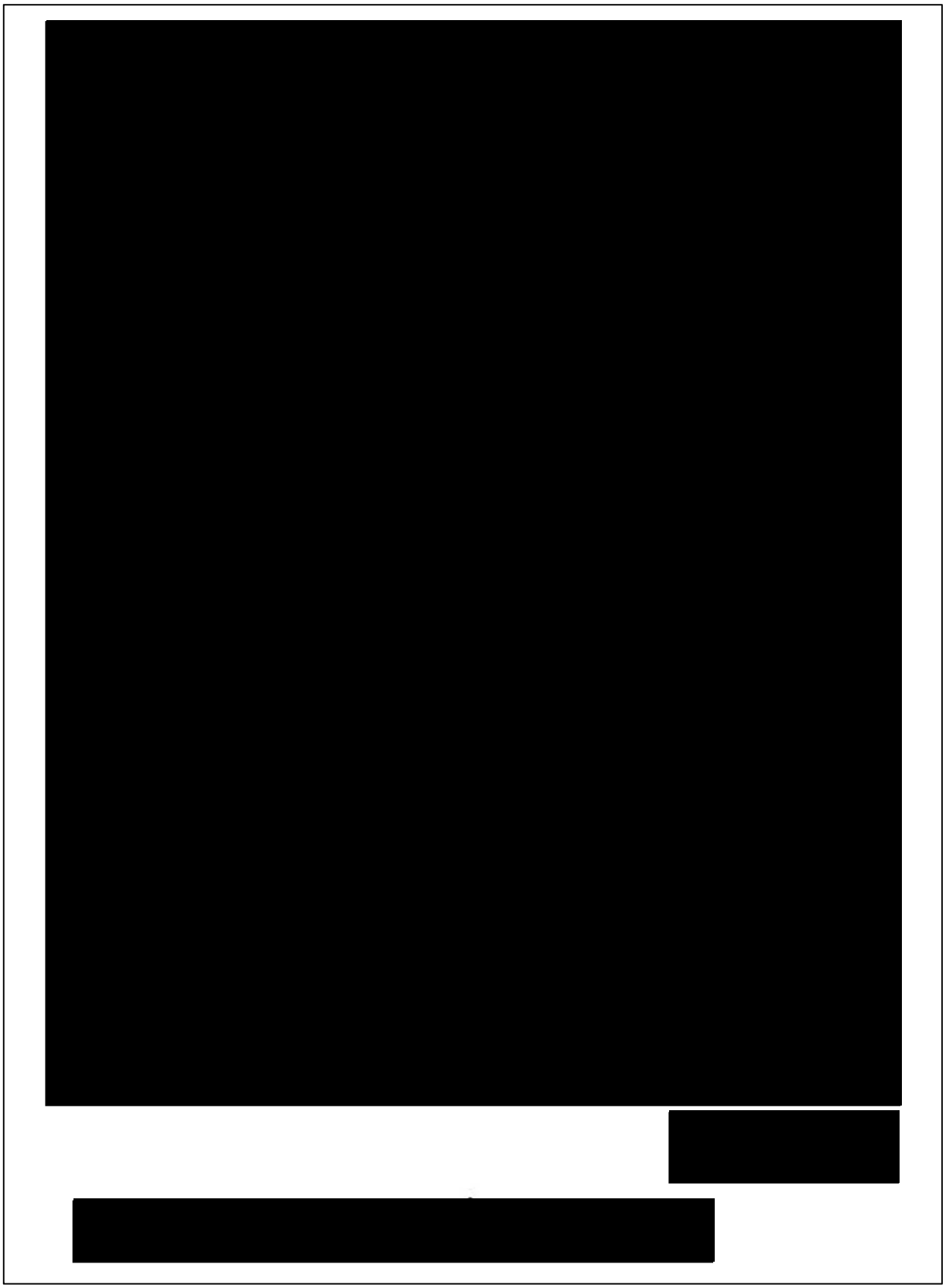

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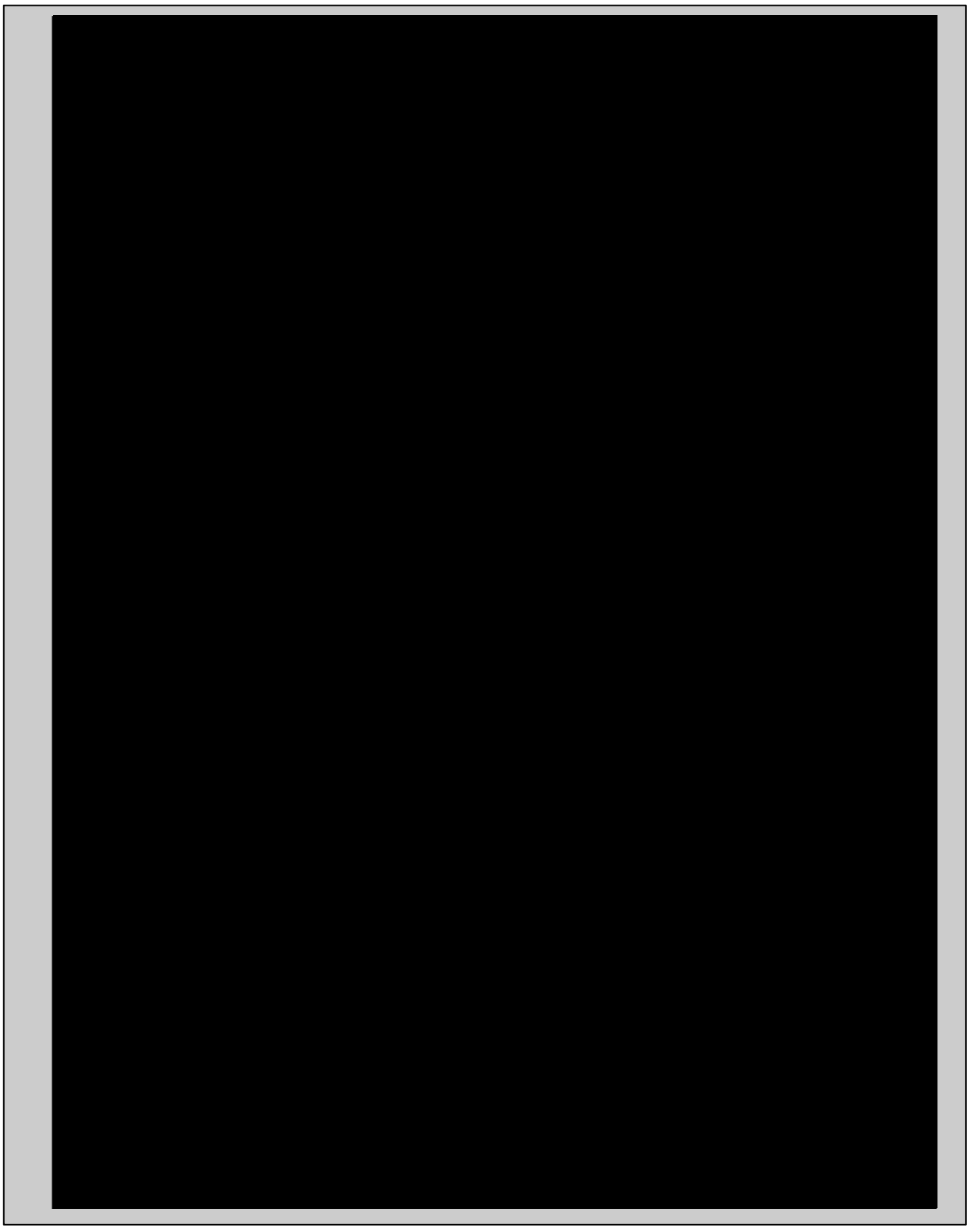

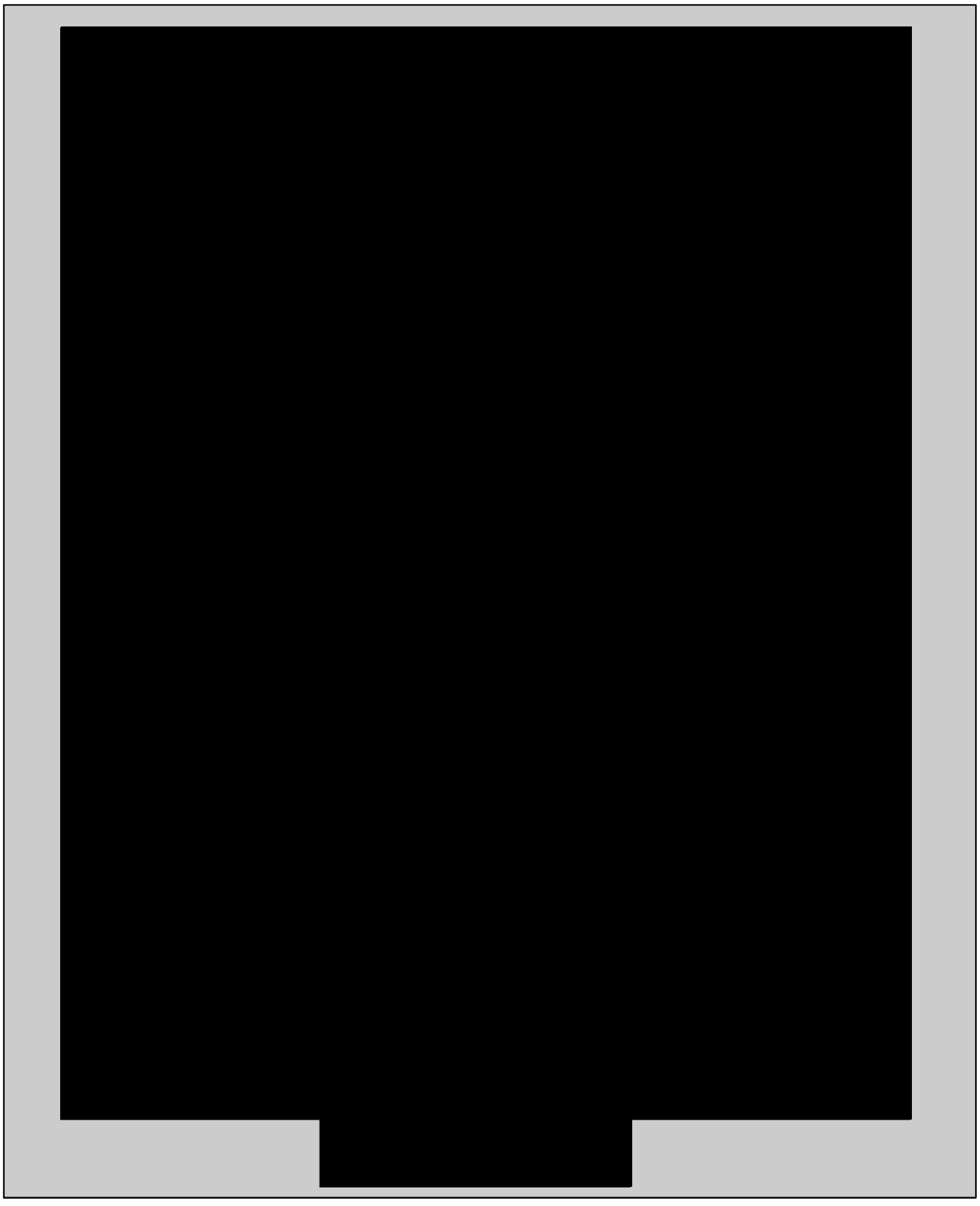

14.3 Appendix 3 - Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

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Glossary

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

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14.3.1 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 14.3.2 and the definition of best response in Section 14.3.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.3.18 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 14.3.29 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.3.2 Efficacy assessments

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

14.3.3 Definitions

14.3.4 Disease measurability

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

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

For patients without measurable disease see Section 14.3.27.

Measurable lesions (both nodal and non-nodal)

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

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

14.3.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.3.27.

14.3.6 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 patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

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- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **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. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

[redacted]

- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers [redacted] can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **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). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.3.7 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 CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.3.4.
- **Nodal target**: See Section 14.3.4.

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

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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.

14.3.8 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 14-5) and non-target lesions (Table 14-6) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-7) as well as the presence or absence of new lesions.

14.3.9 Follow-up and recording of lesions

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

14.3.10 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.

14.3.11 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

[redacted]

for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

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

14.3.12 Determination of target lesion response

Table 14-5 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 14.3.6.)

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 CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-5 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 patients who

have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.

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

[redacted]

- 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.

14.3.13 Determination of non-target lesion response

Table 14-6 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.

[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 does prevail
[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 **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in

[redacted]

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 14.3.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.3.14 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 CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.3.15).
- 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 14.3.6.

14.3.15 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 14-7.

[redacted]

Table 14-7 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 14.3.8.

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.

14.3.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.3.27 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.3.17 Best overall response

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

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

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

[redacted]

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

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

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

[redacted]

PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

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

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

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

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

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

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

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

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

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

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

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

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

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at

[redacted]

8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.3.18 Time to event variables

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

14.3.19 Progression-free survival

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

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

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

14.3.20 Overall survival

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

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

14.3.21 Time to progression

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

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

[redacted]

14.3.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

[redacted]

[redacted]

[redacted]

14.3.26 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 [redacted], the randomization/ date of treatment start will be used as the start date.

For the calculation of [redacted] the following start date should be used:

[redacted]

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 back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.3.27).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.

[redacted]

- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

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

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-8.

Table 14-8 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.3.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which

[redacted]

exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.3.28 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.3.26, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

[redacted]

Table 14-9 Options for event dates used in PFS, TTP [redacted]

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 [redacted])

[1]=Definitions can be found in Section 14.3.26.
[2]=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.3.26.
[3]=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

[redacted]

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/[redacted] 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/[redacted] analysis.

It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-9 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.

[redacted]

14.3.29 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).

14.3.30 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).

14.3.31 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

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

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment

14.3.32 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

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

- Adverse event
- Lost to follow-up

[redacted]

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

14.3.33 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 patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.3.34 Programming rules

The following should be used for programming of efficacy results:

14.3.35 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

[redacted]

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.

14.3.36 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 14.3.26). 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.

14.3.37 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.3.38 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)'.

14.3.39 Study/project specific programming

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

14.3.40 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
- Lost to follow-up

For PFS and TTP [redacted] 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 14-9)

[redacted]

- Death due to reason other than underlying cancer *(only used for TTP [redacted])*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.3.26. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

[redacted]

14.3.41 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791.

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47.

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465.

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

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

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Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16.

[redacted]

14.4 Appendix 4 - Guidelines for the treatment of study drug combination induced diarrhea

Mild to moderate diarrhea has been reported within the ongoing studies of single-agent BYL719. In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, 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; Kornblau et al 2000).

Patient history of diarrhea

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

- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;
- Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;
- Instruct patients regarding risk of developing diarrhea;
- Perform baseline clinical/laboratory studies according to the trial protocol (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients);
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading (Table 14-10).

Table 14-10 NCI CTCAE version 4.03 grading of diarrhea for patients without colostomy

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

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, apple sauce, toast)

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

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

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 again 12-24 hrs:

Diarrhea resolved

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

Diarrhea unresolved

- If diarrhea still persisting (CTCAE grades 1 and 2), after 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 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 et al 1999).

Spot stool analysis

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

Endoscopic examinations

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

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

[redacted]

14.5 Appendix 5 - Guidelines for the treatment of study drug induced stomatitis/oral mucositis

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

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

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

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

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

[redacted]

14.6 Appendix 6 - Statistical methodology

14.6.1 Statistical methodology and operating characteristics – PFS futility criteria in the *PIK3CA* mutant cohort

At the time of the futility analysis, the cohort may be stopped for futility if one or both of the following criteria are met:

1. The observed (i.e. nominal) p-value > 0.128
2. Conditional Probability ($HR_{final} \leq 0.6 | HR_{interim}$) < 0.20

Criterion (2) uses the observed interim data and an assumption regarding the distribution of future unobserved data in the two treatment groups conditioned under the alternative hypothesis (HR_{Ha}). Under the alternative hypothesis, the following formula (Jennison and Turnbull 2000 formula 10.2) can be used to find the futility boundary on the Z-statistic scale (z_t) for criterion (2) that satisfies:

$$\Phi\left[-\frac{1}{\sqrt{1-t}}\left(z_{\alpha'}-\sqrt{t}z_t-\sqrt{1-t}\,\frac{-\log HR_{H_a}}{\sqrt{\left(\frac{a}{D(1-t)}\right)}}\right)\right]<0.2$$

where:

$a=\frac{(r+1)^2}{r}$ with r:1 randomization ratio for treatment and control,

D: Total number of PFS events,

t: Information fraction at the futility interim analysis (i.e. 0.4)

$z_{\alpha'}$: Final boundary on Z scale,

z_t: Observed value on Z scale at futility interim

The critical value for the Z-statistic at the futility interim analysis that will ensure criterion (2) is satisfied is $|z_t|$ = 1.489. The futility boundary in terms of p-value scale is thus calculated as p =0.068.

The operating characteristics of the revised futility criteria are provided in Table 14-11.

Table 14-11 Operating characteristics for PFS futility criteria in the *PIK3CA* mutant cohort

Futility Criteria	**Probability to be stopped for futility**	
True HR	**Under Criterion 1 only**	**Under Criterion 2**
1.0	86.95%	92.98%
0.6	8.89%	15.31%

Criterion 1: Observed (i.e. nominal) p-value greater than 0.128
Criterion 2: Conditional Probability (HRfinal ≤ 0.6¦ HRinterim) < 0.20
Note: Operating characteristics for criterion 1 performed in East 6.3 with number of simulations = 10,000 and randomization seed =37275. Operating characteristics for criterion 2 performed in SAS v9.4 with 10,000 simulations and random seed = 111064

[redacted]

14.6.2 Statistical design and operating characteristics – PFS in the *PIK3CA* non-mutant cohort

A Bayesian double criteria-based design is used to estimate the treatment effect in the *PIK3CA* non-mutant cohort, the methodology and operating characteristics based on simulation are detailed below.

14.6.2.1 Bayesian methodology for proof of concept criteria

Let θ denote the natural logarithm of the hazard ratio (HR) of PFS (experimental arm vs. control, i.e. $\theta < 0$ indicates efficacy in favor of the experimental arm i.e. alpelisib + fulvestrant) and y_m denote the log(HR) estimated from a Cox proportional Hazards model with treatment as covariate based on *m* observed events and then using asymptotic theory of the log hazard ratio (Schoenfeld 1981):

$$Y_m \sim N(\theta, 4/m)$$

Further assume θ follows a conjugate normal prior distribution, written as

$$\theta \sim N(\theta_0, 4/n_0)$$

where θ_0 is the specified prior mean and the prior variance $4/n_0$, n_0 is the number of events worth of prior information.

This results in a posterior distribution of θ as

$$\theta | y_m \sim N(\phi\, y_m, + (1- \phi)\, \theta_0, 4/(m+n_0))$$

where $\phi = m/(m+n_0)$ and in this study we consider a non-informative prior with $n_0=0$.

Therefore the posterior distribution is of the following form;

$$\theta | y_m \sim N(y_m, 4/m)$$

The cumulative posterior distribution will be used to derive the probability that the true HR is less than 1.

14.6.2.2 Proof of concept (PoC) criteria

The following PoC criteria, based on analysis of PFS using Cox proportional Hazards model with treatment as covariate, are considered;

a. Estimated HR ≤ 0.6, and
b. Posterior Probability (HR < 1) $\geq 90\%$

Both criteria need to be met in order to meet primary objective for this part of the study and test PFS in this cohort using a stratified log-rank test at one-sided 0.5% level of significance. The first criterion is met if the estimated HR is 0.6 or less which is the minimum HR of clinical interest. The second criterion provides reasonable evidence that the estimated HR is better than the value of no interest (HR=1) and also guarantees a level of precision for the estimate of HR.

14.6.2.2.1 Sample size considerations and simulation details

Based on the assumption that log (HR) is normally distributed, then the minimum number of events to satisfy criterion (b) can be calculated (Schoenfeld 1981) as:

[redacted]

events = 4 $(z_{1-\alpha} + Z_{1-\beta})^2 / \theta^2$

Taking, $\theta = \log(0.6)$, and one-sided, $\alpha=0.005$, $\beta=0.5$, then 102 events are required. That is, with at least 102 events if the estimated HR is < 0.6 then criterion (b) in Section 14.6.2.2 will be met.

Assuming an enrollment rate of 10 patients during the first 6 months (7 with *PIK3CA* non-mutant status), 30 patients up to 12 months (21 with *PIK3CA* non-mutant status) and 50 patients afterwards (35 with *PIK3CA* non-mutant status) and 10% patients will be lost to follow-up, 220 patients will be randomized (110 per arm), in order to observe the required 102 events in the two arms in approximately 18 months (if the observed HR is 0.6 and the median PFS for the control arm is 7.4 months).

The primary analysis to estimate the HR will be performed after approximately 102 PFS events have been observed. If the true HR is 1, the probability (obtained by simulation) to obtain a positive conclusion is 0.005. If the true HR is 0.60 (reflecting the minimum clinically relevant difference), the probability to meet efficacy criteria is 0.491. In addition if the true HR is 0.6 and the PoC is met, the probability (by simulation) to also observe a positive result with formal testing is 0.983.

Table 14-12 Operating characteristics for PoC criteria in PIK3CA non-mutant cohort

True HR	True Median PFS alpelisib (months)	Probability to meet PoC
0.3	24.67	0.999
0.4	18.50	0.975
0.5	14.80	0.813
0.6	**12.33**	**0.491**
0.7	10.57	0.220
0.8	9.25	0.076
0.9	8.22	0.020
1.0	7.4	0.005
Assumes: (1) HR.=0.6, (2) true median PFS for fulvestrant = 7.4 months, (3) protocol planned accr *Probabilities conditional on PoC criteria being met. Formal testing using log-rank test at a one-sid		

14.7 Appendix 7: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-13 Liver event and laboratory trigger definitions

	Definition/threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN · 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)

[redacted]

	Definition/threshold
	TBL > 2 × 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 TBL > 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*

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

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

[redacted]