NOVARTIS

Novartis Research and Development

BYL719 / Alpelisib

Clinical Trial Protocol CBYL719H12301 / NCT04251533

EPIK-B3: A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of alpelisib (BYL719) in combination with nab-paclitaxel in patients with advanced triple negative breast cancer with either phosphoinositide-3-kinase catalytic subunit alpha (PIK3CA) mutation or phosphatase and tensin homolog protein (PTEN) loss without PIK3CA mutation

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Clinical Trial Protocol Template Version 2.0 (01-Aug-2018)

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aBC	advanced Breast Cancer
ADA	American Diabetes Association
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute Neutrophil Count
ARA	Acid Reducing Agents
ASCO	American Society of Clinical Oncology
ASMA	Antismooth muscle antibody
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AV	Atrioventricular
b.i.d.	twice a day
BAL	Broncho-alveolar lavage
BC	Breast Cancer
BCRP	Breast Cancer Resistant Protein
BIRC	Blinded Independent Review Committee
BMA	Bone Modifying Agents
BMI	Body Mass Index
BOR	Best Overall Response
BP	Blood Pressure
BPI-SF	Brief Pain Inventory-Short form questionnaire
BSA	Body Surface Area
BSEP	Bile Salt Export Pump
BUN	Blood Urea Nitrogen
C	Cycle
CABG	Coronary artery bypass graft
CBR	Clinical Benefit Rate
CD	Carbohydrate-deficient
CD-ROM	Compact disc – read only memory
CD8	Cluster of Differentiation 8
CDx	Companion Diagnostics
CFR	Code of Federal Regulation
CHF	Congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximal plasma concentration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CO	Country Organization

COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CR	Complete Response
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CT	Computerized Tomography
CTA	Clinical Trial Assay
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTT	Clinical Trial Team
CV	Coefficient of Variation
CYP	Cytochrome P450
D	Day
DB	Double-blind
DBP	Diastolic Blood Pressure
DD	Differential Discordance
DDI	Drug-drug interaction
DI	Dose Intensity
DILI	Drug-Induced Liver Injury
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration Of Response
DRESS	Drug Reaction with Eosinophilia and Systemic Syndrome
DTI	Direct Thrombin inhibitors
Dx	Diagnostic
EASD	European Association for the study of Diabetes
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
EDR	Early discrepancy rate
EM	Erythema multiforme
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer’s core quality of life questionnaire
EOT	End of Treatment
EQ-5D-5L	EuroQoL 5-level instrument
ER	Estrogen Receptor
ERCP	Endoscopic retrograde cholangiopancreatography
EU	Europe

FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FDG PET	Fluorodeoxyglucose positron emission tomography
FFPE	Formalin fixed paraffin embedded
FG	Fasting Glucose
FPFV	First Patient First Visit
FPG	Fasting Plasma Glucose
FSH	Follicle-stimulating hormone
G	Grade
GABA	*gamma*-aminobutyric acid
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT/gammaGT/G-GT	Gamma-glutamyltranspeptidase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
h	Hour
HAV	Hepatitis A
HbA1c	Glycosylated Hemoglobin
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatits C virus
HDL	High Density Lipoprotein
HER	Human Epidermal growth factor Receptor
HEV	Hepatitis E virus
HR	Hormone Receptor
HHNKS	Hyperglycemic hyperosmolar non-ketotic syndrome
HR'	Hazard Ratio
HSV	Herpes Simplex Virus
i.v. / IV	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	immunohistochemistry
IIT	Investigator initiated trial
IL-6	Interleukin-6
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent To Treat

IUD	Intrauterine device
IUS	Intrauterine system
LC	Liquid chromatography
LDH	Lactate dehydrogenase
LDL	Low Density Lipoprotein
LDR	Late discrepancy rate
LFT	Liver function test
LLN	Lower limit of normal
LLOQ	Lower limits of quantitation
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
MATE	Multidrug and toxin extrusion
mBC	metastatic Breast Cancer
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic Resonance Imaging
MRP2	Multidrug resistance-associated protein 2
MS	Mass spectrometry
MTD	Maximum tolerated dose
mTOR	mammalian Target Of Rapamycin
MUGA	Multiple Gated Acquisition
NaF	Sodium fluoride
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NTI	Narrow therapeutic index
o.d.	once a day
OATP	Organic Anion-transporting Polypeptide
OCT	Organic Cation Transporter
OL	Open-label
ONJ	Osteonecrosis of the jaw
ORR	Overall Response Rate
OS	Overall Survival
P-gp	P-glycoprotein
p.o.	oral
PARP	Poly ADP Ribose Polymerase
PAS	Pharmacokinetic Analysis Set
pCR	Pathological complete response
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PD'	Progressive Disease
PD-L1	Programmed cell death ligand
PET	Positron emission tomography
PFS	Progression Free Survival
PhRMA	Pharmaceutical Research and Manufacturers in America

PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Phosphoinositide-3-kinase catalytic subunit alpha
PK	Pharmacokinetic(s)
PLT	Platelets
PoC	Proof of Concept
PPE	Proof of preliminary efficacy
PR	Progesterone Receptor
PR'	Partial Response
PRO	Patient Reported Outcome
PS	Performance status
PSDS	Post-study drug supply
PTA	Post-Trial Access
PTEN	Phosphatase and tensin homolog protein
QOL	Quality of Life
QTc	corrected QT interval
QTcF	Fridericia QT correction formula
R Value	ALT/ALP in x ULN
RANK	Receptor Activator of Nuclear Factor Kappa-B
RAS	Randomized Analysis Set
RECIST	Response Evaluation Criteria in Solid Tumors
RGQ	Rotor-Gene Q
RNA	Ribonucleic acid
RoW	Rest of World
RPTD	Recommended Phase II Dose
RTK	Receptor tyrosine kinase
s.c.	subcutaneous
SAE	Serious Adverse Event
sAG	surface antigen
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	standard deviation
SD'	Stable Disease
SGLT2	Sodium-glucose cotransporter 2
SJS	Steven-Johnson Syndrome
SMQ	Standardized MedDRA Query
SMT	Safety Management Team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TCGA	Translation Cancer Genome Atlas
TEN	Toxic Epidermal Necrolysis
TNBC/mTNBC	Triple-Negative Breast Cancer / metastatic Triple-Negative Breast Cancer
TTR	Time To Response
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
WBC	White blood cell(s)

WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristics, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). The action of enrolling one or more participants.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug	The study drug whose properties are being tested in the study.

Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of medication kits.
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial participants, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant’s report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study. The participant is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study completion	Point/time at which the participant came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when participant permanently stops taking study drug for any reason; may or may not also be the point/time of premature participant withdrawal.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy.
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment
Treatment number	A unique identifier assigned in non-randomized studies to each dosed participant, corresponding to a specific treatment arm
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

Amendment 02 (14-Mar-2023)

Amendment rationale

Study CBYL719H12301 was initiated in June 2020.

The recruitment for Part A was halted on 11-Nov-2022 due to slow recruitment. This decision was not triggered by any new or unexpected safety findings. In total, 102 participants were randomized in Part A.

Part B1 recruitment was completed in February 2022 with 35 participants enrolled. Part B1 did not meet its primary objective for confirmed overall response rate. Therefore, Part B2 will not be initiated.

Thus, recruitment was halted for the entire study, and the primary analysis for Part A will now be descriptive only.

Ongoing participants were allowed to continue study treatment if they were deriving benefit as assessed by the investigator.

At the time of protocol amendment version 02 release, 29 participants were on study treatment in Part A and 3 participants in Part B1.

Participants in Part A will be unblinded when all participants have completed 6 months of study treatment or have been discontinued from the study treatment, whichever occurs earlier. Treatment crossover from the control arm to the experimental arm will not be permitted.

Participants in the experimental arm will be allowed to continue on the combination of alpelisib and nab-paclitaxel, based on the investigator's judgement and individualized benefit/risk assessment, after discussion with the participant and documentation in the medical record.

Participants in the control arm will be allowed to continue on nab-paclitaxel only, based on the investigator's judgement and individualized benefit/risk assessment and after discussion with the participant and documentation in the medical record. Placebo tablets will no longer be administered.

The main purposes of this amendment are to revise the protocol following the decision of recruitment halt:

- To adjust the study objectives and endpoints due to the limited sample size in Part A
  - The primary analysis will be descriptive only
  - The overall survival (OS) will be a secondary rather than a key secondary endpoint,
  - [redacted]
- To allow unblinding of all participants in Part A for investigators to know participant's current treatment allocation
- To streamline the safety and efficacy assessments once all participants have completed 6 months of study treatment or have been discontinued from study treatment
  - The imaging assessments will be performed locally as clinically indicated,

  - The laboratory assessments will be performed locally,
  - [redacted]
  - The collection of biopsies in case of skin toxicity is at Investigator's discretion and will not be centrally collected,
  - The collection of survival, and antineoplastic therapies since discontinuation of study treatment will stop.
  - To clarify that the imaging data will not be centrally collected and no BIRC assessment will be performed
- To update the protocol based on the Investigator's Brochure (IB) Edition 17:
  - Recommendation to consider metformin extended release (XR) as a suitable alternative to metformin immediate release (IR). Metformin XR is associated with less gastrointestinal toxicities, and once daily dosing, both of which may lead to better participant compliance and improved glucose management compared to the immediate release formulation (Jabbour and Ziring 2011).
  - Updated guidance regarding diarrhea; addition of colitis and its management
  - Updated definition of hypersensitivity to include angioedema
  - Removal of the requirement to monitor effectiveness when co-administering oral antidiabetics predominantly metabolized by CYP2C9 and CYP2C8, based on results from a post-marketing study (Cocktail Study CBYL719A2111) concluding that no dose adjustment is required when co-administering alpelisib with sensitive substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through font for deletions and underline for insertions. The following sections have been changed in the amended protocol:

- Editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency.
- In Section 5 and the following ones, the term "subject" is replaced with the term "participant", the section titles have been updated in line with the latest protocol template v5.0 (dated 14-Jan-2022, wherever applicable)
- List of abbreviations updated
- Glossary of terms: aligned with protocol template v 5.0
- Protocol summary: aligned with changes applicable in protocol amendment 2 and to correct the release date of protocol amendment 01
- Section 1.1.3.2 has been updated with the latest Investigator's Brochure information on the number of clinical studies in which alpelisib has been investigated as of 23-May-2022
- Table 2-1, Table 2-2 and Table 2-3 objectives and endpoints have been updated post study revision after recruitment halt
- Section 2.2 is no longer applicable following implementation of protocol amendment 02

- Section 3 has been updated with the the changes based on the study revision after recruitment halt
- Figure 3-1: updated to reflect changes applicable in protocol amendment 2
- Figure 3-2: updated to reflect changes applicable in protocol amendment 2
- Section 4.4 not applicable anymore: header was kept to preserve the section numbering
- Section 4.5.2 was updated with potential fetal harm results in animal studies and the update that the assessment of Benefit/Risk assessment did not reveal any additional risks related to coronaviurs disease 2019 (COVID-19)
- Section 5 has been updated with the recruitment halt for the study and the new protocol amendment 02 study workflow
- Section 6 was updated to specify that participants will be unblinded and options post unblinding were presented
- Table 6-1 updated with footnotes to clarify that post unblinding participants in the experimental arm will continue with alpelisib and participants in the control arm will stop receiving placebo supplies
- Section 6.2.1 was updated with the latest language for the guidelines for the treatment of alpelisib-induced hyperglycemia
- Section 6.4 was updated to mention that Part A patients will be unblinded and options post unblinding were presented
- Table 6-4 has been updated with the latest language for the management of fasting Glucose, gastro-intestinal and skin related adverse events
- Section 6.5.2.3 was updated to clarify that with protocol amendment 02, skin biopsy sample collection will no longer need to be submitted to Novartis for central assessment and for Grade 4 or any grade of suspected severe cutaneous reaction, skin toxicity it is no longer a must to perform skin photographs and skin biopsy
- Section 6.5.2.4 has been updated for guidelines for the treatment of alpelisib-induced hyperglycemia
- Section 6.5.2.6 was updated to add “angiodema” as a hypersensitivitiy reaction to alpelisib and nab-paclitaxel
- Section 6.6.2 was updated to remove “name (if applicable)” and to clarify that with protocol amendment 02 this section is no longer applicable as all participants in Part A are to be unblinded
- Figure 6.1 updated to clarify that PROs are to be performed until all participants have completed 6 months of study treatment or have been discontinued from study treatment
- Table 8-1 was updated with the changes based on protocol amendment 2
- Table 8-2 assessment schedule was updated for Part A participants based on changes following protocol amendment 02
- Table 8-3 assessment schedule was updated for Part B1 participants based on changes following protocol amendment 02
- Section 8.1 was updated to no longer keep a small amount of any remaining tissue for the development of future companion diagnostic

- Section 8.1.2 was updated to include local PIK3CA mutational status for screening failures
- Section 8.3.1 was updated to remove central collection and review of the scans, to clarify that tumor assessment will be collected locally as clinically indicated and survival assessment will continue until all participants have completed 6 months of study treatment or have been discontinued from study treatment
- Table 8-4 was updated to clarify that imaging assessments will continue as clinically indicated until all participants have completed 6 months of study treatment or have been discontinued from study treatment
- Section 8.3.3 renumbered further to the removal of previous Section 8.3.2 (no longer applicable following protocol amendment 02) and updated to reflect that BIRC assessments will not be performed for any participants
- Section 8.4.1 was updated to reflect safety assessments will be collected and analysed only by local laboratory once all participants have completed 6 months of study treatment or have been discontinued from the study
- Section 8.5.1.1 was updated to reflect that PRO assessments will no longer performed once all participants have completed 6 months of study treatment or have been discontinued from the study
- Table 8-9: Footnote was added to reflect that PRO assessments will no longer performed once all participants have completed 6 months of study treatment or have been discontinued from the study treatment
- Section 8.5.2 the sentence “Following implementation of protocol amendment 02, PK samples collection will stop was added
- Section 8.5.2.1 the sentence “Following implementation of protocol amendment 02, PK samples collection will stop was added
- Section 8.5.3.1.3 removed since no longer applicable with protocol amendment 02
- Table 8-10, Table 8-11, Table 8-13 Pharmacokinetic blood collection log - nab-paclitaxel - Part A and Table 8-14 were updated each with a footnote reflecting that collection of unscheduled samples will stop after all participants have completed 6 months of study treatment or have been discontinued from the study treatment
- Table 8-12 was updated with the sentence “Not applicable following protocol amendment 02.”
- [redacted]
- Section 9.1.1 was updated with “if applicable” for New antineoplastic therapy
- Section 9.1.3 was updated with clarification of the conditions meeting withdrawal of infomred consent and clarifications on procedures for withdrawal of consent
- Section 9.1.4 was updated with clarifications on lost to follow-up as per protocol template v 5.0
- Section 9.2 was updated to match protocol amendment 02 updates regarding study completion and post study treatment

- Section 9.2.2 was updated with the changes regarding efficacy evaluations following protocol amendment 02
- Section 9.2.3 was updated with the changes regarding disease progression following protocol amendment 02
- Section 9.2.4 was updated with the changes regarding survival follow-up following protocol amendment 02
- Section 10.1.1 Clarifications on adverse events have been added
- Section 10.1.3 Reporting of SAE was clarified regarding disease progression as per protocol template v 5.0
- Section 10.1.4 Clarifications on procedures and reporting in case of pregnancy as per protocol template v 5.0
- Section 10.1.5 Study treatment misuses have been clarified and Table 10-1 has been removed
- Section 10.2.1 Update of liver safety monitoring as per protocol template v 5.0
- Section 11.1 Updated to clarify which data will be captured on CRF and on external originating source
- Section 11.2 was updated to match protocol amendment 02
- Section 12 was updated to match protocol amendment 02
- Section 12.1 the following sentence was added “Part B2 was never initiated”
- Section 12.4 the primary objective was updated accordingly to Section 2 updates and sentence added that Part B2 was never initiated
- Section 12.4.1 the primary endpoints updated for Part A and sentence added that Part B2 was never initiated
- Section 12.4.2 updated for Part A primary efficacy analysis and sentence added that Part B2 was never initiated
- Section 12.4.3 was updated to reflect that Part B2 was never initiated
- Section 12.4.4 was updated to reflect that Part B2 was never initiated
- Section 12.4.5 Sensitivity analysis is not applicable anymore
- Section 12.5 was updated according to changes with protocol amendment 02
- Section 12.5.1.1 is not applicable anymore
- Section 12.5.3 and Section 12.5.4 removed from secondary endpoints
- [redacted]
- Section 12.7 Interim analysis updated for Part A and Part B2 removed as no longer applicable
- Section 12.8 Clarification added on the sample size calculation after recruitment halt
- Section 12.8.1 Audit size for BIRC assessment removed as no longer applicable
- Section 12.8.2 was updated to clarify that it referred to the original design
- Section 13.1 Section clarified with additional details added as per protocol template v 5.0

- Section 13.2 Clarification on Investigator's responsibilities have been added as per protocol template v 5.0
- Section 13.3 Clarifications added on CTIS public website. Addition that any data analyses carried out independently by the Investigator should be submitted to Novartis before publication or presentation
- Section 13.4 Clarifications added as per protocol template v 5.0
- Section 13.5 Addition of data protection section as per protocol template v 5.0
- Section 15 Addition of new reference
- Table 16-11 was updated according to the protocol template v 5.0

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.

Amendment 01 (25-May-2021)

As of the release of this amendment, 21 participants have received study treatment in the randomized study Part A, and 10 participants have received study treatment in the non-randomized study Part B1 of this clinical trial.

Amendment rationale

The main purposes of this amendment are:

- To incorporate guidance related to the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors for the management of hyperglycemia, an on-target side effect of the PI3K inhibitor alpelisib. It is recommended to start treatment with metformin, however SGLT2 inhibitors may be a suitable alternative or add-on therapy to metformin based on available data from the SOLAR-1 study (see Section 6.2.1).
- To incorporate further guidance on alpelisib associated rash and its optimal management.
- [redacted]
- To allow TNBC patients with tumor harboring PTEN loss and unknown PIK3CA status to enroll into study Part B1. PIK3CA status is defined as 'unknown' if the PIK3CA results from the PIK3CA mutation assay are reported as invalid based on specified assay control parameters. The incidence of a PIK3CA unknown tumor to be PIK3CA mutant is estimated to be low (2%) based on the prevalence of PIK3CA mutation and PTEN loss overlap in TNBC (Cossu-Rocca et al 2015).

In addition, the following changes are implemented:

- Addition of language related to a Public Health emergency (when it limits or prevents on-site study visits during the Public Health emergency, such as a pandemic).
- Wording changes to align with new Novartis guidance on the estimand framework and protocol template v4.0 language
- Clarifications and updates in response to Health Authority feedback:
  - exclusion criteria # 2 modified to add examples intolerance to glucose due to the presence of lactose in the placebo formulation;
  - inclusion criteria #7 modified to align with nab-paclitaxel label (USPI Abraxane®) and alpelisib program language;
  - correction of discrepancies in several sections of the protocol;
  - assessment of the Benefit/Risk identified no additional risks related to COVID-19 and no changes were made as a result

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through font for deletions and underline for insertions. The following sections have been changed in the amended protocol:

- Editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency.
- Throughout the protocol, the term “subject” is replaced with the term “participant”, the section titles have been updated in line with the latest protocol template v4.0 (dated 15-Feb-2021, wherever applicable)
- List of abbreviations: new abbreviations added
- Glossary of terms: aligned with protocol template v 4.0
- Protocol summary: aligned with changes applicable in Amendment 1
- Section 1.1.3.2: updated the number of clinical studies in which alpelisib has been investigated as of 13-May-2020
- Table 2-1, Table 2-2 and Table 2-3: Clarification of the Endpoints to corresponding to specific Objectives; update of title of Table 2-2
- Section 2.1: For Part A/B2, start of new anti-neoplastic therapy was removed from intercurrent events since it has been incorporated in the treatment attribute; clarification on justification for targeting the treatment effect was added for Part A, B1 and B2 ; scientific question of interest, primary estimand and summary measure corrected for part B1 to reflect open-label design
- Section 2.2: Secondary estimand updated
- Section 3: Stratification factor definition clarified; Clarification that endocrine-based therapy for HR+ advanced/metastatic BC should not be counted as a line of treatment; modification to allow TNBC patients with tumor harboring PTEN loss and unknown PIK3CA status to enroll into study Part B1; addition of ‘unknown’ PIK3CA status definition; Modification of Screening period into Pre-screening and Screening period; Clarification that local testing for PIK3CA mutation status is not limited to tumor tissue
- Figure 3-1: Correction to reflect changes applicable in Amendment 1
- Figure 3-2: Correction that Parts A & B2 are double-blind, randomized, placebo-controlled, update to reflect revision of eligibility criteria and to add the molecular pre-screening period
- Section 4.1: Modification to allow TNBC patients with tumor harboring PTEN loss and unknown PIK3CA status to enroll into study Part B1; clarification on “Line of therapy” wording.
- Section 4.5.2: Update regarding risk benefit assessment related to COVID-19
- Section 4.6: Addition of section on the rationale for mitigation procedures in case of public health emergency
- Consistent with this rationale, mitigation procedures in case of public health emergency have been added to the following sections:
  - Section 6.7 – Preparation and dispensation (applicable for alpelisib/placebo)
  - Section 7 – Informed consent procedures
  - Section 8 – Visit schedule and assessments
  - Section 8.4 – Safety
  - Section 8.4.1 – Laboratory evaluations
  - Section 8.4.3 – Pregnancy and assessments of fertility

- Section 5.1 Inclusion criteria:
  - #4: Renumbered from 4 to 4a. Change to allow patients with PTEN loss and unknown PIK3CA status to enrol into study Part B1; Clarification that local testing for PIK3CA mutation status is not limited to tumor tissue
  - #6: Clarification that endocrine-based therapy for HR+ advanced/metastatic BC should not be counted as a line of treatment
  - #7: Renumbered from 7 to 7a. Modification laboratory criteria (for AST/ALT and Total bilirubin values) that defines adequate bone marrow and organ function to align with nab-paclitaxel label (USPI Abraxane®) and alpelisib program language
- Section 5.2 Exclusion criteria
  - # 2: Clarification of possible intolerance due to excipients present in the placebo tablet
  - #3, #9, #10, #11, #13, #15, #16, #24: Clarification of criteria, respectively, related to inflammatory breast cancer, prior malignancy, CNS involvement, diabetes mellitus, pancreatitis, pneumonitis/interstitial lung disease, cardiac events, male participants
  - #23: Addition of the provision for locally regulated methods of contraception
- Section 6.1: Clarification of criteria for nab-paclitaxel brands that need to be met for use in the study
- Table 6-1 & Section 6.1.1.2: Addition of powder for infusion dispersion as another nab-paclitaxel pharmaceutical dosage form
- Table 6-1: Clarification that nab-paclitaxel can be supplied by study site
- Section 6.1.1.1 and Section 6.1.1.2: Recommendation for prophylactic antihistamine use added to decrease frequency and severity of alpelisib associated rash; clarification on nab-paclitaxel administration after alpelisib/placebo dosing
- Section 6.1.5: Addition of post-trial access information
- Section 6.1.5.1: Clarification that disease progression is assessed locally by investigator as per RECIST 1.1
- Section 6.2.1: Recommendations for use of sodium-glucose cotransporter 2 (SGLT2) inhibitors as additional oral anti-diabetics to manage alpelisib associated hyperglycemia
- Section 6.2.1.2: Update of drug classification of denosumab as a RANK-ligand inhibitor
- Section 6.3.1: Clarification that participant number is assigned by the clinical database and that a new patient number is assigned in case of re-screening
- Section 6.3.2: Clarification on disclosure of Randomization codes to PK Bioanalysts
- Section 6.4: Clarification that unblinding at site for safety reasons results in discontinuation from the study treatment
- Section 6.5.1.1: Addition of cross-references for specific events requiring permanent treatment discontinuation; dose changes must be recoreded in the appropriate eCRF
- Table 6-4: Update of table title and dose modification recommendation for alpelisib/placebo for specified adverse drug reactions
- Section 6.5.2.1 Update of follow-up on potential drug-induced liver injury (DILI) cases
- Section 6.5.2.3: Update of guidelines for treatment of alpelisib-induced skin toxicity

- Section 6.5.2.4: Update of guidelines for the treatment of alpelisib-induced hyperglycemia
- Section 6.5.2.5: Addition of of CTCAE version number
- Section 6.7: Clarification added that participants will receive alpelisib/placebo on an outpatient basis)
- Section 6.7.1.1: Possibility of on-site destruction of study treatment added
- Figure 6-1: Correction of diagram depicting blood draw order to be consistent with blood draw order as described in the Central Laboratory manual and Flow chart
- Section 7: Addition of a list indicating informed consents used in the study
- Section 8: Update to clarify assessments to be recorded in the clinical database and visits to be performed in case of study treatment and study discontinuation or Withdrawal of consent/Opposition to use data/biological samples
- Table 8-1: Addition of molecular pre-screening visit and update of screening visit window. Clarification of C1D1 visit and dosing; extension of allowed time window for follow-up after disease progression
- Table 8-2 and Table 8-3
  - Modification of study period, time window for tumor tissue collection, information on prior local PIK3CA mutation testing and IRT registration consistent with addition of Pre-screening to determine participant's molecular status
  - IRT Randomization and IRT Study Drug Dispensation corrected to be recorded in the clinical database or received from a vendor
  - Physical examination frequency modified and visits requiring a short or full physical examination updated, footnotes added in these tables to reflect those changes
  - Clarification on the collection of skin photography in case of Grade 3/4 skin toxicity
  - Applicable only to Table 8-3: Removal of ECOG assessments at visits after Screening to align with Part B1 objectives

[redacted]

- Section 8.1.1: Update to align with the addition of Pre-screening
- Section 8.1.2: Clarification of information collected on screen failures
- Section 8.2: Addition of rationale on the collection of demography information
- Section 8.3.1: Clarification that imaging data will be centrally collected for Parts A and B2 participants and that no central imaging collection/BIRC assessment will be made for Part B1 participants
- Table 8-4: Clarification on the timeframe within which imaging assessments is considered as baseline images
- Table 8-5: Modification of the frequency for short physical examinations
- Section 8.4.1: Clarification that clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events
- Section 8.4.2: Clarification on use of Fridericia QTcF for clinical decisions
- Section 8.5.1.1: Clarification on self-administration of PROs by study participants

- Section 8.5.2.1: Correction of order of PK sample collection to be consistent with blood collection order as specified in the Central laboratory manual and Flow Chart

[redacted]

- Section 9.1.1: Removal of six treatment cycles as target for nab-paclitaxel administration in absence of disease progression or unaccepted toxicities; Clarification provided on visits to be completed upon discontinuation from study treatment
- Section 9.1.2: Addition of section on discontinuation from study
- Section 9.1.3, Section 9.1.4, Section 9.2.2: Modification to include Opposition to use data/biological samples with Withdrawal of informed consent; Modification of the conditions meeting withdrawal of informed consent and clarification on procedures for withdrawal of consent/opposition to use data/biological samples
  - Following the grouping of Opposition to use data/biological samples with Withdrawal of informed consent, the mention of "opposition to use data/biological samples" have been added in other protocol sections where previously only withdrawal of informed consent is mentioned
- Section 10.1.1: Clarification of AE collection during the Molecular Pre-screening period; Inclusion of CTCAE 4.03 Grade 5 (AEs leading to deaths) in AE assessment and grading; Clarification of AE reporting in case of progression of malignancy
- Section 10.1.3: Clarification on SAE reporting
- Section 10.1.4: Clarification on procedures and reporting in case of pregnancy
- Section 10.2.1: Update of liver safety monitoring
- Section 11.2: Clarification of data tracked in the IRT system
- Section 12.4.3: Deletion of start of new anti-neoplastic therapy as an intercurrent event attribute that characterizes the primary estimand for Parts A and B2
- Section 12.5: For Parts A and B2, summary statistics of plasma alpelisib (Parts A & B2) and paclitaxel (Part A only) concentrations by time point were added; For Part B1, the removal of time to deterioration in ECOG performance status and the addition of summary statistics of plasma alpelisib and paclitaxel concentrations by time point
- Section 12.5.1.1: removal of start of new antineoplastic therapy' from the intercurrent events)
- Section 12.5.1.2: Clarification of summary statistics that will be presented for ORR and CBR
- Section 12.5.2: Clarification of safety summaries that will presented in data analyses
- Section 12.5.4: Clarification of PRO assessments that will be included in the data analysis
- Section 13.5: Addition of materials provided to patient as part of patient engagement initiatives
- Section 15: Addition of new references
- Table 16-9: Protease inhibitors term has been deleted from the List of prohibited BCRP inhibitors to keep only drug name
- Section 16.3: Update of laboratory trigger definitions and follow-up requirements in case of Liver events

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.

Amendment 00-CN.01 (16-Oct-2020)

Amendment rationale

As of the release of this amendment, no site has been initiated and no subject has been screened or has received study treatment in China.

The main objective of this local amendment 00-CN.01 is to implement the Human Genetic Resources Administration of China (HGRAC) request to reduce the number of tumor slides requested for central PIK3CA mutation and PTEN expression testing in China. A total of 7 slides from a resection tissue or 11 slides from a core needle biopsy are considered adequate for prospective patient selection to determine a subject's biomarker eligibility of either having a PIK3CA mutation or PTEN loss.

Changes to the protocol

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.

- Section 5.1 Inclusion criteria 4: The number of slides required for screening is removed and instead reference to [redacted]
- Section 8.1 Screening: The number of slides required for screening is removed and instead references [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.

Protocol summary

Protocol number	CBYL719H12301
Full Title	EPIK-B3: A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of alpelisib (BYL719) in combination with nab-paclitaxel in patients with advanced triple negative breast cancer with either phosphoinositide-3-kinase catalytic subunit alpha (PIK3CA) mutation or phosphatase and tensin homolog protein (PTEN) loss without PIK3CA mutation
Brief title	Study assessing the efficacy and safety of alpelisib plus nab-paclitaxel in participants with advanced triple negative breast cancer who carry either a PIK3CA mutation or have PTEN loss without PIK3CA mutation
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 in combination with nab-paclitaxel is safe and effective in participants with advanced triple negative breast cancer (aTNBC) who carry either a PIK3CA mutation (Study Part A) or have PTEN loss (Study Parts B1 and B2). An investigator-initiated study in HER2-negative metastatic breast cancer patients who were treated with alpelisib combined with nab-paclitaxel included 12 participants with aTNBC. These TNBC participants had an Overall Response Rate (ORR) of 58%. Five of the 12 TNBC participants carried a Phosphatidylinositol-3-kinase (PI3K) pathway alteration in their tumor samples: 3 had a PIK3CA mutation, 1 had a PTEN loss without a PIK3CA mutation and 1 had both a PIK3CA mutation and PTEN loss. Clinical benefit was observed in all these participants.
Primary Objective(s)	**Part A** • to assess whether treatment with alpelisib in combination with nab-paclitaxel prolongs Progression Free Survival (PFS) compared to placebo in combination with nab-paclitaxel **Part B2*** • to determine whether treatment with alpelisib in combination with nab-paclitaxel prolongs Progression Free Survival (PFS) compared to placebo in combination with nab-paclitaxel **Part B1** • to assess the antitumor activity of alpelisib in combination with nab-paclitaxel based on the Overall Response Rate (ORR) with confirmed response at 6 months via local radiology assessments *Part B2 was not initiated
Secondary Objectives	**Part A and Part B2* secondary objectives:** • To assess whether treatment with alpelisib in combination with nab-paclitaxel prolongs Overall Survival (OS) compared to placebo in combination with nab-paclitaxel • To evaluate safety and tolerability • To evaluate the efficacy of alpelisib in combination with nab-paclitaxel measuring the ORR with confirmed response, Clinical Benefit Rate (CBR) with confirmed response, Duration of response (DOR) with confirmed response and Time To Response (TTR) based on local radiological assessments • To evaluate the association between PIK3CA mutation status as measured in Circulating Tumor Deoxyribonucleic Acid (ctDNA) at baseline with PFS upon treatment with alpelisib *Part B2 was not initiated **Part B1 secondary objectives:** • To evaluate safety and tolerability

	• To evaluate the efficacy measuring the CBR with confirmed response, DOR with confirmed response and TTR based on local radiological assessments
Study design	This is a phase III, multicenter, international, randomized, double-blind, placebo-controlled study in participants with aTNBC with either PIK3CA mutation or PTEN loss. Upon confirming either PIK3CA mutation and/or PTEN loss status, advanced TNBC participants meeting all other eligibility criteria will be assigned to either Part A (PIK3CA mutation regardless of PTEN loss), Part B1 (PTEN loss with PIK3CA unknown or non mutant) or B2 (PTEN loss without PIK3CA mutation). Part B1 is single-arm and open-label with approximately 32 participants receiving alpelisib combined with nab-paclitaxel. ORR and safety data after 6 months of follow-up will be used to make the decision on whether or not to initiate part B2. If the results of part B1 warrant further development in this patient population, additional participants with PTEN loss and without PIK3CA mutation and meeting all other eligibility criteria will be enrolled into Part B2. For both Part A and Part B2, participants will be randomized in a 1:1 ratio to receive alpelisib or placebo, combined with nab-paclitaxel. Randomization will be stratified by the line of therapy in the advanced/metastatic setting (1st line versus 2nd line); Hormone Receptor (HR) status of primary tumour (HR+ versus HR-); and prior treatment with checkpoint inhibitors (Yes versus No). In all Part A, Part B1 and Part B2, participants will continue to receive the study treatment until discontinuation due to disease progression, death, unacceptable toxicity, lost to follow-up or withdrawal of consent/opposition to use data/biological samples. Part B1, in participants with PTEN loss and without PIK3CA mutation, didn't meet its primary endpoint of ORR. Hence, Part B2 will not be initiated. Inaddition, Novartis decided to halt enrollment of Part A due to slow recruitment.
Study Population	The study was initially planned to include approximately 566 male or female adult participants with aTNBC who carry either a PIK3CA mutation (approximately 252 participants in Part A) or have PTEN loss (approximately 32 participants in Part B1 and 282 participants in Part B2*) and who have received no more than one prior line of therapy for metastatic disease. When recruitment was permanently halted, a total of 137 participants were randomized/enrolled (102 participants in Part A and 35 participants in Part B1). *Part B2 was not initiated
Key Inclusion criteria	No changes were made to the eligibility criteria since all participants were randomized prior to the permanent recruitment halt and the release of the protocol amendment 02. • Participant is ≥ 18 years old at the time of informed consent • Participant has histologically confirmed diagnosis of advanced (loco-regionally recurrent and not amenable to curative therapy, or metastatic (stage IV)) TNBC • Participant has either a measurable disease per RECIST 1.1 criteria or, if no measurable disease is present, then at least one predominantly lytic bone lesion or mixed lytic-blastic bone lesion with identifiable soft tissue component (that can be evaluated by CT/MRI) must be presentParticipant has adequate tumor tissue to identify the PIK3CA mutation status (either carrying a mutation or without a mutation) and the PTEN loss status; both of which will determine whether the Participant can be allocated to Part A - PIK3CA mutation regardless of PTEN status; or to Part B - PTEN loss • Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Participant has received no more than one line of therapy for metastatic disease. • Participant has adequate bone marrow and organ function
Key Exclusion criteria	• Participant has received prior treatment with any PI3K, mTOR or AKT inhibitor • Participant has a known hypersensitivity to alpelisib, nab-paclitaxel or to any of their excipients • Participant has not recovered from all toxicities related to prior anticancer therapies to NCI CTCAE version 4.03 Grade ≤1; with the exception of alopecia • Participant has central nervous system (CNS) involvement

	• Participant with an established diagnosis of diabetes mellitus type I or uncontrolled type II based on Fasting Plasma Glucose and HbA1c • Participant has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) based on investigator discretion • Participant has a history of acute pancreatitis within 1 year prior to screening or past medical history of chronic pancreatitis • Participant has currently documented pneumonitis/interstitial lung disease • Participant has a history of severe cutaneous reactions, such as Steven-Johnson Syndrome (SJS), erythema multiforme (EM),Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Syndrome (DRESS) • Participant with unresolved osteonecrosis of the jaw
Study treatment	For Study Part A and B2*, participants will be randomized 1:1 to receive either: • Experimental arm: alpelisib (at 300 mg orally, once daily) + nab-paclitaxel (at 100 mg/m2 intravenously at Days 1, 8 and 15 of a 28-day cycle); or • Control arm: placebo (orally, once daily) + nab-paclitaxel (at 100mg/m2 intravenously at Days 1, 8 and 15 of a 28-day cycle) For Study Part B1, all participants will receive alpelisib (at 300 mg orally, once daily) + nab-paclitaxel (at 100 mg/m^2 intravenously at Days 1, 8 and 15 of a 28-day cycle) *Part B2 was not initiated
Efficacy assessments	• Chest, abdomen, and pelvis, CT/MRI at screening and every 8 weeks (+/- 7 days) during the first 18 months and every 12 weeks thereafter until disease progression, end of treatment, death, withdrawal of consent/opposition to use data/biological samples, or lost to follow-up. Once all participants have completed 6 months of study treatment or have been discontinued from the study treatment, efficacy assessments will be performed locally as clinically indicated. • Survival status every 12 weeks (or earlier if required) until all participants have completed 6 months of study treatment or have been discontinued from study treatment
Pharmacokinetic assessments	• Blood samples to calculate PK parameters for alpelisib for participants enrolled in in Part [redacted] B2* • Blood samples to calculate PK parameters for paclitaxel for participants enrolled in Part [redacted] B1 *Part B2 was not initiated Following implementation of protocol Amendment 02, PK samples collection will stop
Key safety assessments	• Physical examination • Body weight and vital signs • ECOG performance status • Laboratory assessment including hematology, biochemistry, urinalysis and coagulation • Serum pregnancy test for women of child-bearing potential • Electrocardiogram (ECG) • Cardiac imaging • Monitoring of adverse events (AEs) and serious adverse events (SAE) Once all participants have completed 6 months of study treatment or have been discontinued from the study treatment, laboratory assessments will be performed locally.
Other assessments	[redacted]

	[redacted]
Data analysis	**Part A:** The primary efficacy analysis for Part A is to compare and summarize PFS between the two treatment groups descriptively. The primary analysis will be performed when all participants in Part A have completed 6 months of study treatment or have discontinued from study treatment, whichever occurs earlier. PFS will be analyzed based on the FAS according to the randomized treatment group and strata at randomization. The stratification factors include (i) line of therapy in advanced/metastatic setting (1st line versus 2nd line), ii) hormone receptor status at initial breast cancer diagnosis (HR+ versus HR-), and iii) prior therapy with checkpoint inhibitors (Yes/No). The PFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the stratification factors at randomization. **Part B1:** The primary efficacy variable is ORR with confirmed response at 6 months. Proof of preliminary efficacy of alpelisib in combination with nab-paclitaxel will be declared if both of the following conditions are met: (1) the mean of the posterior distribution of ORR is at least 35%; and (2) the posterior probability that the ORR is ≥ 25% is at least 0.9. The posterior distribution of ORR will be derived from the prior distribution and all available data from the participants included in the FAS. A minimally informative unimodal Beta prior will be used for ORR (see Section 16.4 for further details). Additionally, ORR will be summarized by a two-sided exact binomial 95% confidence interval. OS as one of the secondary variables will be analyzed in the FAS. The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model as PFS. Other secondary variables ORR with confirmed response and CBR with confirmed response will be calculated based on the FAS and according to the ITT principle. ORR and its 95% confidence interval will be presented by treatment group. TTR and DOR will be listed and summarized by treatment group. Time to definitive deterioration of ECOG performance status and EORTC QLQ-C30 global health status will be estimated using the Kaplan-Meier method. The median time along with 95% confidence intervals will be presented by treatment group. A stratified Cox regression model will be used to estimate the hazard ratio (HR) of time to definitive deterioration, along with 95% confidence interval. Safety assessment will be based on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. **Part B2:** Never initiated based on Part B1 results.
Key words	advanced triple negative breast cancer (aTNBC), alpelisib, nab-paclitaxel, PIK3CA, PTEN, PI3K pathway, PI3K inhibitor

1 Introduction

1.1 Background

1.1.1 Triple Negative Breast Cancer

Breast cancer (BC) is the most common cancer in women and the second leading cause of cancer-related death (National Breast Cancer Foundation 2018, Goetz et al 2019). In men, breast cancer is a rare condition constituting < 1% of all breast cancer diagnoses (Siegel et al 2019). Breast cancer can be categorized into different histopathologic subtypes based on the expression of the estrogen receptor (ER), the progesterone receptor (PR), and human epidermal growths factor receptor (HER2) overexpression or gene amplification. Triple-negative breast cancer (TNBC) is an aggressive clinical subset of BC defined by the lack of estrogen receptors (ERs) and progesterone receptors (PRs) and by human epidermal growth factor receptor 2 (HER2)-negative status and accounts for 15% to 20% of newly diagnosed breast cancer cases (Kohler et al 2015). TNBCs are sub-classified into multiple different subtypes based on their gene expression profiles (Lehmann et al 2011, Millis et al 2015, Burstein et al 2015, Bareche et al 2018, Shi et al 2018) making it challenging to treat.

Without hormone receptors to target, no specific recommendations or treatment standards existed for advanced TNBC until recently (Gradishar et al 2017, NCCN Breast Cancer 4.2017, Cardoso et al 2017). Cytotoxic chemotherapy was and is still the foundation of treatment for advanced TNBC. Sequential use of single-agent chemotherapy is the most widely practiced treatment strategy for metastatic TNBC (mTNBC) and is typically continued until disease progression or significant/unacceptable toxicity (Zeichner et al 2016, O'Dea AP 2017). Commonly used single chemotherapy agents include taxanes, platinum based agents, anthracyclines, antimetabolites, gemcitabine, vinca alkaloids, and nontaxane tubulin polymerizing agents, such as ixabepilone and eribulin (O'Dea AP 2017). The chemotherapy agent and sequence is individualized for each patient based on prior chemotherapy treatments, previous/ persisting toxicities, and patient preference. Although less common, combination chemotherapy may also be utilized in cases of visceral involvement or an aggressive clinical course (Zeichner et al 2016, Lebert et al 2018). Despite a high initial sensitivity to chemotherapy (Murray et al 2012, Zeichner et al 2016), patients with TNBC suffer high relapse rates, more aggressive visceral disease, a higher likelihood of distant disease progression, and a higher frequency of brain metastases than other breast cancer subtypes (Lebert et al 2018, Pascual and Turner 2019). Consequently, patients with TNBC have a shorter median survival, only 9-18 months (Liedtke et al 2008, Yardley et al 2018), representing a population with a high unmet medical need for targeted therapies to delay disease progression.

Recent approvals of the poly ADP ribose polymerase (PARP) inhibitors, olaparib and talazoparib, in HER2-negative advanced BC, as well as the approval of atezolizumab in combination with nab-paclitaxel in programmed cell death 1 ligand 1 (PD-L1) positive metastatic TNBC (Table 1-1), signal the beginning of targeted therapies for molecularly defined mTNBC subtypes. These therapies have been adapted into the most recent treatment guidelines (Lebert et al 2018, Cardoso et al 2018, NCCN Breast Cancer 1.2019, Goetz et al 2019). Various other therapeutic targets are also being investigated in mTNBC, both as single agent therapy and in combination with chemotherapy (Denkert et al 2017, Gerratana et al 2018,

Kim et al 2017, Kok et al 2017, Marra et al 2019, Miles et al 2016, Nanda et al 2016, Schmid et al 2019, Stover et al 2018, Traina et al 2017).

Table 1-1 Recently approved targeted therapies

Indication	Registration study summary
Olaparib(LYNPARZA®) monotherapy	
Lynparza is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments.	The OlympiAD, open-label, phase III, registration trial randomized 302 patients (205 olaparib, 97 placebo) to either olaparib or standard single agent chemotherapy. Median PFS was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs. 4.2 months; HR for disease progression or death = 0.58; 95% CI, 0.43 - 0.80; P<0.001). The response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group (Robson et al 2017).At the final OS analysis, median OS was 19.3 months with olaparib versus 17.1 months with standard single agent chemotherapy (HR = 0.90, 95% CI: 0.66, 1.23; P=0.513) (Robson et al 2019).
Talazoparib (Talzenna®) monotherapy	
Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments	The EMBRACA, open-label, phase III, registration trial randomized 287 patients to talazoparib and 144 to standard single agent chemotherapy. Median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months vs. 5.6 months; HR for disease progression or death = 0.54; 95% CI: 0.41, 0.71; P<0.001). The OS hazard ratio at the time of the PFS analysis was 0.76 (95% CI: 0.55,1.06; P=0.11; median of 22.3 vs 19.5 months) [57% of projected events]). The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% vs. 27.2%; P<0.001); (Litton et al 2018).
Atezolizumab (Tecentriq®), in combination with nab-paclitaxel	
TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1.	Impassion130, a double-blind, phase III study, randomized 451 untreated metastatic TNBC patients to atezolizumab plus nab-paclitaxel and 451 patients to placebo plus nab-paclitaxel. Median PFS, irrespective of PD-L1 status, was 7.2 months with atezolizumab plus nab-paclitaxel, as compared to 5.5 months with placebo plus nab-paclitaxel (HR=0.80; 95% CI: 0.69, 0.92; P=0.002). Among patients with PD-L1 positive tumors, the median PFS was 7.5 months and 5.0 months, respectively (HR=0.62; 95% CI: 0.49, 0.78; P<0.001). The median OS was 21.3 months with atezolizumab plus nab-paclitaxel versus 17.6 months with placebo plus nab-paclitaxel (HR=0.84; 95% CI: 0.69, 1.02; P = 0.08; [59% of projected events]); among patients with PD-L1 positive tumors, the median OS was 25.0 months and 15.5 months, respectively (HR=0.62; 95% CI: 0.45, 0.86) (Schmid et al 2018).

Indication	Registration study summary
	At the second interim OS analysis [80% of projected events], median OS for all subjects was 21.0 months versus 18.7 months, respectively (HR=0.86, 95% CI: 0.72, 1.02; P=0.0777); among patients with PD-L1 positive tumors, the median OS was 25.0 months and 18.0 months, respectively (HR=0.71; 95% CI: 0.54, 0.93 (Schmid et al 2019)).Recently, the CHMP also adopted a positive opinion for this combination in adult, chemotherapy-naive patients with unresectable locally advanced or metastatic triple-negative PD-L1-positive TNBC.

While a few targeted treatment options have been approved, overall, the treatment of TNBC remains challenging and new therapeutic options are needed to improve efficacy in patients with biomarker targets.

1.1.2 The PI3K pathway overview and the PI3K pathway in TNBC

PI3K Pathway

The phosphatidylinositol-3-kinase (PI3K) pathway is a central oncogenic pathway that regulates cell proliferation, cell metabolism, growth, survival and apoptosis. Constitutive activation of PI3K signaling is a critical step in mediating the transforming potential of oncogenes and tumor suppressors in many tumor types, with PI3K as the oncogenic driver of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway (Liu et al 2009).

Aberrant PI3K pathway activation can occur through several events including alterations in receptor tyrosine kinases (RTKs) (Chan et al 2002), mutations in Phosphoinositide-3-kinase catalytic subunit alpha (PIK3CA) gene, the gene encoding the p110α catalytic subunit of the class IA phosphatidylinositol 3-kinases (PI3Ks) PI3Kα (Burke et al 2012, Rodon et al 2013), and loss-of-function mutations, gene deletions, or transcriptional down-regulation in the tumor suppressor genes such as the phosphatase and tensin homolog (PTEN) (Lin et al 2012, Cossu-Rocca et al 2015, Bareche et al 2018). In TNBC, the majority of activating mutations occur in the alpha subunit (p110α) encoded by the PIK3CA gene, which are detected in approximately 9% of primary TNBC tumors and this may be enhanced in advanced TNBC (Lin et al 2012, TCGA 2012, Weisman et al 2016, Pascual and Turner 2019). The prevalence of PIK3CA mutations was higher in Chinese TNBC populations at 18% (Jiang et al 2019) and 28% (Chen et al 2018), compared to the prevalence of 9% reported in the global Translation Cancer Genome Atlas (TCGA) database (TCGA 2012).

Role of PTEN in PI3K pathway activation

Phosphatase and tensin homolog (PTEN) is a protein (phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase) that is encoded by the PTEN gene, a tumor suppressor gene. Inactivation of the PTEN gene can result in abnormal PI3K pathway activation via loss-of-function mutations, gene deletions, or transcriptional down-regulation. PTEN loss and PIK3CA hotspot mutations appear to be generally mutually exclusive in TNBC. The TCGA analysis showed an overlap of approximately 3% between PTEN loss hetero/homozygosity and PIK3CA mutations, an overlap of approximately 15% with PTEN loss hetero/homozygosity and PD-L1 upregulation, an overlap of approximately 10% with PTEN loss and PIK3CA amplification, and an overlap of approximately 9% between PIK3CA amplification and PIK3CA mutation (TCGA 2012).

PTEN loss is typically determined by reduction in PTEN protein expression based on immunohistochemistry (IHC) because PTEN is regulated post-transcriptionally (Zhang and Yu 2010). PTEN loss has been reported in approximately 11-66% of TNBC patients, as determined by different IHC assays and thresholds, with an average of approximately 36% between these studies (Gonzalez-Angulo et al 2011, Lin et al 2012,TCGA 2012 , Millis et al 2015, Cossu-Rocca et al 2015).

In the SAFIR02 trial (NCT02299999), 649 patients with metastatic BC (mBC), available mutational profile and clinical data were selected for outcome analyses with PIK3CA mutations, which were prospectively determined by next-generation sequencing (NGS) on metastatic samples. Ten percent (n=27) of TNBC tumors presented with a PIK3CA mutation. PIK3CA mutations were noted at a higher frequency in patients whose primary tumor was HR-positive and then changed to HR-negative (39% (14/36) of patients) as compared to those that were HR-negative at primary and metastatic tumor assessment (7% (9/138)). The median OS in the TNBC patients with a PIK3CA mutation was 24.2 months vs. 14.0 months for patients with TNBC PIK3CA wild type tumors (p=0.028) This improvement in median OS could be explained by an enrichment of PIK3CA mutations in luminal breast cancer tumors who lost HR positivity in the metastatic setting (Mosele et al 2019).

PI3K pathway and therapy resistance

Activation of the PI3K pathway plays a role in endocrine resistance in HR-positive BC (Campbell et al 2001, Mills et al 2018). Additionally it has been linked to intrinsic and acquired resistance to paclitaxel (McCubrey et al 2006). While the exact mechanisms underlying the development of treatment resistance towards taxanes are not well elucidated, it has been shown that inhibition of the PI3K/AKT pathway increased sensitivity of taxane resistant breast cancer cell lines to paclitaxel (Zhang et al 2015, Zhang et al 2017, Zhou et al 2019). In addition, concomitant inhibition of the PI3K pathway enhanced the efficacy of taxanes in both human breast cancer cell lines and xenograft breast cancer mouse models (Wallin et al 2012).

Clinical data on PI3K pathway activation in TNBC

Recent clinical studies have demonstrated that inhibition of the PI3K pathway improved efficacy in advanced TNBC. In a double-blind, placebo-controlled Phase II study (LOTUS) in first-line, advanced TNBC subjects with a PIK3CA/AKT1/PTEN alteration (by NGS) or PTEN low status (by IHC), 62 subjects were randomized to ipatasertib (an AKT inhibitor) plus paclitaxel and 62 subjects were randomized to placebo plus paclitaxel. For the intent-to-treat (ITT) population, median Progression Free Survival (PFS) was 6.2 months for ipatasertib plus paclitaxel compared to 4.9 months for placebo plus paclitaxel (HR=0.60, 95% CI: 0.37, 0.98, p=0.037). For subjects with PTEN low status, median PFS was 6.2 months with ipatasertib plus paclitaxel (n=25) vs 3.6 months with paclitaxel (n=23), stratified HR=0.59, 95% CI: 0.26, 1.32, p=0.18). For subjects with PIK3CA/AKT1/PTEN alterations, median PFS was 9.0 months with ipatasertib plus paclitaxel (n=26) vs 4.9 months with paclitaxel (n=16), HR=0.44, 95% CI: 0.20, 0.99). Of the 42 subjects with PIK3CA/AKT1/PTEN alterations, 18 (43%) had PIK3CA alterations, 8 (19%) had AKT1 alterations, and 16 (38%) had PTEN alterations. Overall Response Rate (ORR) was 40% vs 32% for all subjects, 48% vs 26% for subjects with PTEN low status, and 50% vs 44% for subjects with PIK3CA/AKT1/PTEN alterations. Duration of response was 7.9 vs 7.4 months for all subjects, 6.5 vs 7.5 months for subjects with PTEN low

status, and 11.2 vs 6.1 months for subjects with PIK3CA/AKT1/PTEN alterations (Kim et al 2017).

In the double-blind, placebo-controlled Phase II PAKT study in previously untreated metastatic TNBC, 70 subjects were randomized to capivasertib (another AKT inhibitor) in combination with paclitaxel and 70 subjects were randomized to placebo in combination with paclitaxel. For the intent-to-treat population, median PFS was 5.9 months for capivasertib plus paclitaxel compared to 4.2 months for placebo plus paclitaxel (HR=0.74, 95% CI: 0.50, 1.08, P=0.06). For subjects with PIK3CA/AKT1/PTEN alterations, median PFS was 9.3 months in 17 subjects in the capivasertib arm versus 3.7 months in 11 subjects in the placebo arm, HR=0.30, 95% CI: 0.11, 0.79, p=0.01)(Schmid et al 2018). Therefore, the PI3K pathway is an important target in advanced TNBC.

1.1.3 Overview of Alpelisib

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

1.1.3.1 Non-clinical experience

Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα and Akt-signaling, cellular transformation and the generation of tumors in in vitro and in vivo models.

In breast cancer cell lines, alpelisib inhibited the phosphorylation of PI3K downstream targets, including Akt and showed activity in cell lines harboring a PIK3CA mutation. In vivo, alpelisib inhibited the PI3K/Akt signaling pathway and reduced tumor growth in xenograft models, including models of breast cancer.

More detailed information on the pharmacology of alpelisib, single and multiple dose pharmacokinetic (PK) studies conducted in multiple species and nonclinical safety evaluations can be found in the Investigator's Brochure (IB).

1.1.3.2 Clinical experience

Clinical Study CBYL719C2301 leading to alpelisib approval:

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 42 clinical studies and as of 23-May 2022, 25 studies have been completed and 17 studies are ongoing. In general, the data suggest that the safety profile of alpelisib is acceptable with manageable, and reversible AEs. The IB provides a more detailed review of the preclinical and clinical information on alpelisib.

Approval of alpelisib was primarily based on efficacy and safety data from Study CBYL719C2301 (SOLAR-1, Study CBYL719C2301, André et al 2019), which met its primary endpoint in subjects with a PIK3CA mutation. A statistically significant and clinically meaningful improvement in median PFS in favor of the alpelisib plus fulvestrant arm (HR = 0.65; 95% CI: 0.50, 0.85; p=0.00065, one-sided) was observed. Median PFS was prolonged by 5.3 months, from 5.7 months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm to 11.0 months (95% CI: 7.5, 14.5) in the alpelisib plus fulvestrant arm.

[redacted]

Clinical trials with alpelisib data in TNBC:

Alpelisib has been explored, and demonstrated activity, in two studies including patients with advanced TNBC.

Study CBYL719X2101

Study CBYL719X2101 was a Phase I dose escalation study in patients with advanced solid tumors. Five subjects with TNBC were included in this study and treated with alpelisib monotherapy. Of these, 3 had tumors harboring a PIK3CA amplification or mutation and were treated with once daily alpelisib. Encouraging early activity of alpelisib was observed in 2 of these three heavily pre-treated subjects with TNBC:

- One subject (alpelisib starting dose of 300 mg per day) was on study treatment for 442 days and had a best response of Stable Disease (SD) with 23.5% tumor shrinkage
- A second subject (alpelisib starting of dose 400 mg per day) was on study treatment for 168 days and had an unconfirmed Partial Response (PR) with 37.5% tumor shrinkage

The third subject (alpelisib starting dose of 300 mg per day) was on study for 3 days.

Study CBYL719XUS06T

Alpelisib in combination with nab-paclitaxel was explored in a Phase I/II investigator initiated study, Study CBYL719XUS06T (NCT02379247), in 43 subjects with HER2-negative, advanced breast cancer (regardless of PI3K pathway activation or PTEN status) who had received ≥ 1 prior line of chemotherapy (prior taxane treatment, except nab-paclitaxel, was permitted) in either advanced or adjuvant setting (Sharma et al 2018, Sharma et al 2021).

The primary objectives were to determine the recommended phase II dose (RPTD) of alpelisib + nab-paclitaxel and to assess the overall response rate (ORR). Phase I was a 3+3 dose-escalation design with 3 dose levels of alpelisib (250 mg, 300 mg, and 350 mg) administered PO once daily (Days 1-28) with nab-paclitaxel at 100 mg/m^2 i.v. on Days 1, 8, and 15 of a 28 day cycle. Phase II was a Simon's two stage minimax design targeting an ORR of 40% (NCT02379247).

In the Phase I portion of the study, there were no DLTs and no PK interactions reported for the 9 evaluable subjects (n=10; 1 patient stopped treatment within 10 days). The recommended Phase II dose (RP2D) for alpelisib was 350 mg with nab-paclitaxel at 100 mg/m^2 i.v. on Days 1, 8, and 15 of a 28 day cycle. In the Phase II portion of the study, 33 subjects were treated at the RP2D. PI3K pathway-activation, defined as the presence of PIK3CA-activating or PTEN-inactivating mutations, was tested in either tumor tissue or ctDNA and was observed in 44% (19/43) of patients.

In the overall study population, 23%, 69%, and 8% of subjects had been treated with 0, 1, or ≥ 2 lines of prior chemotherapy for metastatic breast cancer, respectively. Nine subjects continued on treatment for > 12 months; 5 of these had a PIK3CA mutation. For the 42 evaluable subjects (1 subject did not have response data), the ORR was 60% and CBR was 79%. For subjects with a PIK3CA mutation, the ORR was 74% and CBR was 100%. Median PFS was 13 months for subjects with a PIK3CA mutation (n=19) compared to 7 months for those without a PIK3CA mutation (n=23) (HR=0.40; 95% CI: 0.18, 0.90, p=0.017).

Twelve of the 43 subjects had advanced TNBC. The majority of these subjects were treated with an alpelisib dose of 350 mg (250 mg (n=2), 300 mg (n=1), and 350 mg (n=9)), in combination with nab-paclitaxel. The ORR and CBR for these 12 TNBC subjects was 58%.

Five of the 12 TNBC subjects' tumors harbored a PI3K pathway alteration: 3 had a PIK3CA mutation, 1 had PTEN loss without a PIK3CA mutation, and 1 had both a PIK3CA mutation and PTEN loss. Clinical benefit was observed in all TNBC patients with a PI3K pathway activated tumor.

The following best overall responses were observed among the 12 subjects with TNBC:

- Two (17%) subjects had a CR (one with a PIK3CA mutation without PTEN loss, one with PIK3CA mutation with PTEN loss).
- Five (42%) subjects had a PR (one with a PIK3CA mutation without PTEN loss, one with PTEN loss without a PIK3CA mutation).
- Two (17%) subjects had SD (one with a PIK3CA mutation without PTEN loss).
- Three (25%) subjects had PD (none had a PIK3CA mutation or PTEN loss).

Clinical benefit was observed in all TNBC patients with a PI3K pathway activated tumor.

In study CBYL719XUS06T, the safety profile for alpelisib in combination with nab-paclitaxel was consistent with the known adverse event profiles of each medication. The following is a summary of the safety observations among the 43 patients:

- Hyperglycemia was noted in 76% of subjects (grade 3 = 27%, no grade 4 events) with 32% of patients requiring metformin for hyperglycemia management.
- Rash was noted in 63% of subjects (grade 3 = 7%, no grade 4 events). All subjects received second or third generation H1-anti-histaminic for rash prophylaxis.
- Alpelisib dose reductions occurred in 26% (11/43) of subjects (n=1 at 250 mg dose, n=10 at 350 mg dose). The reasons for alpelisib dose reductions were: fatigue/anorexia (n=3), diarrhea (n=3), rash (n=2), hyperglycemia (n=1), hypokalemia (n=1), and investigator's choice (n=1).
- Two subjects discontinued therapy (after two cycles) due to grade 2 pneumonitis.
- Nab-Paclitaxel dose reductions occurred in 28% (10/43) of subjects. The reasons for nab-paclitaxel dose reductions were: peripheral neuropathy (n=3), fatigue (n=1), rash (n=1), diarrhea (n=1), thrombocytopenia (n=1), neutropenia (n=1), and investigator's choice (n=2).
- Two subjects stopped nab-paclitaxel and continued on single agent alpelisib. Both of these subjects stopped alpelisib at 12 weeks due to progressive disease (one subject's tumor had a PIK3CA mutation, the other did not.)

The incidence of AEs reported, by severity are presented in protocol Section 4.2, Table 4-1. Overall, the combination of alpelisib and nab-paclitaxel was well tolerated with manageable toxicities. No unexpected toxicity signals were observed.

In summary, these data demonstrate promising early anti-tumor activity of alpelisib in advanced Breast Cancer (aBC) where the PI3K pathway is activated by the presence of a PIK3CA mutation or PTEN loss and warrant the investigation of the combination of alpelisib with nab-paclitaxel in advanced TNBC.

Clinical Pharmacology

The pharmacokinetics of alpelisib has been studied in healthy subjects and adult patients with solid tumors. Steady-state alpelisib maximum plasma concentration (Cmax) and Area under the curve (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 Study CBYL719C2301, 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 approach analysis. The median time to reach peak plasma concentration (Tmax) ranged between 2.0 to 4.0 hours. The half-life of alpelisib is predicted to be 8 to 9 hours. The mean (%CV) clearance of alpelisib is predicted to be 9.2 L/hr (21%) under fed conditions.

A high-fat high-calorie meal (985 calories with 58.1 g of fat) increased alpelisib AUC by 73% and Cmax by 84%, and a low-fat low-calorie meal (334 calories with 8.7 g of fat) increased alpelisib AUC by 77% and Cmax by 145% following a single dose of alpelisib. No clinically

significant differences in alpelisib AUC were observed between low-fat low-calorie and high-fat high-calorie meals. Alpelisib can be co-administered with acid reducing agents, as long as it is taken following food, since food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH.

Alpelisib is primarily metabolized by chemical and enzymatic hydrolysis to form its metabolite BZG791 and to a lesser extent by Cytochrome P450 (CYP)3A4 in vitro. 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 Breast Cancer Resistance Protein (BCRP), its elimination may be affected when co-administered with BCRP inhibitors.

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

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

1.2 Purpose

Advanced TNBC is a heterogeneous disease and effective treatments are lacking (see Section 1.1.1). There is a high, unmet need for novel therapies or the combination of new therapies with established chemotherapy agents. Although taxanes are effective early on in advanced stage breast cancer, resistance often develops (O'Reilly et al 2015). While the exact mechanism(s) underlying the development of treatment resistance towards taxanes remain largely unknown, it has been demonstrated that activation of the PI3K/AKT pathway confers resistance to paclitaxel (Hu et al 2002, Zhang et al 2017, Zhou et al 2019) and that increased AKT activity may be an early compensatory mechanism of chemotherapy resistance (Clark et al 2002). Additionally, in preclinical models, concomitant inhibition of the PI3K pathway enhances the efficacy of taxanes as compared to each agent given separately (Hu et al 2002). PI3K/AKT/mTOR represents the main signaling pathway responsible for cell proliferation, survival, metabolism and motility regulation and is often activated in breast cancer. Targeting the PI3K/AKT/mTOR pathway is of increasing interest in patients which harbor genetic alterations in this pathway and provides the rationale for studying the combination of nab-paclitaxel with the alpha-specific PI3K inhibitor alpelisib in advanced TNBC.

In the Study CBYL719C2301, alpelisib plus fulvestrant significantly improved PFS and ORR in patients with hormone receptor positive, HER2-negative advanced breast cancer with PIK3CA mutation, which progressed on or after aromatase inhibitor treatment, compared to fulvestrant alone (André et al 2019). Approximately 40% of HR+ advanced breast cancer patients harbor a PIK3CA mutation, which is associated with poor prognosis. Since approximately 9% of TNBC patients also harbor PIK3CA mutations, and it is believed that

these mutations are both a driver of tumor development as well as therapy resistance (Massihnia et al 2016, Zhang et al 2017) alpelisib given in combination with nab-paclitaxel may provide additional clinical benefit.

Given promising efficacy signals from a phase I/II investigator initiated trial in HER2-negative mBC patients, including 12 patients with metastatic TNBC (PIK3CA mutant, PIK3CA wild type, and PTEN loss) (CBYL719XUS06T; Sharma et al 2018, Sharma et al 2021), the goal of this study is to determine if targeted therapy with the alpha-specific PIK3CA inhibitor, alpelisib, in combination with nab-paclitaxel, is safe and effective in patients with advanced TNBC harboring a PIK3CA mutation, or PTEN loss.

2 Objectives, endpoints and estimands

Table 2-1 Objectives, and related endpoints for Part A (TNBC with PIK3CA mutation)

	Objective	Endpoint (s)
Primary	To assess whether treatment with alpelisib in combination with nab-paclitaxel prolongs PFS compared to placebo in combination with nab-paclitaxel	Progression Free Survival (PFS) based on investigator assessment using RECIST 1.1 criteria (refer to Section 2.1 for the primary estimand)
Secondary	To assess whether treatment with alpelisib in combination with nab-paclitaxel prolongs OS compared to placebo in combination with nab-paclitaxel	Overall Survival (OS)
	To assess safety and tolerability of alpelisib in combination with nab-paclitaxel	**Safety:** Incidence, type, and severity of adverse events per CTCAE v4.03 criteria including changes in laboratory values, vital signs, liver assessments, renal and cardiac assessments **Tolerability:** dose interruptions, reductions, dose intensity, and duration of exposure for all drug components
	To assess additional efficacy parameters	ORR with confirmed response, CBR with confirmed response, Duration Of Response (DOR) with confirmed response, TTR based on local radiology assessments and using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria Refer to Section 2.2 for the ORR endpoint definition (the summary measure attribute of the secondary estimand).
	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 using RECIST 1.1 criteria for participants by PIK3CA mutation status measured in baseline ctDNA
[redacted]		

[redacted]

Table 2-2 Objectives and related endpoints for Part B1 (TNBC with PTEN loss)

	Objective	Endpoint (s)
Primary	To assess the antitumor activity of alpelisib in combination with nab-paclitaxel	Overall response rate (ORR) with confirmed response using RECIST 1.1 criteria (refer to Section 2.1 for the primary estimand)
Secondary	To determine the safety and tolerability of alpelisib in combination with nab-paclitaxel	**Safety:** Incidence, type, and severity of adverse events per CTCAE v4.03 criteria including changes in laboratory values, vital signs, liver assessments, renal and cardiac assessments **Tolerability:** dose interruptions, reductions, dose intensity, and duration of exposure for all drug components
	To evaluate additional efficacy parameters of alpelisib in combination with nab-paclitaxel	CBR with confirmed response, DOR with confirmed response, TTR, and PFS (based on local radiology assessments and using RECIST 1.1 criteria), OS

[redacted]

[redacted]

Table 2-3 Objectives and related endpoints for Part B2 (TNBC with PTEN loss without PIK3CA mutation)

The enrollment in Part B1 was completed in February 2022. In November 2022, Novartis decided to halt enrollment to Part A due to slow recruitment. Part B2 was not initiated since Part B1 results didn't meet the primary endpoint of ORR.

	Objective	Endpoint (s)
Primary	To determine whether treatment with alpelisib in combination with nab-paclitaxel prolongs PFS compared to placebo in combination with nab-paclitaxel	Progression Free Survival (PFS) based on investigator assessment using RECIST 1.1 criteria (refer to Section 2.1 for the primary estimand)
Key Secondary	To determine whether treatment with alpelisib in combination with nab-paclitaxel prolongs OS compared to placebo in combination with nab-paclitaxel	Overall Survival (OS) (refer to Section 2.2 for the key secondary estimand)
Secondary	To assess safety and tolerability of alpelisib in combination with nab-paclitaxel	**Safety**: Incidence, type, and severity of adverse events per CTCAE v4.03 criteria including changes in laboratory values, vital signs, liver assessments, renal and cardiac assessments **Tolerability**: dose interruptions, reductions, dose intensity, and duration of exposure for all drug components
	To assess additional efficacy parameters	ORR with confirmed response, CBR with confirmed response, DOR with confirmed response, TTR based on local radiology assessments and using RECIST 1.1 criteria Refer to Section 2.2 for the ORR endpoint definition (the variable attribute of the secondary estimand).
	To characterize exposure of alpelisib when administered in combination with nab-paclitaxel	Summary statistics of plasma alpelisib concentrations by time point
	To evaluate patient-reported outcomes of alpelisib in combination with nab-paclitaxel versus placebo with nab-paclitaxel	1) Change from baseline in the global health status/QoL scale score of the EORTC QLQ-C30 2) Time to 10% definitive deterioration in the global health status/QOL scale score of the EORTC QLQ-C30
	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 using RECIST 1.1 criteria for participants by PIK3CA mutation status measured in baseline ctDNA
	To evaluate alpelisib in combination with nab-paclitaxel versus placebo with nab-paclitaxel with respect to time to deterioration of ECOG performance status	Time to definitive deterioration of the ECOG performance status from baseline

2.1 Primary estimand

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g. premature discontinuation of treatment). The section below describes the primary estimand for all Study Parts. Supplementary estimands to the primary estimand are defined in Section 12.

Part A:

The primary scientific question of interest is: what is the treatment effect based on PFS for alpelisib in combination with nab-paclitaxel versus placebo in combination with nab-paclitaxel in men and women with advanced (locally recurrent or metastatic) TNBC with a PIK3CA mutation (with or without concurrent PTEN loss), regardless of study treatment discontinuation or start of new anti-neoplastic therapy?

The justification for targeting this treatment effect is that we wish to estimate the treatment effect during the whole course of the study including after study treatment discontinuation; and compare not just alpelisib+nab-paclitaxel versus placebo+nab-paclitaxel, but alpelisib+nab-paclitaxel followed by any new anti-neoplastic therapy versus placebo+nab-paclitaxel followed by any new anti-neoplastic therapy, i.e. any subsequent anti-neoplastic therapy is part of the treatment attribute.

The primary estimand is characterized by the following attributes:

1. Population: all participants randomized with advanced (locally recurrent or metastatic) TNBC with a PIK3CA mutation. Further details on the population are provided in Section 5.

2. Treatment: the investigational treatment is alpelisib in combination with nab-paclitaxel plus any subsequent anti-neoplastic therapy as needed. The control treatment is placebo in combination with nab-paclitaxel plus any subsequent anti-neoplastic therapy as needed. Further details about the investigational treatment and control treatment are provided in Section 6.

3. Variable: PFS based on local investigator assessment and using RECIST 1.1 criteria. Further details on PFS are provided in Section 12.4.1.

4. Intercurrent events:

discontinuation of study treatment for any reason (treatment policy strategy).

Details on how to handle intercurrent events are provided in Section 12.4.3.

5. Summary measure: PFS hazard ratio (alpelisib versus placebo) and its 95% confidence interval, estimated using a Cox proportional hazard model stratified by the randomization stratification factors. Further details on how the summary measure will be tested are provided in Section 12.4.2.

Part B1

The scientific question of interest is: what is the treatment effect based on ORR for alpelisib in combination with nab-paclitaxel in men and women with advanced (locally recurrent or metastatic) TNBC with PTEN loss prior to treatment discontinuation date+30 days or prior to start of new anti-neoplastic therapy, whichever occurs first.

The justification for targeting this treatment effect is the intent to assess the treatment effect during the on-treatment period and up to 30 days after the discontinuation of treatment.

The primary estimand is characterized by the following attributes:

1. Population: all participants enrolled with advanced (locally recurrent or metastatic) TNBC with PTEN loss. Further details on the population are provided in Section 5.

2. Treatment: the investigational treatment is alpelisib in combination with nab-paclitaxel. Further details about the investigational treatment are provided in Section 6.

3. Variable: Best overall response with confirmed response after 6 months of treatment based on local investigator assessment and using RECIST 1.1 criteria. Further details on ORR are provided in Section 12.4.1.

4. Intercurrent events:

· discontinuation of study treatment for any reason (while on-treatment strategy).

· start of new anti-neoplastic therapy (while on-treatment strategy)

Details on how to handle intercurrent events are provided in Section 12.4.3.

5. Summary measure: ORR with confirmed response and its 95% confidence interval . Further details on how the summary measure will be tested are provided in Section 12.4.2.

Part B2:

The primary scientific question of interest is: what is the treatment effect based on PFS for alpelisib in combination with nab-paclitaxel versus placebo in combination with nab-paclitaxel in participants with advanced (locally recurrent or metastatic) TNBC with PTEN loss (without PIK3CA mutation), regardless of study treatment discontinuation or start of new anti-neoplastic therapy?

The justification for targeting this treatment effect is that we wish to estimate the treatment effect during the whole course of the study including after study treatment discontinuation; and compare not just alpelisib+nab-paclitaxel versus placebo+nab-paclitaxel, but alpelisib+nab-paclitaxel followed by any new anti-neoplastic therapy versus placebo+nab-paclitaxel followed by any new anti-neoplastic therapy, i.e. any subsequent anti-neoplastic therapy is part of the treatment attribute.

The primary estimand is characterized by the following attributes:

1. Population: all participants randomized with advanced (locally recurrent or metastatic) TNBC with PTEN loss (without PIK3CA mutation). Further details on the population are provided in Section 5.

2. Treatment: the investigational treatment is alpelisib in combination with nab-paclitaxel plus any subsequent anti-neoplastic therapy as needed. The control treatment is placebo in combination with nab-paclitaxel plus any subsequent anti-neoplastic therapy as needed. Further details about the investigational treatment and control treatment are provided in Section 6.

3. Variable: PFS based on local investigator assessment and using RECIST 1.1 criteria. Further details on PFS are provided in Section 12.4.1.

4. Intercurrent events:

· discontinuation of study treatment for any reason (treatment policy strategy).

Details on how to handle intercurrent events are provided in Section 12.4.3.

5. Summary measure: PFS hazard ratio (alpelisib versus placebo) and its 95% confidence interval, estimated using a Cox proportional hazard model stratified by the randomization stratification factors. Further details on how the summary measure will be tested are provided in Section 12.4.2.

2.2 Key secondary estimand

Part A:

Not applicable following protocol amendment 02.

Part B2:

Not applicable following protocol amendment 02.

3 Study design

Study CBYL719H12301 has been designed as a three part, Phase III, multicenter, international trial evaluating the efficacy and safety of alpelisib in combination with nab-paclitaxel in 1st or 2nd line therapy of advanced (loco-regionally recurrent or metastatic) TNBC with a PIK3CA mutation or PTEN loss.

- Part A: randomized, double-blind (DB) and placebo-controlled.
- Part B1: single-arm, open-label (OL).
- Part B2: randomized, double-blind and placebo-controlled.

Enrollment in Part B1 was completed in February 2022. In November 2022, Novartis took the decision to halt the enrollment to the Part A due to slow recruitment. Additionally, Part B2 was not initiated since Part B1 didn't meet its primary endpoint of ORR.

The reference to Part B2 remains in the protocol to reflect the initial study design and avoid confusion. Part B2 will not be conducted.

Part A: Advanced TNBC with PIK3CA mutation

The purpose of study Part A is to assess PFS in participants treated with alpelisib in combination with nab-paclitaxel vs. participants treated with placebo in combination with nab-paclitaxel in advanced TNBC participants with a PIK3CA mutation (with or without concurrent PTEN loss). Approximately 252 participants were intially planned to be randomly assigned to receive either alpelisib plus nab-paclitaxel or placebo plus nab-paclitaxel. With the halt of recruitment in Part A, a total of 102 participants were randomized in this part of the study.Randomization to treatment will follow a 1:1 ratio and will be stratified by three factors of prognostic value: i) line of therapy in advanced/metastatic setting (1st line versus 2nd line), ii) hormone receptor status at initial breast cancer diagnosis (HR+ versus HR-), and iii) prior therapy with a checkpoint inhibitor (Yes versus No).

For stratification factor i) line of therapy in advanced/metastatic setting the following applies:

- A patient will be stratified as 1st line if he/she has NOT received any prior treatment for advanced/metastatic BC.
- A patient will be stratified as 2nd line if he/she has received one prior line of treatment for advanced/metastatic BC and subsequently progressed.

Note: Endocrine-based therapy for HR+ advanced/metastatic BC should not be counted as a line of treatment. If a treatment regimen was stopped for toxicity without documentation of disease progression and another treatment regimen started subsequently, this should be considered as the same "line of therapy".

Part B1: Advanced TNBC with PTEN loss

The purpose of study part B1 is to determine whether alpelisib in combination with nab-paclitaxel in 32 participants with advanced TNBC and PTEN loss (with PIK3CA unknown or non-mutant) warrants further development. PIK3CA status is defined as 'unknown' if the PIK3CA results from the PIK3CA mutation assay are reported as invalid based on specified assay control parameters. ORR and safety data after 6 months of follow-up will be used to make the decision on whether or not to initiate part B2.

Enrollment was completed for Part B1; a total of 35 participants were enrolled.

Note: Participants with a PIK3CA mutation and concurrent PTEN loss are only eligible to be randomized into Part A of this study.

Part B2: Advanced TNBC with PTEN loss (without PIK3CA mutation)

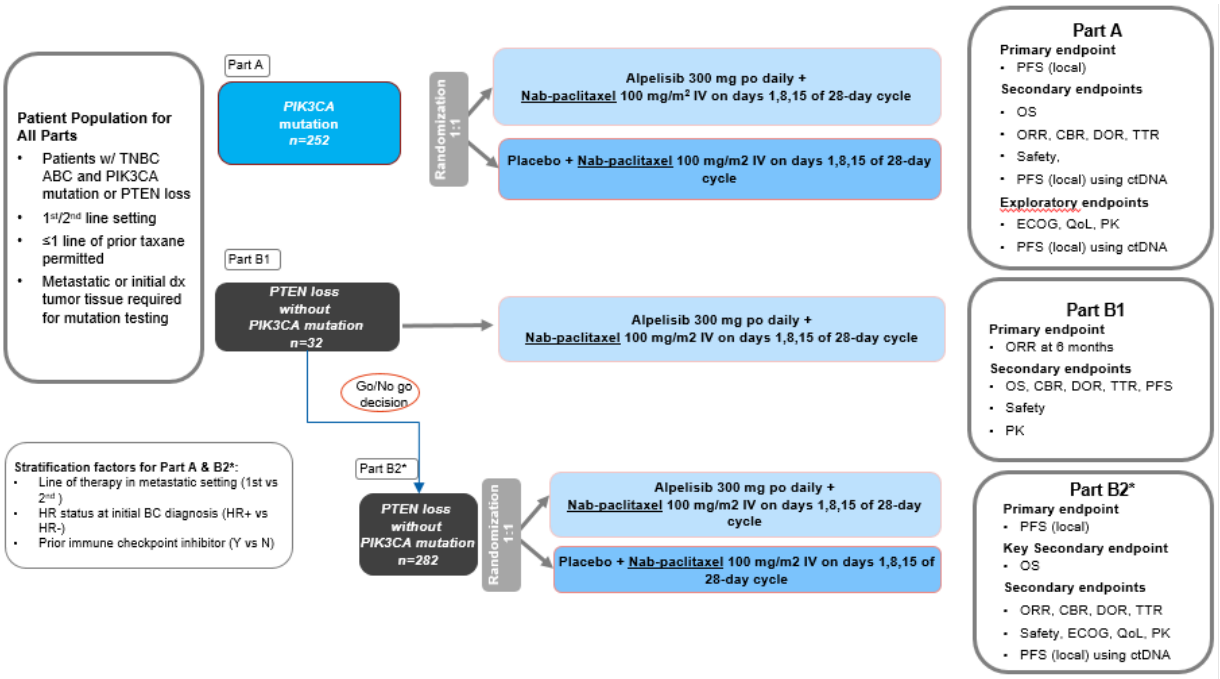
If review of Part B1 results leads to the decision to open Part B2, (refer to Section 12.4.1), the purpose of Part B2 is to determine whether treatment with alpelisib in combination with nab-paclitaxel prolongs PFS compared to placebo in combination with nab-paclitaxel in advanced TNBC participants with PTEN loss (without a concurrent PIK3CA mutation).

Approximately 282 participants will be randomly assigned to receive either alpelisib plus nab-paclitaxel or placebo plus nab-paclitaxel.

Randomization to treatment will follow a 1:1 ratio and will be stratified by three factors of prognostic value: i) line of therapy in advanced/metastatic setting (1st line versus 2nd line), ii) hormone receptor status at initial breast cancer diagnosis (HR+ versus HR-), and iii) prior therapy with a checkpoint inhibitor (Yes versus No). The stratification factors and definition of line of therapy for Parts A and B2 are identical.

Part B2 was not initiated since Part B1 did not meet its primary endpoint of ORR.

Figure 3-1 Study design



*Not applicable after protocol amendment 02.

Pre-Screening period

Pre-Screening starts upon signature of the molecular pre-screening Informed Consent Form (ICF) by the study participant.

PIK3CA mutation status (refer to Section 8.1) and PTEN expression status will be assessed centrally using fresh or archival tumor samples (locally advanced or metastatic tumor tissue) by a Novartis designated laboratory. If a participant's PIK3CA mutation status is already available and was assessed by a local laboratory using either a Food and Drug Administration (FDA)-approved PIK3CA Companion Diagnostic (CDx) test for alpelisib or the CE-IVD QIAGEN *therascreen*® PIK3CA RGQ Polymerase Chain Reaction (PCR) test (Refer to Section 8.1), the mutation status may be used for enrollment into this study and must be documented in the source documents. In such cases central confirmation of PIK3CA mutation

status by a Novartis designated laboratory is not required prior to randomization. [redacted]

PIK3CA mutation results generated by "research use only" version of the Qiagen test, or other laboratory-developed tests, are not acceptable.

- Participants with a PIK3CA mutation (regardless of PTEN loss) will be eligible only for Part A of the study.
- Participants with PTEN loss without a PIK3CA mutation will be eligible for part B1 or part B2 of the study.
- Participant with PTEN loss and unknown PIK3CA mutation status will be eligible for part B1 only
- Participants with unknown or unconfirmed PIK3CA mutation status and with unknown or unconfirmed PTEN status will not be eligible for this study.

Screening period

Screening starts upon signature of the main study ICF by any study participant who meets the molecular pre-screening criteria.

Treatment period

This period begins when the first dose of study treatment is administered to a participant and ends with documentation of progressive disease per RECIST 1.1, unacceptable toxicity or until discontinuation of study treatment due to any other reason.

Once all participants have completed 6 months of study treatment or have been discontinued from the study treatment, participants and investigators will be unblinded and participants will have the option to continue with their assigned treatment.

Participants in the control arm receiving placebo in combination with nab-paclitaxel will not have the option to transition to the experimental arm (alpelisib in combination with nab-paclitaxel).

End of treatment

Participants will be scheduled for an End of Treatment (EOT) visit within 14 days after discontinuation of study treatment due to any reason (except death).

Safety follow-up

Participants will be followed for safety evaluations 30 days after last administration of study treatment dose as outlined in Section 10.

Efficacy follow-up*

Participants who discontinued study treatment for reasons other than disease progression by RECIST 1.1, death, lost to follow up, or withdrawal of consent/opposition to use data/biological samples will continue tumor assessments as outlined in Section 8.3.1 until documented disease progression. PRO data will also be collected using the same schedule as tumor assessments, for participants enrolled in Parts A and B2.

Follow-up after disease progression*

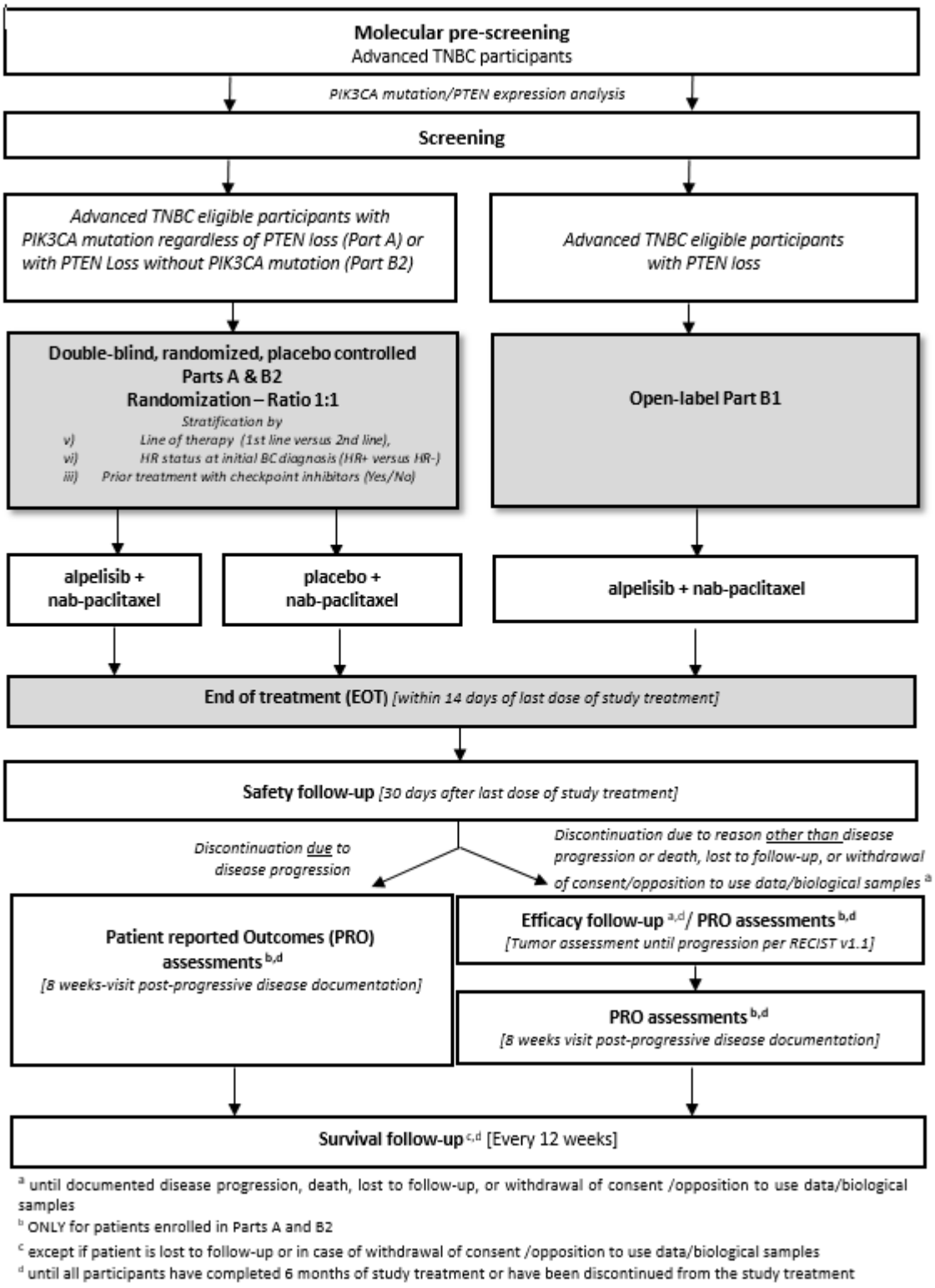
PRO data will be collected 8 weeks after documentation of disease progression for participants enrolled in Parts A and B2.

Survival follow-up*

Participants will be followed for survival as outlined in Section 8.

* Once all participants have completed 6 months of study treatment or have been discontinued from the study treatment, the tumor assessments in the efficacy follow-up, the collection of PRO data in the efficacy follow-up and 8 weeks after disease progression, and the collection of survival data will stop.

Figure 3-2 Study flow



[a] until documented disease progression, death, lost to follow-up, or withdrawal of consent /opposition to use data/biological samples

[b] ONLY for patients enrolled in Parts A and B2

[c] except if patient is lost to follow-up or in case of withdrawal of consent /opposition to use data/biological samples

[d] until all participants have completed 6 months of study treatment or have been discontinued from the study treatment

4 Rationale

4.1 Rationale for study design

Part A

To assess the treatment effect of alpelisib in combination with nab-paclitaxel specifically in participants with advanced TNBC and *PIK3CA* mutations, approximately 252 participants will be randomized into Part A. The majority of the mutations increasing the kinase activity of PIK3α, referred to as "hotspot mutations", occur in exons 9 and 20, and to a lesser extent in exon 7 (Zhao and Vogt 2008). Part A will therefore limit the inclusion of participants with PIK3CA mutation meeting these "hotspot" criteria based on the tumor biomarker status from the Novartis designated laboratory using the Qiagen Therascreen PIK3CA RGQ PCR kit or by a local laboratory using either a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN *therascreen*® PIK3CA RGQ PCR test. PIK3CA mutation results generated by research use only version of the Qiagen test, or other laboratory-developed tests, are not acceptable.

Part B1

To assess if alpelisib in combination with nab-paclitaxel provides a benefit for participants with advanced TNBC with PTEN loss (with PIK3CA unknown or non-mutant), a single-arm, open-label part B1 will assess ORR data after 6 months of follow-up in approximately 32 participants. These ORR results, in combination with safety data, will be used to determine if part B2 of this study will be opened. PTEN loss status will be assessed centrally on fresh or archival tumor samples (locally advanced or metastatic tumor tissue preferred) from the Novartis designated laboratory using the PTEN immunohistochemistry (IHC) Clinical Trial Assay (CTA).

Part B2

To assess the treatment effect of alpelisib in combination with nab-paclitaxel specifically in participants with advanced TNBC with PTEN loss (without PIK3CA mutation), approximately 282 participants will be randomized into part B2 of this study. PTEN loss status will be assessed centrally on fresh or archival tumor samples (locally advanced or metastatic tumor tissue preferred) from the Novartis designated laboratory using the PTEN IHC CTA.

Stratification factors for Parts A and B2

In order to control for critical prognostic factors and to avoid imbalances between the two arms (Kernan et al 1999), randomization of participants in Part A and B2 will be stratified by:

a. line of therapy in advanced/metastatic setting (1st line versus 2nd line)
b. hormone receptor status at initial breast cancer diagnosis (HR+ versus HR-), and
c. prior therapy with a checkpoint inhibitor (yes versus no).

Line of therapy in the metastatic setting is a prognostic indicator. Participants in later lines of therapy generally fare worse with faster progression, shorter treatment duration, and shorter survival (Kassam et al 2009, Bajaj et al 2017, Fietz et al 2017).

Furthermore, participants with HR+ BC at initial breast cancer diagnosis, which became TNBC in the advanced setting, likely constitute a different tumor entity compared to those that were TNBC since initial breast cancer diagnosis. Those participants, who were originally diagnosed

with HR-positive BC, received different treatment modalities in the primary setting (including hormonal therapy), and may have a different prognosis and possibly a different response to targeted therapy with alpelisib. In the SAFIR02 trial (NCT02299999), 649 patients with metastatic breast cancer with available mutational profile and clinical data were selected for outcome analyses with PIK3CA mutations prospectively determined by NGS on metastatic samples. Ten percent (n=27) of these TNBC tumors had a PIK3CA mutation. PIK3CA mutations were noted at a higher frequency in patients whose primary tumor was HR-positive at initial breast cancer diagnosis and then changed to HR-negative (39% (14/36) of patients) as compared to those that were HR-negative at primary and metastatic tumor assessments (7% (9/138), Mosele et al 2019). These data form the rationale for the first two stratification factors.

With regard to the third stratification factor, the therapeutic landscape for TNBC is rapidly changing. Atezolizumab in combination with nab-paclitaxel was recently approved in the first line metastatic TNBC (Schmid et al 2018). Additionally, according to ClinicalTrials.gov there are 32 ongoing clinical studies which evaluate combinations with targeted therapies and immuno-oncology (IO) investigational drugs. Currently, no data are available to show if and how dual presence of PD-L1 positivity and a PIK3CA mutation, or pretreatment with a checkpoint inhibitor, may impact the outcome of any subsequent treatment with nab-paclitaxel and/or PI3K inhibitors, or if it may have any prognostic value. Therefore, it is important to assess the impact of prior IO treatment (immunomodulatory effect) on the safety and efficacy of alpelisib in combination with nab-paclitaxel. Stratification of randomization based on previous checkpoint inhibitor treatment in Study H12301 will prevent imbalance between the two treatment arms given that the published data currently predicts a small number of tumors with PD-L1 positivity and a PIK3CA mutation. Any possible influence of prior therapy can be better assessed by stratifying participants as to whether or not they received prior IO treatment (Emens and Middleton 2015).

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Alpelisib antitumor activity in TNBC

Alpelisib has demonstrated preliminary anti-tumor activity, in two studies including patients with advanced TNBC.

Study CBYL719X2101

In the Phase Ia dose escalation study CBYL719X2101 in patients with advanced solid tumors alpelisib doses of 30 mg - 450 mg were explored; the maximum tolerated dose (MTD) for single-agent treatment was declared at 400 mg alpelisib under fed conditions. Clinical responses for alpelisib monotherapy were observed at doses of ≥ 270 mg once daily, though signs of tumor growth suppression were observed at doses ≥ 180 mg based on pharmacodynamic markers (Juric et al 2018). Five subjects with TNBC were included in this study and treated with alpelisib monotherapy. Of these, 3 had tumors harboring a PIK3CA amplification or mutation and were treated with once daily alpelisib. Encouraging early activity of alpelisib was observed in 2 of these three highly pre-treated subjects with TNBC:

- One subject (alpelisib starting dose of 300 mg per day) was on study treatment for 442 days and had a best response of SD with 23.5% tumor shrinkage.

- A second subject (alpelisib starting dose of 400 mg per day) was on study treatment for 168 days and had an unconfirmed PR with 37.5% tumor shrinkage.
- The third subject (alpelisib starting dose of 300 mg per day) was on study for 3 days.

Study CBYL719XUS06T

Alpelisib in combination with nab-paclitaxel was explored in a Phase I/II investigator initiated study, Study CBYL719XUS06T (NCT02379247), in 43 subjects with HER2-negative, advanced breast cancer (regardless of PI3K pathway activation or PTEN status) who had received ≥ 1 prior line of chemotherapy (prior taxane treatment, except nab-paclitaxel, was permitted) in either the advanced or adjuvant setting.

The primary objectives were to determine the recommended phase II dose (RPTD) of alpelisib + nab-paclitaxel and to assess the overall response rate (ORR). Phase I was a 3+3 dose-escalation design with 3 dose levels of alpelisib (250 mg, 300 mg, and 350 mg) administered PO once daily (Days 1-28) with nab-paclitaxel at 100 mg/m^2 i.v. on Days 1, 8, and 15 of a 28 day cycle. Phase II was a Simon's two stage minimax design targeting an ORR of 40% (NCT02379247).

In the Phase I portion of the study, there were no DLTs and no PK interactions reported for the 9 evaluable subjects (n=10; 1 patient stopped treatment within 10 days). The recommended Phase II dose (RP2D) for alpelisib was 350 mg with nab-paclitaxel at 100 mg/m^2 i.v. on Days 1, 8, and 15 of a 28 day cycle. In the Phase II portion of the study, 33 subjects were treated at the RP2D (Sharma et al 2018, Sharma et al 2021). PI3K pathway-activation, defined as the presence of PIK3CA-activating or PTEN-inactivating mutations, was tested in either tumor tissue or ctDNA and was observed in 44% (19/43) of patients.). PI3K pathway-activation, defined as the presence of PIK3CA-activating or PTEN-inactivating mutations, was tested in either tumor tissue or ctDNA and was observed in 44% (19/43) of patients.

In the overall study population, 23%, 69%, and 8% of subjects had been treated with 0, 1, or ≥ 2 lines of prior chemotherapy for metastatic breast cancer, respectively. Nine subjects continued on treatment for > 12 months; 5 of these had a PIK3CA mutation. For the 42 evaluable subjects (1 subject did not have response data), the ORR was 60% and CBR was 79%. For subjects with a PIK3CA mutation, the ORR was 74% and CBR was 100%. Median PFS was 13 months for subjects with a PIK3CA mutation (n=19) compared to 7 months for those without a PIK3CA mutation (n=23) (HR=0.40; 95% CI: 0.18, 0.90, p=0.017).

TNBC Subjects in Study CBYL719XUS06T

Twelve of the 43 subjects had advanced TNBC. The majority of these subjects were treated with an alpelisib dose of 350 mg (250 mg (n=2), 300 mg (n=1), and 350 mg (n=9)), in combination with nab-paclitaxel. The ORR and CBR for these 12 TNBC subjects was 58%.

Five of the 12 TNBC subjects' tumors harbored a PI3K pathway alteration: 3 had a PIK3CA mutation, 1 had PTEN loss without a PIK3CA mutation, and 1 had both a PIK3CA mutation and PTEN loss. Clinical benefit was observed in all TNBC patients with a PI3K pathway activated tumor.

The following best overall responses were observed among the 12 subjects with TNBC:

- Two (17%) subjects had a CR (one with a PIK3CA mutation without PTEN loss, one with PIK3CA mutation with PTEN loss).

- Five (42%) subjects had a PR (one with a PIK3CA mutation without PTEN loss, one with PTEN loss without a PIK3CA mutation).
- Two (17%) subjects had SD (one with a PIK3CA mutation without PTEN loss).
- Three (25%) subjects had PD (none had a PIK3CA mutation or PTEN loss).

In study CBYL719XUS06T, the safety profile for alpelisib in combination with nab-paclitaxel is consistent with the known adverse event profiles of each medication (see Section 1.1.3.2). The following is a summary of the safety observations among the 43 patients:

- Hyperglycemia was noted in 76% of subjects (grade 3 = 27%, no grade 4 events) with 32% of patients requiring metformin for hyperglycemia management.
- Rash was noted in 63% of subjects (grade 3 = 7%, no grade 4 events). All subjects received second or third generation H1-anti-histaminic for rash prophylaxis.
- Alpelisib dose reductions occurred in 26% (11/43) of subjects (n=1 at 250 mg dose, n=10 at 350 mg dose). The reasons for alpelisib dose reductions were: fatigue/anorexia (n=3), diarrhea (n=3), rash (n=2), hyperglycemia (n=1), hypokalemia (n=1), and investigator's choice (n=1).
- Two subjects discontinued therapy (after two cycles) due to grade 2 pneumonitis.
- Nab-Paclitaxel dose reductions occurred in 28% (10/43) of subjects. The reasons for nab-paclitaxel dose reductions were: peripheral neuropathy (n=3), fatigue (n=1), rash (n=1), diarrhea (n=1), thrombocytopenia (n=1), neutropenia (n=1), and investigator's choice (n=2).
- Two subjects stopped nab-paclitaxel and continued on single agent alpelisib. Both of these subjects stopped alpelisib at 12 weeks due to progressive disease (one subject's tumor had a PIK3CA mutation, the other did not.)

The incidence of AEs reported, by severity, are displayed in Table 4-1:

Table 4-1 Adverse events reported for alpelisib in combination with nab-paclitaxel in Study CBYL719XUS06T

N = 43	CTCAE Grade				
	Grade 1	Grade 2	Grade 3	Grade 4	All Grades (%)
Musculoskeletal	26 (63%)	10 (24%)	2 (5%)	0 (0%)	38 (93%)
Diarrhea	23 (56%)	11 (27%)	2 (5%)	0 (0%)	36 (88%)
Hyperglycemia	9 (22%)	11 (27%)	11(27%)	0 (0%)	31 (76%)
Fatigue	12 (29%)	14 (34%)	2 (5%)	0 (0%)	28 (68%)
Nausea	21 (51%)	7 (17%)	0 (0%)	0 (0%)	28 (68%)
Peripheral neuropathy	16 (39%)	9 (22%)	1 (2%)	0 (0%)	26 (63%)
Rash	21 (51%)	2 (5%)	3 (7%)	0 (0%)	26 (63%)
Infections	7 (17%)	15 (37%)	2 (5%)	0 (0%)	24 (59%)
Anorexia	17 (41%)	5 (12%)	0 (0%)	0 (0%)	22 (54%)
Anemia	12 (29%)	4 (10%)	5 (12%)	0 (0%)	21 (51%)
Neutropenia	3 (7%)	5 (12%)	10 (24%)	3 (7%)	21 (51%)
Mucositis/Oral Pain	15 (37%)	4 (10%)	1 (2%)	0 (0%)	20 (49%)
Electrolyte imbalance	16 (39%)	2 (5%)	1 (2%)	1 (2%)	20 (49%)
GI Other	15 (37%)	5 (12%)	0 (0%)	0 (0%)	20 (49%)
Dysgeusia	17 (41%)	2 (5%)	0 (0%)	0 (0%)	19 (46%)

N = 43	CTCAE Grade				
	Grade 1	Grade 2	Grade 3	Grade 4	All Grades (%)
Pulmonary Other	11 (27%)	6 (15%)	1 (2%)	0 (0%)	18 (44%)
Others	10 (24%)	8 (20%)	0 (0%)	0 (0%)	18 (44%)
Liver enzyme increase	14 (34%)	1 (2%)	0 (0%)	0 (0%)	15 (37%)
Eye Disorders	11 (27%)	3 (7%)	0 (0%)	0 (0%)	14 (34%)
Nail Changes	11 (27%)	2 (5%)	0 (0%)	0 (0%)	13 (32%)
Vomiting	6 (15%)	5 (12%)	0 (0%)	0 (0%)	11 (27%)
Myalgia	8 (20%)	2 (5%)	0 (0%)	0 (0%)	10 (24%)
Neurological	8 (20%)	0 (0%)	0 (0%)	0 (0%)	8 (20%)
Dry Mouth/Skin	7 (17%)	1 (2%)	0 (0%)	0 (0%)	8 (20%)
Weight loss	2 (5%)	5 (12%)	0 (0%)	0 (0%)	7 (17%)
Renal	2 (5%)	2 (5%)	1 (2%)	0 (0%)	5 (12%)
Edema	2 (5%)	1 (2%)	0 (0%)	0 (0%)	3 (7%)
Pneumonitis	1 (2%)	2 (5%)	0 (0%)	0 (0%)	3 (7%)
Thrombocytopenia	1 (2%)	1 (2%)	0 (0%)	0 (0%)	2 (5%)

In summary, these data demonstrate a tolerable safety profile and promising early anti-tumor activity of alpelisib in combination with nab-paclitaxel in advanced TNBC aBC where the PI3K pathway is activated by the presence of a PIK3CA mutation or PTEN loss and warrant the investigation of the combination of alpelisib with nab-paclitaxel in advanced TNBC.

4.2.2 Alpelisib Phase III dose

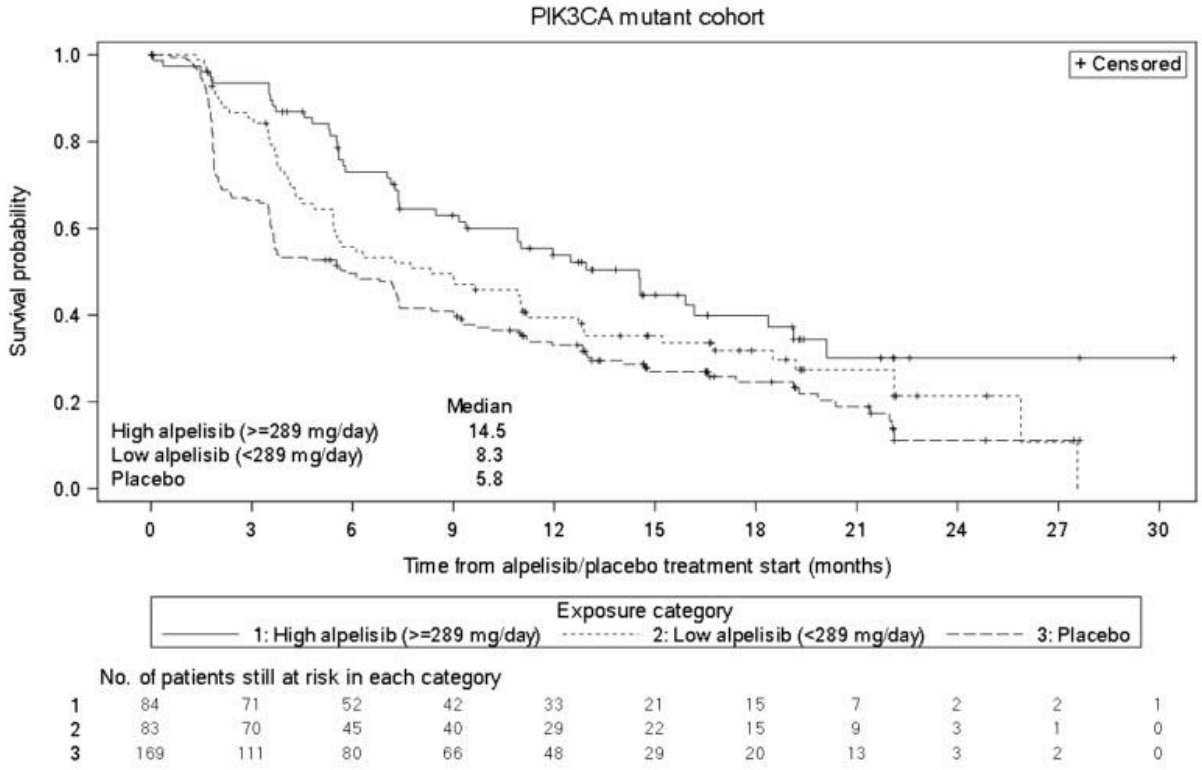
Phase III dose selection of 300 mg of alpelisib in combination with nab-paclitaxel was based on an integrated assessment of the results of Study CBYL719XUS06T and analyses conducted by Novartis with data from the Phase III study of alpelisib plus fulvestrant in HR-positive, HER2-negative aBC (Study CBYL719C2301), and earlier Phase I studies, showing a relationship between plasma exposure and risk of hyperglycemia and rash in subjects with metastatic breast cancer. Overall, the alpelisib dose of 300 mg administered once daily provides the best benefit-risk profile.

In Study CBYL719XUS06T, the recommended Phase II alpelisib dose was 350 mg in combination with nab-paclitaxel. However, dose reductions for subjects receiving 350 mg occurred in 30% of subjects (10 of the 33 treated at this dose level), primarily due to adverse events. Assuming a similar exposure-safety relationship in metastatic TNBC subjects as HR-positive, HER2-negative aBC subjects, where the safety of the 300 mg dose is well characterized, the 300 mg alpelisib dose is considered more tolerable.

Study CBYL719C2301 investigated both PIK3CA mutant and non-mutant cohorts. Since the PIK3CA non-mutant cohort did not meet the Proof of Concept (PoC) criteria, exposure-efficacy analysis using PFS data was only conducted for the PIK3CA mutant cohort. To investigate the benefit of starting alpelisib treatment at or close to the planned initial dose (300 mg) compared to a reduced level, dose intensity (DI) over the first 4 weeks of treatment (before the majority of subjects experienced dose reductions) was calculated. The PFS analysis by median DI at 4 weeks demonstrated a clearer benefit for subjects with a DI greater than or equal to the median DI of 289 mg/day compared to a lower DI (<289 mg/day), with a median PFS of 14.5 months vs. 8.3 months, respectively (Figure 4-1). In summary, there is a greater treatment benefit of alpelisib plus fulvestrant for subjects with a starting dose of 300 mg compared to lower dose

levels. As clinical responses were observed in combination with nab-paclitaxel at the 300 mg dose level in CBYL719XUS06T (with 3 subjects enrolled at 300 mg, 1 PR and 2 SD) and assuming a similar exposure-efficacy relationship, 300 mg is more likely to optimize a sufficient dose intensity to provide clinical benefit with a better safety profile.

Figure 4-1 Kaplan-Meier plot of PFS by median dose intensity (first 4 weeks) in the PIK3CA mutant cohort - Study CBYL719C2301 (Full analysis set)



Alpelisib 300 mg orally daily and nab-paclitaxel 100 mg/m^2 i.v. on Days 1, 8 and 15 of a 28-day cycle was selected for further evaluation in this Phase III study to maximize treatment benefit while retaining an acceptable and manageable safety profile.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

4.3.1 Nab-Paclitaxel in TNBC

Taxanes (paclitaxel, docetaxel, nab-paclitaxel) are microtubule inhibitors and have significant antitumor activity in breast cancer. They are recommended in TNBC in both the adjuvant and metastatic setting (Senkus et al 2015, Mustacchi and De Laurentiis 2015, Schettini et al 2016, Park et al 2018, NCCN Breast Cancer 1.2019). Nab-paclitaxel is an albumin-bound formulation of paclitaxel. It was developed to take advantage of the antitumor activity of paclitaxel while decreasing or eliminating toxicities typically associated with the solvent (Cremophor) used to administer the most common formulation of paclitaxel (Martín 2015). Nab-paclitaxel has an advantageous PK profile compared to solvent-based paclitaxel with 33% higher tumor uptake in preclinical models (Yardley 2013) and allows the infusion of higher

doses of paclitaxel compared with standard paclitaxel therapy, in a shorter infusion time, without premedication. Nab-paclitaxel is approved in the EU, US, and many other countries worldwide for metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

Nab-paclitaxel demonstrated higher response rates compared with standard paclitaxel (33% vs 19%, respectively; p=0.001) and longer time to tumor progression (23.0 vs 16.9 weeks, respectively; HR = 0.75; p=0.006) in a Phase III trial of patients with mBC (Gradishar et al 2005). Various studies demonstrated high pathological complete response rates (pCR) in early-stage breast cancer, particularly in TNBC and encouraging overall survival in metastatic breast cancer across different doses and schedules (Brufsky 2017).

Therefore, because of the proven efficacy in metastatic TNBC and its more advantageous administration method (including absence of steroid pre-medication), nab-paclitaxel is an appropriate combination partner for alpelisib.

4.3.2 Nab-Paclitaxel dose schedule 100 mg/m^2 on Day 1, 8, and 15 of 28 Day treatment cycle

Nab-paclitaxel at a dose of 260 mg/m^2 as a once every 3-week (q3w) dose schedule is approved for the treatment of mBC (Gradishar et al 2005). Neither the 260 mg/m^2 dose nor the once every 3-week schedule are commonly used in clinical practice (Mustacchi and De Laurentiis 2015). Furthermore, Nab-paclitaxel is frequently used in TNBC patients that do not precisely fall into the defined category specified in the nab-paclitaxel label (Mustacchi and De Laurentiis 2015). Both the NCCN and ESMO clinical practice guidelines include nab-paclitaxel as a standard of care that may be administered as a single agent to patients with newly diagnosed recurrent or metastatic breast cancer (Cardoso et al 2018, NCCN Breast Cancer 1.2019).

Findings from a later phase II study by Gradishar (2009) which examined the antitumor activity and safety of weekly and every 3-week nab-paclitaxel compared with docetaxel in first-line mBC suggested that nab-paclitaxel at 150 mg/m² given weekly for 3 weeks followed by a week break was more effective in terms of progression-free survival than 100 mg/m² nab-paclitaxel given weekly or 100 mg/m² docetaxel given once every 3 weeks followed by a week break (Gradishar et al 2009). In the four arms of this study, the ORRs were:

- 37% with nab-paclitaxel 300 mg/m^2 every 3-week,
- 45% with nab-paclitaxel 100 mg/m^2 weekly (3-weeks-on/1-week-off schedule),
- 49% with nab-paclitaxel 150 mg/m^2 weekly (3-weeks-on/1-week-off) weeks, and
- 35% with q3w docetaxel 100 mg/m^2.

PFS were 11.0 months, 12.8 months, 12.9 months and 7.5 months for each of the four arms, respectively. These results illustrate the advantages of the nab-paclitaxel weekly dosing schedule over the every-3-week dosing schedule. Of note, improvement in ORR and PFS of nab-paclitaxel 150 mg/m^2 weekly over 100 mg/m^2 was not statistically significant. Additionally, patients receiving the higher nab-paclitaxel dose experienced higher incidences of Grade 3 or 4 neutropenia (44% vs. 25%) and Grade 3 sensory neuropathy (14% vs. 8%).

Subsequent clinical studies have not clearly demonstrated that weekly doses of nab-paclitaxel above 100 mg/m^2 are more efficacious. Furthermore, higher doses of nab-paclitaxel are

associated with greater toxicities (Gradishar et al 2009, Untch et al 2016). The CALGB 40502 Phase III trial randomized patients with chemotherapy-naïve, HER2-negative mBC to receive weekly paclitaxel, weekly nab-paclitaxel at a higher dose of 150 mg/m^2, or ixabepilone, with all agents given in combination with bevacizumab, and on a 3-week-on/1-week-off schedule (Rugo et al 2015). Nab-paclitaxel was not tolerable at this higher weekly dose and did not improve PFS in any aBC subtype over the standard dose of paclitaxel, leading to the conclusion that nab-paclitaxel 150 mg/m^2 should not be utilized.

The Impassion130 Phase III study in first-line mTNBC also administered nab-paclitaxel at 100 mg/m^2 weekly on a 3-week-on/1-week-off schedule. This trial led to the FDA approval of atezolizumab plus nab-paclitaxel in PDL1-positive advanced TNBC (Schmid et al 2018). The Phase I/II investigator initiated trial (IIT) in 43 subjects with HER2-negative, aBC demonstrated promising efficacy results, including 12 subjects with TNBC (Sharma et al 2018, Sharma et al 2021) with this nab-paclitaxel regimen. Subjects, regardless of PIK3CA mutation status, received nab-paclitaxel 100 mg/m^2 on days 1, 8 and 15 of a 28-day cycle (3 weeks on/ 1 week off) with alpelisib 250 mg, 300 mg, or 350 mg orally daily; this dosing schedule of nab-paclitaxel was tolerable and efficacious.

In summary, nab-paclitaxel at a dosing schedule of 100 mg/m^2 i.v. on days 1, 8, and 15 of a 28 day cycle is a well-studied and tolerated dose regimen with suggestions of improved efficacy and decreased toxicities in mBC and mTNBC compared with both higher weekly doses and the every 3-week nab-paclitaxel dosing schedule (Gradishar et al 2009, Brufsky 2017). As a result, subjects on this study will receive nab-paclitaxel 100 mg/m$_2$ i.v. on Days 1, 8 and 15 of a 28-day cycle.

4.4 Purpose and timing of interim analyses/design adaptations

With protocol amendment 02, no interim efficacy analyses will be performed.

4.5 Risks and benefits

4.5.1 Potential benefits to clinical trial participants

Treatment with alpelisib in combination with nab-paclitaxel may provide a clinical benefit compared to nab-paclitaxel alone in men and women with advanced TNBC with either a PIK3CA mutation and/or PTEN loss in first or second line metastatic setting. All participants enrolled in this trial will receive nab-paclitaxel as active treatment for their disease (see Section 6.1), with either the addition of alpelisib or placebo. Based on preliminary clinical data (see Section 1.1.3.2), treatment with alpelisib in combination with nab-paclitaxel is expected to be tolerated with a manageable side effect profile.

For further details on clinical safety, please refer to Section 1.1.3 and the latest version of [Alpelisib (BYL719) Investigator's Brochure] as well as local prescribing information for nab-paclitaxel.

4.5.2 Potential risks to clinical trial participants

Participants in this study will be carefully monitored using periodic laboratory, renal and liver function parameters and Electrocardiogram (ECG) for key toxicities that have been observed

with alpelisib (see Section 1.1.3), nab-paclitaxel (see Section 4.3) or the combination of both treatments (see Section 4.2).

Risks will be further minimized by adherence to inclusion/exclusion selection criteria (see Section 5), avoidance of prohibited medication (see Section 6.2.2), close safety monitoring (see Section 10 and Section 6.5.2), adherence to dose adjustment guidelines (see Section 6.5.1), and training of site personnel. An independent data monitoring committee (DMC) (see Section 10.2.2) will monitor safety, efficacy and available PK data as outlined in the protocol. A Steering Committee (SC) (see Section 10.2.3) comprising investigators and Novartis personnel participating in the trial will 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.

Male and female rat fertility studies revealed effects on fertility-associated parameters confirming previously obtained evidence of toxic effects of alpelisib on female fertility and on male reproductive organs, without affecting the fertility of male rats. In summary those data confirm that alpelisib can have effects on both male and female fertility in humans.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

The assessment of the Benefit/Risk did not reveal any additional risks related to coronavirus disease 2019 (COVID-19) and no changes were made as a result.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

This study will include approximately 566 men and women with advanced (locally recurrent or metastatic) TNBC with a PIK3CA mutation (Part A) or with PTEN loss (Parts B1 and B2), who have received no prior therapy, or only one prior therapy for their advanced disease. Participants will therefore be enrolled either in 1st line or 2nd line advanced/metastatic setting. Participants enrolled in this study are not permitted to participate in additional parallel investigational studies. The investigator or designee must ensure that only participants who meet all the following inclusion and none of the following exclusion criteria are offered treatment in this study.

The recruitment in Part B1 was completed; 35 participants were enrolled. The decision to stop the enrollment in Part A was due to slow recruitment; a total of 102 participants were randomized in Part A. Part B2 wasn't initiated based on Part B1 results.

5.1 Inclusion criteria

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

1. Participant is ≥ 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. Participant has histologically confirmed diagnosis of advanced (loco-regionally recurrent and not amenable to curative therapy, or metastatic (stage IV)) TNBC. This diagnosis should be established from the most recently analyzed biopsy from a metastatic or locally recurrent site (local lab) and meet the following criteria:
   a. HER2 negative in situ hybridization (ISH) test or an immunohistochemistry (IHC) status of 0 or 1+, and
   b. ER and PR expression is <1 percent as determined by IHC (Hammond et al 2010).

   Note: Participants that were previously identified with ER-positive, or PR-positive or HER2-positive early disease are allowed into the study if they have confirmed TNBC (meeting criteria 2a and 2b) by tumor biopsy in the locally advanced or metastatic setting at the time of screening.

   Note: TNBC status confirmation from a primary tumor biopsy can be accepted if it is unsafe or not clinically feasible to obtain a metastatic biopsy.
3. Participant has either:
   a. Measurable disease, i.e., at least one measurable lesion 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
   b. If no measurable disease is present, then at least one predominantly lytic bone lesion or mixed lytic-blastic bone lesion with identifiable soft tissue component (that can be evaluated by Computerized Tomography (CT) /Magnetic Resonance Imaging (MRI)) must be present. Participants 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.

   Note: Only participants with measurable disease are eligible for Part B1.

4a. Participant has adequate tumor tissue for analysis of PIK3CA mutation and PTEN loss status by a Novartis designated laboratory (refer to Section 8.1). A formalin fixed paraffin embedded (FFPE) tumor block from a new or archival biopsy or unstained FFPE glass slides as described on Table 8-15 in Section 8.5.3 must be provided. If an archival tumor sample (preferably within 3 years prior to screening) is not available, a new or recent biopsy (collected at screening if feasible) is required.
   a. If a PIK3CA mutation is detected, then the participant may be eligible for Part A, if all other criteria are met
   b. If PTEN loss without a PIK3CA mutation is detected, then the participant may be eligible for Part B1 or B2, if all other criteria are met
   c. If PTEN loss is detected and PIK3CA status is unknown, then the participant may be eligible for Part B1, if all other criteria are met

Note: If a PIK3CA mutation was already confirmed by a local laboratory with either a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN therascreen® PIK3CA RGQ PCR test, this can serve as confirmation of the PIK3CA mutation status.

Note: Analysis of PIK3CA mutation and PTEN loss from a primary tumor biopsy can be accepted if it is unsafe or not clinically feasible to obtain a metastatic biopsy.

5. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Participant has received no more than one line of therapy for metastatic disease. Participant with de novo metastatic disease are eligible.
   a. Participant may have received prior taxane-based chemotherapy in the neoadjuvant or adjuvant setting, provided it has been completed ≥ 12 months prior to Day 1 of Cycle 1.
   b. Participant may have received prior taxane-based chemotherapy for metastatic disease, provided the best response was not progressive and it has been completed ≥ 12 months prior to Day 1 of Cycle 1.

   Note: Endocrine-based therapy for HR+ advanced/metastatic BC should not be counted as a line of treatment.

7a. Participant has adequate bone marrow and organ function as defined by the following laboratory values (assessed by central laboratory for eligibility):
   a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
   b. Platelets (PLT) ≥ 100 × 109/L
   c. Hemoglobin ≥ 9.0 g/dL
   d. Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ grade 1 according to National Cancer Institute (NCI)-CTCAE version 4.03 if judged clinically not significant by the investigator
   e. Potassium within normal limits, or corrected with supplements
   f. International Normalized Ratio (INR) ≤1.5
   g. Creatinine Clearance ≥ 35 mL/min using Cockcroft-Gault formula
   h. In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3 × Upper limit of normal (ULN). If the patient has liver metastases, ALT and AST ≤ 5 × ULN he/she will be eligible for the study
   i. Total bilirubin < 1.5 x ULN (any elevated bilirubin should be asymptomatic at enrollment) except for participants with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
   j. Fasting plasma glucose (FPG) ≤ 140 mg/dL (7.7 mmol/L) and Glycosylated Hemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met)
   k. Fasting Serum amylase ≤ 2 × ULN
   l. Fasting Serum lipase ≤ ULN
   m. Albumin ≥ 2.5 g/dL

5.2 Exclusion criteria

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

1. Participant has received prior treatment with any PI3K, mTOR or AKT inhibitor.

2. Participant has a known hypersensitivity to alpelisib, nab-paclitaxel or to any of their excipients (e.g. rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption, due to the excipient in the placebo tablet).
3. Participant with inflammatory breast cancer at screening.
4. Participant is concurrently using other anti-cancer therapy.
5. Participant has had surgery within 14 days prior to starting study drug or has not recovered from major side effects.
6. Participant has not recovered from all toxicities related to prior anticancer therapies to NCI CTCAE version 4.03 Grade ≤1. Exception to this criterion: participants with any grade of alopecia are allowed to enter the study.
7. Participant with Child Pugh score B or C.
8. Participant has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia).
9. Participant has a concurrent malignancy or malignancy within 3 years prior to start of study treatment, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer.
10. Participant has central nervous system (CNS) involvement which was not previously treated and/or was newly detected at screening. Previously treated CNS involvement must fulfill the following criteria to be eligible for the trial:
    a. Completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study and
    b. CNS tumor is clinically stable at the time of screening, and
    c. Participant is not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases
11. Participant with an established diagnosis of diabetes mellitus type I or uncontrolled type II based on Fasting Plasma Glucose and HbA1c as per inclusion criterion 7.
12. Participant has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) based on investigator discretion.
13. Participant has a history of acute pancreatitis within 1 year prior to screening or past medical history of chronic pancreatitis.
14. Participant 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 [testing not mandatory unless required by local regulations or requirements], severe hepatic impairment).
15. Participant has currently documented pneumonitis/interstitial lung disease (the chest CT scan performed before start of study treatment for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).
16. Participant has clinically significant, uncontrolled heart disease and/or recent cardiac events including any of the following:

a. History of angina pectoris, coronary artery bypass graft (CABG), symptomatic pericarditis, or myocardial infarction within 6 months prior to the start of study treatment
b. History of documented congestive heart failure (CHF) (New York Heart Association functional classification III-IV)
c. Left Ventricular Ejection Fraction (LVEF) <50% at screening as determined by MRI/Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
d. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), high-grade AV block (e.g., bifascicular block, Mobitz type II; third degree AV block without pacemaker in place)
e. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or Fridericia QT correction formula (QTcF) >470 msec at screening.
f. 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

17. Participant has a history of severe cutaneous reactions, such as Steven-Johnson Syndrome (SJS), erythema multiforme (EM), Toxic Epidermal Necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Syndrome (DRESS).
18. Participant with unresolved osteonecrosis of the jaw
19. Participant is currently receiving any of the following medications and cannot be discontinued 7 days prior to the start of the treatment:
    a. Strong inducers of CYP3A4
    b. Inhibitors of BCRP
20. Participant is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.

    Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
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. Participant is not able to understand and to comply with study instructions and requirements.
23. Participant is a woman of child-bearing potential defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study treatment and for 6 months after the last dose of any study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before

taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female participants on the study the vasectomized male partner should be the sole partner for that patient
- Placement of an intrauterine device (IUD) or intrauterine system (IUS) without hormonal components.

Note: Women are considered postmenopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 6 weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

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

24. Participant is a sexually active male unwilling to use a condom during intercourse while taking study treatment, and up to 6 months after the last dose of study treatment. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm during the study and up to the time period specified above.

    If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.
25. Participant is a nursing (lactating) or pregnant woman as confirmed by a positive serum (hCG) test prior to initiating study treatment.

6 Treatment

6.1 Study treatment

In this study, the “study treatment” refers to the combination of alpelisib or placebo with nab-paclitaxel in Parts A and B2, and alpelisib in combination with nab-paclitaxel in part B1. The term “investigational drug” refers to the Novartis study drug, alpelisib.

Novartis Global Clinical Supply (GCS) will provide study drug for Part A and part B2 as global clinical double-blind labeled supplies (alpelisib/BYL719 and placebo as 200 mg or 50 mg tablets as individual participant supply packed in bottle). Study drug for part B1 will be provided as global clinical open-label supplies (alpelisib/BYL719 as 200 mg or 50 mg tablets as individual participant supply packed in bottle.). They will be packed and labeled under the responsibility of Novartis GCS.

Once all participants have completed 6 months of study treatment or have been discontinued from the study treatment, Part A participants will be unblinded.

Part A participants on the experimental arm will continue to receive alpelisib supplies while Part A participants on control arm will no longer be administered placebo supplies.Nab-paclitaxel, also known as albumin-bound paclitaxel, will be provided locally by the study site,

subsidiary or designee as commercially available or centrally by Novartis, according to local practices and local regulations. The generic or brand name used in the study must conform to the definition of albumin-bound paclitaxel. 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. Generic nab-paclitaxel that was rejected by or withdrawn from regulatory agencies (e.g. FDA and/or European Medicines Agency (EMA)) should not be used.

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

6.1.1 Investigational and control drugs

6.1.1.1 Dosing regimen for Parts A and B2

Table 6-1 Investigational and control drug - Parts A and B2

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Double-blind (DB) alpelisib/BYL719 200 mg*	Tablet	Oral use	Double-Blind label participant packs; bottles	Sponsor (global)
DB placebo 200 mg*	Tablet	Oral use	Double-Blind label participant packs; bottles	Sponsor (global)
DB alpelisib/BYL719 50 mg*	Tablet	Oral use	Double-Blind label participant packs; bottles	Sponsor (global)
DB placebo 50 mg*	Tablet	Oral use	Double-Blind label participant packs; bottles	Sponsor (global)
Nab-paclitaxel 5 mg/mL	Powder for suspension for Injection or Powder for infusion dispersion	Intravenous	Vial	Sponsor (local/global), study site

* Once all participants have completed 6 months of study treatment or have been discontinued from study treatment and after participant's unblinding, participants in the experimental arm will receive alpelisib and participants in the control arm will no longer be dispensed placebo supplies. The reference to "placebo" and double-blind remains in the protocol text to avoid confusion.

In the double-blind, randomized, placebo-controlled parts (Parts A and B2), participants will be randomized in a 1:1 ratio to receive either:

- Experimental arm (Arm 1) - alpelisib + nab-paclitaxel, or
- Control arm (Arm 2) - placebo + nab-paclitaxel.

Alpelisib or placebo will be administered at 300 mg orally once daily on a continuous basis immediately after food starting on Cycle 1 Day 1 in a 28-day cycle.

A non-sedating antihistamine, such as cetirizine once daily on a continuous basis, is recommended to start on Cycle 1 Day 1 for approximately 8 weeks for the prevention of rash associated with PI3K inhibition. For participants benefiting from the antihistamine, treatment

can be continued beyond the first 8 weeks, if clinically indicated at the investigator's discretion (Wang et al 2020). Refer to Section 6.5.2.3 for additional information on antihistamine treatment and incidence/severity of rash based on alpelisib clinical trial experience.Nab-paclitaxel at 100 mg/m^2 will be administered approximately 1 hour after alpelisib or alpelisib/placebo on Days 1, 8 and 15 of a 28-day cycle as a 30-minute i.v. infusion according to local standard practice. For instructions to reconstitute vials prior to administration please refer to the local prescribing information for nab-paclitaxel.

A complete cycle of treatment is defined as 28 days (+/- 3 days) of once daily continuous treatment of alpelisib or placebo in combination with nab-paclitaxel administered on Days 1, 8, and 15.

The last day of a complete treatment cycle is Day 28 (+/- 3 days). Day 1 of the next cycle starts on Day 29 (+/- 3 days).

Treatment crossover from placebo in combination with nab-paclitaxel to alpelisib in combination with nab-paclitaxel will not be permitted in this study.

6.1.1.2 Dosing regimen for Part B1

Table 6-2 Investigational and control drug – Part B1

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Open-label (OL) alpelisib/BYL719 200 mg	Tablet	Oral Use	Open-label participant packs; bottles	Sponsor (global)
OL alpelisib/BYL719 50 mg	Tablet	Oral Use	Open-label participant packs; bottles	Sponsor (global)
Nab-paclitaxel 5 mg/mL	Powder for suspension for Injection or Powder for infusion dispersion	Intravenous	Vials	Sponsor (local/global), study site

Alpelisib will be administered at 300 mg orally once daily on a continuous basis immediately after food starting on Cycle 1 Day 1 in a 28-day cycle.

A non-sedating antihistamine, such as cetirizine once daily on a continuous basis, is recommended to start on Cycle 1 Day 1 for approximately 8 weeks for the prevention of rash associated with PI3K inhibition. For participants benefiting from the antihistamine, treatment can be continued beyond the first 8 weeks, if clinically indicated at the investigator's discretion (Wang et al 2020). Refer to Section 6.5.2.3 for additional information on antihistamine treatment and incidence/severity of rash based on alpelisib clinical trial experience.

Nab-paclitaxel at 100 mg/m^2 will be administered approximately 1 hour after alpelisib on Days 1, 8 and 15 of a 28-day cycle as a 30-minute i.v. infusion according to local standard practice. For instructions to reconstitute vials prior to administration, please refer to the local prescribing information for nab-paclitaxel.

A complete cycle of treatment is defined as 28 days (± 3 days) of once daily continuous treatment of alpelisib in combination with nab-paclitaxel administered on Days 1, 8 and 15.

The last day of a complete treatment cycle is Day 28 (+/- 3 days). Day 1 of the next cycle starts on Day 29 (+/- 3 days).

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

In the double-blind, randomized, placebo-controlled parts (Parts A and B2), participants will be assigned to one of the following treatment arms in a 1:1 ratio:

- Experimental arm (Arm 1): alpelisib + nab-paclitaxel or
- Control arm (Arm 2): alpelisib matching placebo + nab-paclitaxel.

In the open-label part B1, all participants will be assigned to the alpelisib + nab-paclitaxel combination.

6.1.4 Guidelines for continuation of treatment

Refer to guidelines for management of toxicities and doses modifications instruction, see Section 6.5.1

6.1.5 Treatment duration

Participants will continue to receive study treatment until disease progression is radiologically documented according to RECIST 1.1, unacceptable toxicity that precludes further treatment, or until discontinuation of study treatment due to any other reason (Section 9.1.1).

Nab-paclitaxel and alpelisib may be discontinued independently of each other for unacceptable toxicities or at the discretion of the treating physician.

Participants who complete participation in this trial and continue to derive clinical benefit from the treatment based on the investigator's evaluation may receive post-trial access (PTA). PTA means the provision of treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, treatment is discontinued at the discretion of the investigator or the participant, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

Mechanisms for provision of PTA may include an extension phase to this study, a separate extension protocol, a rollover protocol, provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with investigators to transition participants onto locally available alternative treatment, or standard of care.

6.1.5.1 Treatment beyond disease progression

Study treatment beyond disease progression per RECIST 1.1 as assessed locally by investigator will not be allowed in this study.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

The investigator should instruct the participant to notify the study site about any new medications and/or non-drug therapies/procedures he/she takes after signing the informed consent. All medications, procedures, and significant non-drug therapies (including vitamins, physical therapy, herbal/natural medications and blood transfusions) administered within 30 days prior to the start of study treatment and up to 30 days after the last dose of study treatment must be recorded on the appropriate eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Oral anti-diabetics

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

Consultation with a diabetologist or healthcare provider experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia. It is recommended to start treatment with metformin, however sodium-glucose cotransporter 2 (SGLT2) inhibitors, as per local standard practices, may be a suitable alternative or add-on therapy to metformin. SGLT2 inhibitors are a class of diabetic medications that improve hyperglycemia primarily by promoting urinary glucose excretion.

In the SOLAR-1 study, among the 284 participants who were randomized to receive alpelisib plus fulvestrant, 190 participants (67%) developed hyperglycemia, with 18 participants (6%) discontinuing alpelisib treatment due to hyperglycemia, as of 30-Sep-2019 (Lu et al 2020).

Among those with hyperglycemia, 166 participants received concomitant anti-diabetic medications, primarily consisting of metformin (87%). However, in addition to metformin, 6 participants also received an SGLT2 inhibitor, consisting of empagliflozin, ipragliflozin, or dapagliflozin (Lu et al 2020). All 6 participants had ≥ 1 risk factor at baseline for developing hyperglycemia, defined as prediabetes (n = 4; 1 of whom had documented history of type 2 diabetes), diabetes (n = 2), and obesity (n = 2). The most severe hyperglycemia in these participants was grade (G) 3 (n = 5). After initiating an SGLT2 inhibitor, all subsequent hyperglycemia events were G 1/2, except one G 3 event with steroids as a confounding factor.

Among those 6 participants, the duration of alpelisib ranged from 9.5 to 27.7 months in 4 participants who discontinued alpelisib; and notably, the remaining 2 participants continued to receive alpelisib after 37.0 and 40.0 months. None of the 6 participants discontinued alpelisib due to hyperglycemia.

Based on these data, participants may benefit from the initiation of an SGLT2 inhibitor with metformin, which is available as a single oral combination pill or as two separate medications. Particularly in participants with at least one risk factor for the development of severe hyperglycemia, defined as prediabetes/diabetes, and/or obesity (Body Mass Index (BMI) $\geq$ 30), and/or age $\geq$ 75 years, early or prophylactic initiation of an SGLT2 inhibitor alone or in combination with metformin may help to reduce the incidence and frequency of severe hyperglycemia events. The decision to initiate an SGLT2 inhibitor alone in combination with metformin prophylactically or at the onset of hyperglycemia (first fasting glucose level above the normal range) is at the discretion of the investigator, and as per local standard practice.

While the adverse drug profile of metformin IR (immediate release) and metformin XR (extended release) are generally similar, up to 25% of participants on metformin IR may experience gastrointestinal toxicities that lead to treatment discontinuation in 5-10% of participants (Jabbour and Ziring 2011). Metformin XR was developed to allow a slower release of drug into the upper gastrointestinal tract to reduce toxicities such as diarrhea. The use of metformin XR as a suitable alternative to metformin IR is justified by its better tolerability and once daily dosing, which may potentially allow for a more rapid dose titration and improved adherence. Therefore, the use of metformin XR can be considered as a suitable alternative to metformin IR, alone or in combination with an SGLT2 inhibitor, particularly for participants with at least one risk factor for the development of severe hyperglycemia, at the discretion of the Investigator (Jabbour and Ziring 2011).

Gastric protection agents

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

Palliative radiotherapy

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

Hematopoietic growth factors

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

Corticosteroids

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during combined alpelisib/placebo and nab-paclitaxel treatment in this study are listed below (Table 16-6 and Table 16-7 in Section 16.2). This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions.

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

Medications to be used with caution:

- **CYP2C9 substrates with narrow therapeutic index (NTI) (e.g. anticoagulants):** In vitro evaluations indicated that pharmacological activity may be reduced by the CYP2C9 induction effects of alpelisib. In the absence of clinical data, caution is recommended with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants as alpelisib may reduce the clinical activity of such drugs. Alternatively, therapeutic anticoagulation may be accomplished using low- molecular weight heparin or Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors.
- **CYP2B6 sensitive substrates or CYP2B6 substrates with NTI :** Based on a static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib. In absence of clinical data, sensitive CYP2B6 substrates (e.g. bupropion, evafirenz) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib, as alpelisib may reduce the clinical activity of such drugs.
- **Selected CYP3A4 substrates:** Alpelisib can be co-administered with sensitive CYP3A4 substrates (e.g. everolimus, midazolam) and CYP3A4 substrates with narrow therapeutic window (e.g. fentanyl). Caution is recommended when alpelisib is used in combination with CYP3A4 substrates that also possess an additional time dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. ribociclib, encorafenib, refer to Table 16-6). Systemic exposures of such CYP3A4 auto inhibitors and auto inducers may be either decreased or increased depending on the drug and nature of auto-perpetrator potential, respectively, when alpelsib is co administered, based on PBPK simulations.
- **Inhibitors or inducers of CYP2C8 and strong inhibitors of CYP3A4:** As paclitaxel is metabolized by CYP2C8 and CYP3A4 these drugs may increase or decrease the pharmacokinetics of paclitaxel, refer to Table 16-7.
- **Herbal Medications:** The use of herbal preparations/medications and dietary supplements are permitted with caution unless explicitly prohibited (see Section 6.2.2) for being strong

inducers of CYP3A such as St. John's Wort (Hypericum perforatum) and Avasimibe (see Table 16-8) or BCRP inhibitors such as Curcumin (see Table 16-9). Medications such as Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng should be avoided if possible due to their potential for complex interactions. Since cannaboids have been shown to inhibit BCRP in vitro, medical cannabis should be used with caution. The use/frequency of use should be documented as a concomitant medication. Participants closely monitored for increased adverse reactions (as the relevance of this interaction in vivo is currently unknown). In case of unexpected toxicities, participants should stop using all herbal medications.

6.2.1.2 Use of bone modifying agents

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

BMAs (e.g. bisphosphonates, denosumab) may be given according to the local prescribing information and routine clinical practice, at the investigator's discretion.

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

Osteonecrosis of the jaw (ONJ) is a known adverse reaction for BMAs. In the phase III Study CBYL719C2301, ONJ was reported in 4.2% participants (12/284) in the alpelisib plus fulvestrant arm compared to 1.4% participants (4/287) in the placebo plus fulvestrant arm. All participants experiencing ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid). Therefore, in participants receiving alpelisib and bisphosphonates, an increased risk of development of ONJ cannot be excluded. For prevention and clinical management of ONJ, prescribing information of bisphosphonates should be followed.

6.2.2 Prohibited medication

The following medications are prohibited during combined alpelisib/placebo and nab-paclitaxel treatment in this study (Table 16-9 in Section 16.2.2). This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions

- **Strong inducers of CYP3A4:** Avoid coadministration of alpelisib with a strong CYP3A4 inducers as it could potentially reduce the effectiveness of alpelisib, refer to Table 16-8.
- **Inhibitors of BCRP:** Avoid the use of BCRP inhibitors in participants treated with alpelisib. If unable to use alternative drugs, closely monitor for increased adverse reactions, refer to Table 16-9.
- **Other investigational and antineoplastic therapies**

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned by the clinical database when the participant is first enrolled for molecular pre-screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial (except in case of rescreening, refer to Section 8.1).The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information to register the participant into the IRT. Once assigned, the Participant No. must not be reused for any other participant.

A new main study ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new participant number.

6.3.2 Treatment assignment, randomization

The assignment of a participant to a particular study part will be coordinated via Interactive Response Technology (IRT) based on the PIK3CA mutation and PTEN expression status.

Parts A and B2 (randomized)

In the double-blind, randomized, placebo-controlled Parts A and B2, all eligible participants will be randomized prior to dosing at Cycle 1 Day 1 via IRT to one of the treatment arms (Section 6.1.1.1). The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

Part B1 open-label

In the single-arm, open-label study part B1, no randomization will be performed. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system. Approximately 32 eligible participants will be enrolled via IRT for treatment with alpelisib in combination with nab-paclitaxel prior to dosing at C1D1.

Note: Cycle 1 Day 1 visit and dosing should occur no later than 3 days after IRT registration.

At study entry, participants with confirmed PIK3CA mutation status regardless of PTEN loss will be enrolled in Part A.

Participants with a confirmed PTEN loss status and PIK3CA unknown or non mutant will be enrolled in part B1 until approximately 32 participants have been enrolled (Section 8.1).

At this point, the participants will only have the option to be enrolled in part A (providing PIK3CA mutation status is confirmed) until the decision is made to initiate part B2. Participants with PTEN loss and no PIK3CA mutation will be considered as screen failures.

If it is decided to open part B2, participants will be enrolled to either Part A or part B2 based on their molecular status as described above.

In Parts A and B2, randomization will be stratified by line of therapy in advanced/metastatic setting (1st line versus 2nd line), hormone receptor status at initial breast cancer diagnosis (HR+ versus HR-) and prior therapy with checkpoint inhibitors (Yes versus No).

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

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

The randomization codes associated with participants from whom PK samples are to be analyzed will be disclosed to Bioanalysts upon request who will keep PK results confidential until the point when the database is locked for primary endpoint analysis.

6.4 Treatment blinding

Part B1

Treatment will be open to participants, investigator staff, persons performing the assessments, and the clinical trial team (CTT) at Novartis.

Parts A and B2

The CTT will remain blinded to the identity of the treatment from the time of randomization until reporting of the primary endpoint in each Study Part. Participants, investigator staff, and persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization until all Part A participants have completed 6 months of study treatment or have been discontinued from study treatment and upon protocol amendment 02 approval, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: Independent biostatistician and programmer who will perform DMC analysis and the Bioanalysts. The randomization codes associated with participants from whom PK samples are to be analyzed will be disclosed to Bioanalysts upon request who will keep PK results confidential until the point when the database is locked for primary endpoint analysis.

(2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

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 participants. Unblinding will only occur in the case of participant emergencies (see Section 6.6.2), following the Data Monitoring Committee (DMC) recommendations (e.g. after the interim analysis) (see Section 12.7), for regulatory reporting purposes or at the time of Part A primary analysis. Parts A and B2 can be unblinded independently of each other. The decision was taken not to initiate Part B2.

Unblinding a single participant at a site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result the participant should be discontinued from the study treatment. In rare cases when unblinding occurs because of emergency participant management, the actual treatment arm will not be communicated to any of the Novartis employees involved in running the trial.

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

Upon unblinding, the following options will be permitted:

- Participants in the experimental arm will be given the opportunity to continue to take alpelisib in combination with nab-paclitaxel, if they are benefiting based on investigator's judgement and individualized benefit/risk assessment after discussion with the participant and documentation in the medical record.
- Participants in the control arm will be allowed to continue on nab-paclitaxel, if they are benefiting based on investigator's judgement and an individualized benefit/risk assessment after discussion with the participant and documentation in the medical record. No placebo tablets will be given.

Participants randomized to the control arm will not be allowed to cross-over to the experimental arm to receive alpelisib.

6.5 Dose escalation and dose modification

Dose escalation is not applicable.

6.5.1 Dose modifications

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

These dose modifications are summarized in Table 6-3, Table 6-4, Table 6-5, Table 6-6 and Table 6-7. Deviations to stepwise dose reductions are not allowed. Dose changes must be recorded on the appropriate eCRF.

6.5.1.1 Alpelisib dose modifications

Recommendations for dose reduction or dose interruption of alpelisib/placebo in the management of adverse reactions are summarized in Table 6-4. Clinical judgment of the

treating physician, including confirmation of lab values if deemed necessary, should guide the management plan of each participant based on individual benefit/risk assessment.

A maximum of 2 dose reductions will be allowed after which treatment must be discontinued as indicated in Table 6-3.

After treatment is resumed at a lower dose:

- If the same toxicity reoccurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration, except if specified in Table 6-4.
- Once the alpelisib/placebo dose has been reduced, no re-escalation will occur, even upon resolution of AE.

If a participant requires a withholding of alpelisib/placebo dose the participant may continue on nab-paclitaxel, per investigator discretion. All scheduled assessments will continue to be performed as per protocol.

Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-4 or listed in Section 9. These dose changes must be recorded on the appropriate eCRF.

Table 6-3 Stepwise dose reduction 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

Table 6-4 Criteria for dose reduction / interruption and re-initiation of alpelisib/placebo treatment for adverse drug reactions

Dose Modifications for alpelisib/placebo as specified below. Nab-paclitaxel may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Investigations (FG - Fasting Glucose)	
Hyperglycemia (see also Section 6.5.2.4) Consultation with a diabetologist and or healthcare provider experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia. Always recommend/reinforce on lifestyle changes as per American Diabetes Association (ADA and/or European Association for the study of Diabetes (EASD), i.e. exercise and dietary advice (e.g. controlled carbohydrate intake, high fiber, low process food intake. Three macronutrient balance meals and 2 optional small snacks rather than one large meal).	

<table>
<tr><td colspan="2">Dose Modifications for alpelisib/placebo as specified below. Nab-paclitaxel may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified.</td></tr>
<tr><td>Worst toxicity - CTCAE Grade (value)</td><td>Dose Modifications for alpelisib/placebo</td></tr>
<tr><td colspan="2">Note: this table provides dose management recommendations. Local standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting glucose testing may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance. However, dose reductions should only be based on FPG. As metformin is widely available, it is an appropriate choice as initial therapy for alpelisib-induced hyperglycemia. However, SGLT2 inhibitors, as per local standard practice, are acceptable as well and may be administered alone or in combination with metformin. The use of metformin XR can be considered as a suitable alternative to metformin IR, alone or in combination with an SGLT2 inhibitor, particularly for participants with at least one risk factor for the development of severe hyperglycemia, at the discretion of the Investigator and as per local standard practice. Refer to Section 6.5.2.4 (“Guidelines for the treatment of alpelisib induced hyperglycemia”) for additional details regarding the use of metformin XR and/or SGLT2 inhibitors. In case of intolerance to or unavailability of metformin, investigator’s judgment should be exercised and other oral anti-diabetic agents such as thiazolidinediones or dipeptidyl peptidase-4 Inhibitors can be used.
SGLT2i may increase the risk of euglycemic diabetic ketoacidosis and therefore, monitoring with serum / urine ketones and consultation with a healthcare expert experienced in hyperglycemia management or a diabetologist should be considered (please refer to the label or standard of care).</td></tr>
<tr><td>Grade 1 (FG > ULN - 160 mg/dL) [> ULN - 8.9 mmol/L]
For participants with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this apply only for values > 140 mg/dL (7.7 mmol/L)</td><td>• Maintain dose level, and remind participant on lifestyle changes*.
• Start/intensify metformin as per guidance below or in cooperation with a healthcare expert experienced in hyperglycemia management or a diabetologist.
Metformin 500 mg orally once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg b.i.d., with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg b.i.d. with breakfast and dinner. Alternatively, metformin XR once daily dosing may be considered instead of metformin IR.
If not tolerated, reduce to prior tolerated dose.
Titrate to the MTD over a period of 3 weeks.
• Alternatively, consider starting an SGLT2 inhibitor alone or in combination with metformin, especially in participants at risk for developing severe hyperglycemia. Refer to Section 6.5.2.4 (“Guidelines for the treatment of alpelisib induced hyperglycemia”). Starting dose and titration should be in accordance with the local prescribing information and consistent with local practice.
• Monitor fasting glucose levels as clinically indicated and at least twice weekly for 8 weeks, then continue checking at least weekly until FG is within baseline values.</td></tr>
<tr><td>Grade 2 (FG >160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]</td><td>• Maintain dose level and remind participant on lifestyle changes*, exclude confounding factors like e.g. urinary tract infection, consider consultation with a healthcare expert experienced in hyperglycemia management or a diabetologist.
• Start/intensify oral anti-diabetic treatment with metformin or alternatively start an SGLT2 inhibitor alone or in combination with metformin.
• Additional oral anti-diabetic agents may be initiated, if needed. If fasting glucose levels are still rising on maximum tolerated dose of metformin or persistently >160 mg/dL (>8.9 mmol/L), add an SGLT2 inhibitor if not already started, e.g. empagliflozin up to 25 mg (max. dose). Alternatively an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose) can be added.
• Monitor blood glucose levels as clinically indicated and at least twice weekly until FG resolves to ≤ Grade 1</td></tr>
</table>

Dose Modifications for alpelisib/placebo as specified below. Nab-paclitaxel may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
	• 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 blood glucose levels at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FG>250mg/dL
Grade 3 FG > 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. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of alpelisib-induced hyperglycemia given the short half-life of alpelisib. Start or further intensify oral anti-diabetic treatment and titrate as outlined for Grade 2. Monitor fasting glucose levels as clinically indicated and at least twice weekly until FG resolves to ≤ Grade 1. • If FG resolves to ≤ 160 mg/dL within 3-5 days, while off 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 FG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FG>250mg/dL • If FG 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 FG does not resolve to ≤ 160 mg/dL within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue participant from alpelisib/placebo treatment.
Grade 4 FG > 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. • consult with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours. • If grade improves then follow specific grade recommendations • If FG is confirmed as > 500 mg/dL and confounding factors could be excluded, permanently discontinue participant from alpelisib/placebo.
*For specific recommendations please see Section 6.5.2.4	
Investigations (Hepatic) Note: this is for newly occurred or worsened from baseline	
Isolated total Bilirubin elevation	

Dose Modifications for alpelisib/placebo as specified below. Nab-paclitaxel may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Grade 1 (>ULN - 1.5 x ULN)	• No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 1.5 - 3.0 x ULN)	• Interrupt dose until recovery to Grade ≤ 1 and resume at the same dose if resolved in ≤ 14 days or resume at the next lower dose level if resolved in > 14 days
Grade 3 (>3.0 - 10.0 x ULN)	• Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level
Grade 4 (>10.0 x ULN)	• Permanently discontinue
Isolated AST or ALT elevation	
Grade 1 (>ULN - 3.0 x ULN) Grade 2 (>3.0 - 5.0 x ULN)	• No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 (>5.0 - 20.0 x ULN)	• Interrupt dose until recovery to Grade ≤ 1, then decrease dose level
Grade 4 (>20.0 x ULN)	• Permanently discontinue
Combined ALT/AST and TBIL elevation	• Please see specific instructions in Section 6.5.2.1
Gastrointestinal	
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements. Colitis is defined as a disorder characterized by inflammation of the colon.	
Grade 1 (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline) OR Asymptomatic colitis; clinical or diagnostic observations only; intervention not indicated	• Maintain dose level but initiate appropriate medical therapy and monitor as clinically indicated
Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental Activities of Daily Living (ADL)) OR Abdominal pain; mucus or blood in stool	• Omit dose until resolved to ≤ Grade 1, initiate appropriate medical therapy then restart at same dose • If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then decrease 1 dose level • Initiate or intensify appropriate medical therapy and monitor as clinically indicated. • For Grade 2 colitis consider additional treatment, such as steroids.
Grade 3 (Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL) OR Severe abdominal pain; peritoneal signs	• Omit dose until resolved to ≤ Grade 1, then decrease 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 • For Grade 3 colitis consider additional treatment, such as steroids.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	• Discontinue participant from treatment • Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated
Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea	

Dose Modifications for alpelisib/placebo as specified below. Nab-paclitaxel may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Investigations (Pancreatic)	
Pancreatitis	
Grade 2 or Grade 3	• Omit dose until resolved to Grade ≤ 1, then resume treatment at decreased dose level. • If toxicity reoccurs, permanently discontinue participant from alpelisib/placebo
Grade 4	• Permanently discontinue participant from alpelisib/placebo
Skin and subcutaneous tissue disorders	
Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with alpelisib. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. (see also Section 6.5.2.3). Dermatologist consultation is mandated for serious cutaneous reactions (i.e. fulfilling seriousness criteria for AE Reporting) and for severe cutaneous reactions like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms.	
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 for up to 28 days, as long as skin toxicity is active. • If active rash is not resolved within 28 days of appropriate treatment, add low dose systemic corticosteroid (20-40 mg/d), such as prednisone 10 mg 3x daily. For participants with symptoms like burning, stinging and/or pruritus, add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night.
Grade 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 for up to 28 days, as long as skin toxicity is active • Add systemic corticosteroids 20-40mg/d. If rash improves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued For participants with symptoms like burning, stinging and/or pruritus, add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night.
Grade 3 (>30% BSA with active skin toxicity*)	• Omit alpelisib/placebo dose until rash /skin toxicity is improved to Grade 1 or resolved, • Strongly 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 improves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued. • Re-start alpelisib/placebo dose once rash /skin toxicity is fading, but no longer active (Grade 1): - At reduced dose in case of first occurrence.

Dose Modifications for alpelisib/placebo as specified below. Nab-paclitaxel may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
	- 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 participants with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night. Antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib/placebo.
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	• Permanently discontinue participant from alpelisib/placebo • Consult a dermatologist, strongly recommend documentation by photography and consider performing a skin biopsy if clinically indicated • Treatment may follow guidelines for Grade 3 above with the exception of rechallenge • Additional measures may be taken as per local treatment guidance.
Any Grade of Stevens-Johnson-Syndrome /Toxic Epidermal Necrolysis /Drug Reaction with Eosinophilia and Systemic Symptoms or other SJS/TEN/DRESS like severe skin reactions	• Permanently discontinue participant from alpelisib/placebo • Consult a dermatologist, strongly recommend documentation by photography and consider performing a skin biopsy if clinically indicated • Follow local treatment guidelines for SJS/TEN/DRESS.
*“Active” skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered “active” any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.	
Immune system disorders	
Hypersensitivity	
Please see specific instructions in Section 6.5.2.6	
Investigations (Pulmonary disorders)	
Pneumonitis	
Please see specific instructions in Section 6.5.2.2	
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation (see also Section 6.5.2.5)	
Grade 1 (> ULN - 1.5 x ULN)	• Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	• Maintain dose level
Grade ≥ 3 (> 2.0 x ULN)	• Omit dose until resolved to baseline, then • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, then decrease dose level. Note: In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase) as specified in Section 6.5.2.5

Dose Modifications for alpelisib/placebo as specified below. Nab-paclitaxel may be continued while alpelisib/placebo dose is being held, at the investigators discretion, and as specified.	
Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib/placebo
Note: Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Investigations (any other)	
Other adverse events	
Grade 1 or 2	• Maintain dose level
Grade 3	• Omit dose until resolved to ≤ grade 1, then decrease dose level
Grade 4	• Permanently discontinue participant from alpelisib/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)

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

6.5.1.2 Nab-paclitaxel dose modifications

For dose modifications due to toxicities that are suspected to be caused by Nab-Paclitaxel, please refer to Table 6-6, Table 6-7 and the nab-paclitaxel prescribing information and local clinical practice. Of note, the following toxicities are common for both alpelisib and nab-paclitaxel: GI toxicity, skin toxicity, hypersensitivity, pneumonitis. Additional guidance for pneumonitis and hypersensitivity can be found in Section 6.5.2.2 and Section 6.5.2.6.

This section provides additional guidance because the dose regimen and dose strengths for nab-paclitaxel in this study (100 mg/m^2 on days 1, 8 and 15 of a 28-day cycle) differs to the approved dose strengths and regimen of 260 mg/m^2 once every 3 weeks for advanced BC (see Section 4.2). The following guidelines should be considered for dose modifications for AEs that are suspected to be caused by Nab-Paclitaxel.

Table 6-5 Stepwise Dose reduction for Nab-paclitaxel

Nab-paclitaxel dose level	Dose
Starting dose level	100 mg/m^2
First Dose Reduction (20% of prior dose level)	80 mg/m^2
Second Dose Reduction (20% of prior dose level)	64 mg/m^2

Table 6-6 Hematologic Toxicities requiring dose adjustments for Nab-Paclitaxel

Toxicity	Treatment Modification
ANC < 1,500/µl on Day 1 of a treatment cycle	Hold Nab-paclitaxel until ANC ≥ 1,500µl
ANC < 1,000/µl on Day 8 or 15 of a treatment cycle	Hold Nab-Paclitaxel until ANC ≥ 1,000µl. Monitor ANC at least weekly. Resume Nab-Paclitaxel when ANC have recovered, according to the following guidelines: • If ANC recovers to ≥ 1,000/µl in ≤ 1 week, restart Nab-Paclitaxel at current dose. • If ANC recovers to ≥ 1,000/µl after 1-3 weeks, Nab-Paclitaxel dose should be reduced by 20% for subsequent cycles.

Toxicity	Treatment Modification
	• If ANC still < 1,000/µl after the 3-week withholding, permanently discontinue Nab-Paclitaxel.
Platelets < 75,000/µl on Day 1, 8, or 15 of a treatment cycle	Hold Nab-Paclitaxel until platelets recover to ≥ 75,000/µl. Resume Nab-Paclitaxel when platelets have recovered, according to the following guidelines: • If platelets recover to ≥ 75,000/µl in ≤ 1 week, restart Nab-Paclitaxel at the current dose. • If platelets recover to ≥ 75,000/µl after 1-3 weeks, Nab-Paclitaxel dose should be reduced by 20% for subsequent cycles. • If the platelet count fails to recover to ≥ 75,000/µl within 3 weeks, permanently discontinue Nab-Paclitaxel. NOTE: See below for dose modifications for Grade 3-4 thrombocytopenia.
Grade 3/ 4 thrombocytopenia on Day 1, 8, or 15 of a treatment cycle	Hold Nab-Paclitaxel until thrombocytopenia Grade 3/4 has improved to Grade 2 or less. Resume Nab-Paclitaxel when thrombocytopenia have recovered, according to the following guideline: • The dose of Nab-Paclitaxel should be reduced by 20% for subsequent cycles
Febrile Neutropenia* Grade 3 on Day 1, 8, or 15 of a treatment cycle	After the first occurrence of febrile neutropenia, at the investigator discretion, Nab-Paclitaxel may be given in subsequent cycles at either • The same doses, but with prophylactic ciprofloxacin 500mg oral twice daily or an alternative prophylactic antibiotic regimen at the choice of the investigator, or • at a 20% reduced dose (either with or without prophylactic antibiotics). If a second episode of febrile neutropenia occurs • Nab-Paclitaxel should be reduced by 20% (based on the current dose) for subsequent cycles. If a third episode of febrile neutropenia occurs, • Nab-Paclitaxel should be permanently discontinued.
*Febrile neutropenia is defined as fever ≥ 38.5 °C in the presence of neutropenia (ANC < 1,000/µl.) 1. There will be no dose modifications for lymphopenia. 2. There will be no dose modifications for Grade 2 – 4 anemia. Transfusions will be given as clinically indicated.	

The frequency and severity of sensory neuropathy increased with cumulative doses. Sensory neuropathy is dose- and schedule-dependent. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If ≥ Grade 3 sensory neuropathy develops, withhold nab-paclitaxel until improvement to Grade 1 or 2, followed by a dose reduction for all subsequent cycles.

Once the nab-paclitaxel dose has been reduced, no re-escalation will occur, even upon resolution of AE.

A maximum of 2 dose reductions will be allowed after which treatment must be discontinued, please refer to Table 6-5.

Table 6-7 Overlapping toxicities with alpelisib requiring dose adjustments for Nab-Paclitaxel

	Dose modification
Cutaneous toxicity	
Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists
GI toxicity	
Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level

If a participant requires a withholding of nab-paclitaxel dose, the participant may continue on alpelisib/placebo per investigator's discretion. All scheduled assessments will continue to be performed as per protocol.

6.5.2 Follow-up for toxicities

All participants must be followed up for safety (adverse events and serious adverse events) for 30 days following the last dose of study treatment (alpelisib/placebo and/or nab-paclitaxel).

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

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

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

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

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

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

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

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

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

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

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

Perform relevant examinations (ultrasound or MRI, endoscopic retrograde cholangiopancreatography (ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an alkaline phosphatase (ALP) elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the Gamma-glutamyltranspeptidase (GGT) can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

If DILI is confirmed: permanently discontinue study treatment.

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

Table 6-8 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed Liver Function Test (LFT) abnormalities.

Table 6-8 Alternative causes of liver disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-Hepatitis A (HAV) ; HBsAg, IgM anti-HBc, Hepatitis B virus (HBV) DNA; anti-Hepatits C virus (HCV), HCV RNA, IgM & IgG anti-Hepatitis E virus (HEV), HEV RNA
Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Epstein-Barr virus (EBV) infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear antibody (ANA) & Antismooth muscle antibody (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.

Disease	Assessment
Biliary tract disease	Ultrasound or MRI, (Endoscopic retrograde cholangiopancreatography) ERCP as appropriate.
Wilson disease	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).

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

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

6.5.2.2 Management of pneumonitis

Both alpelisib and nab-paclitaxel are associated with pneumonitis/interstitial lung disease.

Closely monitor all participants for signs and symptoms of pneumonitis.

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

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

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

6.5.2.3 Guidelines for the treatment of alpelisib induced skin toxicity

Skin toxicity is an adverse drug reaction observed with PI3K inhibitors.

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 starting treatment and is reversible with adequate concomitant medications and alpelisib treatment interruption/reduction, 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 a severe cutaneous reaction like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme or DRESS (Drug reaction with eosinophilia and systemic symptoms) is suspected.

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

. In case of Grade 3/4 skin toxicity, Novartis strongly recommends that photographs are taken and a skin biopsy is performed. Photographs and skin biopsy should be stored at the site for source documentation.

In Study CBYL719C2301 (SOLAR-1), among the 86 participants in the alpelisib group who received prophylaxis prior to rash onset, 73% did not develop a rash, while among the 198 participants from the alpelisib group who did not receive prophylaxis, 36% did not develop a rash. Similar trends were observed in the CBYL719C2402 (BYLieve) study, where 70% of participants who received prophylaxis (n=10) did not develop a rash compared with 53% of participants who did not receive prophylaxis (n=117) did not develop a rash (Patel and Seminario-Vidal 2020). Additionally, in a single center retrospective analysis of 102 patients receiving alpelisib, prophylaxis with non-sedating antihistamines (n=43) was correlated with a reduction in grade 1/2 rash events (OR 0.39, p=0.09) (Wang et al 2020).

Based on these data, prophylactic treatment with non-sedating antihistamines (e.g. cetirizine (Zyrtec©), fexofenadine (Allegra), loratadine (Claritin)) can be started on Cycle 1 Day 1 and continued for approximately 8 weeks in all participants, especially in those with a history of atopy such as allergic rhinitis, asthma, atopic dermatitis, or drug allergies, at the discretion of the investigator. Preventive strategies, including the administration of non-sedating, oral antihistamines before starting alpelisib and prior to rash onset, may decrease incidence and severity of rash based on alpelisib clinical trial experience.

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

- Consultation with a dermatologist should always be considered. Mid to High potency topical steroids: triamcinolone 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 preparation.
- *Gamma*-aminobutyric acid (GABA) Agonists: gabapentin 300mg every 8 hours, pregabalin 50-75 mg every 8 hours (adjust as tolerated). Depending on participant's clinical condition be aware of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (gabapentin) among others adverse events.

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

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

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

6.5.2.4 Guidelines for the treatment of alpelisib-induced hyperglycemia

Alpelisib, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy et al 2012). Alpelisib induced hyperglycemia is generally manageable with adequate antidiabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Participants with pre-diabetes (i.e. FG 100 – 125 mg/dL; 5.6 - 6.9 mmol/L) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in FG while on alpelisib/placebo treatment. However even participants with FPG within normal limits at screening may develop alpelisib-induced hyperglycemia which is an on-target effect seen with PI3K inhibitors. Participants should always be instructed to follow dietary guidelines provided by the American Diabetes Association and/or the European Association for the study of Diabetes, e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day ; three small meals and 2 small snacks rather than one large meal and exercise, as appropriate.Hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS) and diabetic ketoacidosis (DKA) are two of the most serious metabolic complications associated with hyperglycemia. DKA is characterized by ketoacidosis and a comparatively lower hyperglycemic level (blood glucose 250 mg/dL-600 mg/dL), while HHNKS is characterized by more severe hyperglycemia (blood glucose > 600 mg/dL) together with hyperosmolarity and dehydration without significant ketoacidosis. HHNKS is also known as non-ketotic hyperosmolar syndrome, hyperosmolar hyperglycemic state or hyperglycemic hyperosmolar non-ketotic coma. Most patients with HHNKS have a known history of diabetes mellitus Type 2. HHNKS usually develops over a course of many days to weeks, unlike DKA which can develop over the course of a few hours or days.Detailed guidelines for the management of alpelisib induced hyperglycemia are provided in Table 6-4. This includes early administration of metforminor a SGLT2 inhibitor (alone or in combination with metformin).

Metformin XR was developed to allow a slower release of drug into the upper gastrointestinal tract to reduce toxicities such as diarrhea. The use of metformin XR can be considered as a suitable alternative to metformin IR due to its better tolerability and once daily dosing, alone or in combination with an SGLT2 inhibitor, particularly for participants with at least one risk factor for the development of severe hyperglycemia, at the discretion of the Investigator and as per local standard practice (Jabbour and Ziring 2011).

Local standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting glucose testing may be performed both locally and/or centrally for rapid availability for

safety evaluation and management guidance. However, it is strongly recommended that dose reduction will be based on FPG only.

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

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

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

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

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

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

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

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

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

6.5.2.6 Guidelines for hypersensitivity

Both alpelisib and nab-paclitaxel are associated with hypersensitivity reactions, including anaphylaxis and angioedema. These are manifested by symptoms including, but not limited to: dyspnea, flushing, rash, fever, hypotension, dizziness, tachycardia and facial or laryngeal oedema. Alpelisib and/or nab-paclitaxel should be permanently discontinued and should not be re-introduced in participants with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

Alpelisib and paclitaxel concentrations will be determined as detailed in pharmacokinetics Section 8.5.2. On PK sampling days, compliance will be assured by administrations of alpelisib/placebo after food under the supervision of investigator or his/her designee.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Blinding codes may also be broken after a patient discontinues treatment due to disease progression if deemed essential to allow the investigator to select the patient's next treatment regimen, and after discussion and agreement with the sponsor. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

In addition, the investigator will inform the participant how to contact his/her backup in cases of emergency when he/she is unavailable.

Study treatment must be discontinued once emergency unblinding has occurred. If a participant is unblinded, he/she must be discontinued from the study.

Following protocol amendment 02, the emergency unblinding procedures are no longer applicable as participants will be unblinded and made aware of their study treatment.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section. Participants will be provided with an adequate supply of study drug

(alpelisib/placebo) for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Participants will receive alpelisib/placebo on an outpatient basis.

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

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of Investigational Medicinal Product (IMP) directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of one cycle of alpelisib/placebo (4 weeks supply). In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure (for alpelisib/placebo). Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines.

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Dosing and treatment schedule will be performed according to Section 6.1.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

6.7.2.1 Alpelisib or alpelisib/placebo administration

Participants should be instructed to take the dose of alpelisib/placebo once daily at approximately the same time each day immediately after food (preferably in the morning). An exception is on the days of blood collection at the study site, at which time the participants should take their doses at the study site at any later point of time.

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

On the days of nab-paclitaxel administration, alpelisib/placebo tablets should be taken 1 hour prior to the infusion of nab-paclitaxel.

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

During the treatment phase, the participant should record if the dose was taken or not in the alpelisib/placebo participant diary.

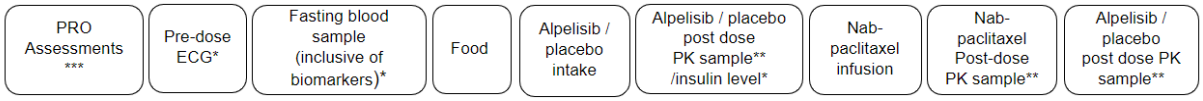
6.7.2.1.1 Additional dosing guidelines for scheduled visit days

On days when pre-dose fasting safety samples are collected as described in Table 8-2 and Table 8-3, participants should be instructed to arrive at the site in fasted state. The following additional guidelines should be followed:

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

- On scheduled visit days, participants must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days, participants will take alpelisib/placebo at home
- The participants must take alpelisib/placebo immediately after food
- PRO assessments must be collected prior to any clinical assessments, drug dosing or diagnostic testing.
- If a pre-dose ECG measurement should be collected, then the ECG measurement should occur before dosing of alpelisib/placebo
- If a pre-dose PK sample should be obtained, then the sample should be collected **after the ECG and before dosing** of alpelisib/placebo
- Pre-dose PK samples should be drawn **prior to** dosing. The sampling time of the PK samples and the dosing time must be precisely recorded in the eCRF. Furthermore, the date and time of alpelisib/placebo dose on the day before the PK assessment must be precisely recorded in the eCRF
- Post-dose PK samples should be collected after dosing of alpelisib/placebo and/or nab-paclitaxel infusion.
- Post-dose Insulin level should be collected 1h (+/- 15min) after dosing of alpelisib/placebo, except at screening and EOT.
- ECG and PK sample collection will be performed according to Section 8.4.2, Section 8.5.2

Figure 6-1 Study drug administration on scheduled visit days



*Please refer to schedule of assessments in Table 8-2 and Table 8-3
**Please refer to PK Blood collection logs Section 8.5.2.1

***Until all participants have completed 6 months of study treatment or have been discontinued from study treatment

7 Informed consent procedures

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

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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

The following informed consents are included in this study:

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

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

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

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The following assessment schedules (Table 8-2 and Table 8-3) list all of the assessments when they are perfomed.An “X” in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. An "S", the assessments that are in the participant’s source documentation only and do not need to be recorded in the clinical database. All data obtained from these assessments must be supported in the participant’s source documentation.

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

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

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, or virtual contacts (e.g. tele consult) can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

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

Table 8-1 Allowable visit windows

Visit Name	Window
Molecular Pre-screening	Anytime before main screening
Main Screening	Within 28 days of first dose of study treatment however selected assessments should be performed -14 days prior start of study treatment (see Table 8-2 and Table 8-3)
C1D1 visit and dosing	No later than 3 days after IRT registration (Section 6.3.2)
All assessments during the treatment period (except nab-paclitaxel injections)	+/- 3 days
Nab-paclitaxel injections (On days 1, 8 and 15 of each cycle)	+/- 1 day
PK sampling	Please refer to Tables in Section 8.5.2.1
Tumor assessments	+/- 7 days
PRO assessments**	+/- 7 days
End of treatment	≤ 14 days after last dose of study treatment
30 days safety follow-up visit	+/- 3 days
Follow-up after disease progression (8 weeks post progression)**	+/- 14 days
Efficacy follow-up visit**	+/- 7 days
Survival follow-up visit (every 12 weeks)**	+/- 7 days
Note: *Imaging assessments should be scheduled using the randomization date as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed. Tumor assessments will be performed as clinically indicated per local standard of care once all participants have completed 6 months of study treatment or have been discontinued from study treatment **: until all participants have completed 6 months of study treatment or have been discontinued from study treatment	

Table 8-2 Assessment Schedule, Parts A and B2

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Informed consent	X	X														
Tumor tissue: New/recent biopsy or archival tumor block/slides	X															
Demography	X															
Inclusion / Exclusion criteria	X	X														
Medical history/current medical conditions		X														

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Diagnosis and Extent of Cancer		X														
Information on prior local testing for BRCA status and PD-L1 status, if available		X														
Information on prior local PIK3CA mutation testing, if applicable	X															
Eligibility checklist (within IRT)		S														

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Locally confirmed TNBC status in advanced setting		X														
Prior antineoplastic therapy		X														
Prior/concomitant medication		X	Continuous up to 30 days after last dose of study treatment													
Procedures and Significant Non-Drug therapies		X	Continuous up to 30 days after last dose of study treatment													
IRT Registration (after molecular pre-screening ICF signature)	S															

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
IRT Registration (after main ICF signature)		S														
IRT Randomization			X													
IRT Study Drug Dispensation[8]			X			X			X							
End of phase disposition		X										X		X		
Physical Examination		S[1, 3]				S[3]			S[4]			S[3]				
Performance status (ECOG)		X[1]				X			X			X				
Body Height		X[1]														
Body Weight		X[1]				X			X			X				
Vital Signs		X[1]	X	X	X	X	X	X	X	X	X	X				

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Hematology		X[1]		X	X	X	X	X	X	X[7]	X[7]	X				
Fasting Chemistry (Full)		X[1]				X			X			X				
Fasting Chemistry (Partial)				X	X		X	X								
Fasting Plasma Glucose		X[1]		X	X	X	X	X	X			X				
Urinalysis		X[1]	As clinically indicated									X				
Fasting lipid panel		X[1]										X				

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
HbA1C		X[1]				X			every 3 cycles from C5D1 onwards			X				
Coagulation panel		X[1]				X			every 2 cycles from C4D1 onwards			X				
Fasting Lipase, Fasting Amylase		X[1]		X		X			X			X				

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Insulin level		X[1]				X[2]			every 2 cycles from C4D1 onwards[2]			X				
Serum pregnancy test (central)		X[1]										X	X			
Serum pregnancy test (local)			S			S			S							

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Tumor Assessment [6] (Section 8.3.1 & Table 8-4)		X	Every 8 weeks (+/- 7 days) during the first 18 months and every 12 weeks (+/- 7 days) thereafter until disease progression, death, withdrawal of consent, loss to follow-up.									If a participant discontinues treatment for reason other than radiological documentation of progression, an efficacy assessment should be performed at the time of End of Treatment unless imaging tumor assessment was performed within 21 days.		Tumor assessments must be continued if study treatment was stopped for other reason than disease progression, death, withdrawal of consent, lost to follow-up irrespective of initiation of new antineoplastic therapy (Every 8 weeks (+/- 7 days) during the first 18 months and every 12 weeks (+/- 7 days) thereafter)		

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Whole body bone scan	X (within 42 days prior to randomization)		As clinically indicated													
Electrocardiogram (ECG), performed locally		X	Predose						C3D1 and C6D1 at predose, thereafter only as clinically indicated			X				

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Cardiac imaging (MRI or MUGA or ECHO)		X	As clinically indicated									X				
Adverse Events	Suspected SAEs	Continuous, up to 30 days after the last dose of study treatment														
Pharmacokinetic sample collection			For collection time points please refer to Section 8.5.2.1													
Meal record				X												
Blood for circulating DNA [5]			X			X			every 2 cycles from C4D1 onwards			X				

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
[redacted]																
Skin biopsies and skin photography (if clinically indicated for G3/G4 skin toxicity) [5]			Anytime at the appearance of G3/4 skin toxicity, or any suspected severe cutaneous reactions. Refer to Section 6.5.2.3													

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
[redacted]																
Alpelisib/Placebo			Daily													

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**
Participant dosing diary			Starts at C1D1 and continues until last dose (source documentation)													
Nab-paclitaxel			X	X	X	X	X	X	X	X	X					
Antineoplastic therapies since discontinuation of study treatment												X	X	X		X
Follow up visit													X	X	X	
Follow up call																X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Within 14 days prior to randomization
[2] Post-alpelisib dose
[3] Complete physical exam
[4] Short Physical exam
[5] Until all participants have completed 6 months of study treatment or have been discontinued from study treatment

Period	**Pre-screening**	**Screening /Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**			
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**							
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Follow up after disease progression [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**8 weeks after PD**	**Every 12 weeks**

[6] Tumor assessments will continue as clinically indicated per local standard of care once all participants have completed 6 months of study treatment or have been discontinued from study treatment

[7] To be performed if participants are receiving nab-paclitaxel

[8] Placebo dispensing and administration will stop after participant's unblinding

Table 8-3 Assessment Schedule, Part B1

Period	**Pre-screening**	**Screening/ Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**Every 12 weeks**
Informed consent	X	X													
Tumor tissue: New/recent biopsy or archival tumor block/slides	X														
Demography	X														
Inclusion / Exclusion criteria	X	X													
Medical history/current medical conditions		X													
Diagnosis and Extent of Cancer		X													
Information on prior local testing for BRCA status and PD-L1 status, if available		X													
Information on prior local PIK3CA mutation testing, if applicable	X														
Eligibility checklist (within IRT)		S													
Locally confirmed TNBC status in advanced setting		X													
Prior antineoplastic therapy		X													

Period	**Pre-screening**	**Screening/ Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**Every 12 weeks**
Prior/concomitant medication		X	Continuous up to 30 days after last dose of study treatment												
Procedures and Significant Non-Drug therapies		X	Continuous up to 30 days after last dose of study treatment												
IRT Registration (after molecular pre-screening ICF signature)	S														
IRT Registration (after main ICF signature)		S													
IRT treatment assignment			X												
IRT Study Drug Dispensation			X			X			X						
End of phase disposition		X										X		X	
Physical Examination		S[1, 3]				S[3]			S[4]			S[3]			
Performance status (ECOG)		X[1]													
Body Height		X[1]													
Body Weight		X[1]				X			X			X			
Vital Signs		X[1]	X	X	X	X	X	X	X	X	X	X			
Hematology		X		X	X	X	X	X	X	X[7]	X[7]	X			
Fasting Chemistry (Full)		X[1]				X			X			X			
Fasting Chemistry (Partial)				X	X		X	X							

Period	**Pre-screening**	**Screening/ Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**Every 12 weeks**
Fasting Plasma Glucose		X[1]		X	X	X	X	X	X			X			
Urinalysis		X[1]	As clinically indicated									X			
Fasting lipid panel		X[1]										X			
HbA1C		X[1]				X			every 3 cycles from C5D1 onwards			X			
Coagulation panel		X[1]				X			every 2 cycles from C4D1 onwards			X			
Fasting Lipase, Fasting Amylase		X[1]		X		X			X			X			
Insulin level		X[1]				X[2]			every 2 cycles from C4D1 onwards[2]			X			
Serum pregnancy test (central)		X[1]										X	X		
Serum pregnancy test (local)			S			S			S						

Period	**Pre-screening**	**Screening/ Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**Every 12 weeks**
Tumor Assessment [6] (Section 8.3.1 & Table 8-4)		X	Every 8 weeks (+/- 7 days) during the first 18 months and every 12 weeks (+/- 7 days) thereafter until disease progression, death, withdrawal of consent, loss to follow-up.									If a participant discontinues treatment for reason other than radiological documentation of progression, an efficacy assessment should be performed at the time of End of Treatment unless imaging tumor assessment was performed within 21 days.		Tumor assessments must be continued if study treatment was stopped for other reason than disease progression, death, withdrawal of consent, lost to follow-up irrespective of initiation of new antineoplastic therapy (Every 8 weeks (+/- 7 days) during the first 18 months and every 12 weeks (+/- 7 days) thereafter)	
Whole body bone scan	X (within 42 days prior to randomization)		As clinically indicated												

Period	**Pre-screening**	**Screening/ Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**Every 12 weeks**
Electrocardiogram (ECG), performed locally		X	Predose						C3D1 and C6D1 at predose, thereafter only as clinically indicated			X			
Cardiac imaging (MRI or MUGA or ECHO)		X	As clinically indicated									X			
Adverse Events	Suspected SAEs	Continuous, up to 30 days after the last dose of study treatment													
Pharmacokinetic sample collection			For collection time points please refer to Section 8.5.2.1												
Meal record				X											
Skin biopsies and skin photography (if clinically indicated for G3/G4 skin toxicity) [5]			Anytime at the appearance of G3/4 skin toxicity, or any suspected severe cutaneous reactions. Refer to Section 6.5.2.3												
Alpelisib			Daily												
Participant dosing diary			Starts at C1D1 and continues until last dose (source documentation)												

Period	**Pre-screening**	**Screening/ Baseline**	**Treatment**									**End of Study Treatment**	**Post-Treatment Follow-Up**		
Cycle			**Cycle 1**			**Cycle 2**			**Cycle 3 (and subsequent cycles)**						
Visit Name	**Molecular Pre-Screening**	**Main Screening**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 8**	**Day 15**	**End of Study Treatment (within 14 days from last dose)**	**Safety Follow-up**	**Efficacy Follow-up, if applicable [5]**	**Survival Follow-up [5]**
Days	**anytime before main screening**	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**-**	**30 Days after last dose**	**Follow tumor assessments**	**Every 12 weeks**
Nab-paclitaxel			X	X	X	X	X	X	X	X	X				
Antineoplastic therapies since discontinuation of study treatment												X	X	X	X
Follow up visit													X	X	
Follow up call															X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Within 14 days prior to randomization
[2] Post-alpelisib dose
[3] Complete physical exam
[4] Short Physical exam
[5] Until all participants have completed 6 months of study treatment or have been discontinued from study treatment
[6] Tumor assessments will continue as clinically indicated per local standard of care once all participants have completed 6 months of study treatment or have been discontinued from study treatment
[7] To be performed if participants are receiving nab-paclitaxel

8.1 Screening

All study participants must be thoroughly informed about all aspects of the study, including the study treatment, visit schedule, required evaluations, and all regulatory requirements for informed consent. Written informed consent must be obtained before any study specific assessments are performed, including molecular pre-screening and screening using the respective consent forms: the molecular Pre-screening consent and main study consent. If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion. For details of screening assessments, refer to Table 8-2 and Table 8-3 .

Molecular Pre-screening

For eligibility into the study Part A, participants must have a PIK3CA mutation as centrally confirmed by a Novartis designated laboratory based on tumor tissue, or if the results are already available, by a local laboratory using either a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN *therascreen*® PIK3CA RGQ PCR test without central confirmation. PIK3CA mutation results generated by research use only version of the Qiagen test, or other laboratory-developed tests, are not acceptable. Participants who are confirmed to have PIK3CA mutations by a local laboratory still need to submit a tumor tissue sample to assess PTEN expression status during pre-screening.

For eligibility into part B1 of the study, participants must have a tumor tissue PTEN loss and PIK3CA unknown or non-mutant. For eligibility into part B2 of the study, participants must have a tumor tissue PTEN loss without concurrent PIK3CA mutation.

PIK3CA status is defined as 'unknown' if the PIK3CA results from the PIK3CA mutation assay are reported as invalid based on specified assay control parameters. A PCR based test is used to detect 11 specific PIK3CA sequences in DNA from a tumor sample, each sequence matching one of the 11 mutations targeted by alpelisib. In this assay the quality of DNA extracted from the provided tissue sample is important as fragmented DNA may increase the possibility of non-specific amplification in one of the 11 PIK3CA sequences, without the sequence actually being present. Therefore control reactions are used to detect for non-specific amplification as opposed to targeted amplification of the gene sequence. If these assay controls show non-specific amplification, then the PIK3CA test results are considered invalid and the PIK3CA status is therefore unknown.

PTEN loss is defined by reduction in PTEN protein expression level below a predefined threshold based on an immunohistochemistry test. The lack of PIK3CA mutation must be centrally confirmed by a Novartis designated laboratory, or if the results are already available, by a local laboratory using either a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN *therascreen*® PIK3CA RGQ PCR test without central confirmation.

All participants must sign the molecular pre-screening informed consent form.

1. Upon participant signature of the molecular pre-screening ICF, the archival tumor sample or new tumor biopsy should be collected and shipped to a Novartis designated laboratory for PIK3CA and PTEN status analysis (refer to Table 8-15 in Section 8.5.3 for number of slides required) as soon as possible to allow time for analyses and availability of biomarker results by the time main screening procedures commence.

- Note: Acceptable biopsies for deep tumor tissue include core needle biopsies; and for cutaneous and subcutaneous lesions include excisional, incisional, punch, or forceps biopsies. NOT ACCEPTABLE are fine-needle aspiration, brushings, cell pellets from pleural effusion, bone biopsy, bone marrow aspirates and lavage samples.

2. The participant will be assigned a participant number by the clinical database (see Section 6.3.1) and be registered into the IRT system. The participant number assigned should be the next sequential participant number available in the clinical database for that site.
3. Demographic information is collected in the eCRF (see Section 8.2).
4. The Novartis designated laboratory will provide the PIK3CA mutation and PTEN expression analysis results to the investigational site.

A formalin fixed paraffin embedded (FFPE) tissue block is preferred for analysis. If a tissue block cannot be sent, then unstained FFPE slides at 5 µm thickness are acceptable (refer to Table 8-15 in Section 8.5.3 for details on number of slides required). Ideally the samples should contain at least 80% tumor. If an archival tumor sample (preferably collected within 3 years) is not available, a newly collected formalin fixed biopsy is required. If more than one archival samples is available, tumor sample from the most recent archival biopsy is preferred. Please refer to the laboratory manual for sample requirements.

Participants who have PIK3CA mutation status confirmed by a local laboratory using either a FDA-approved PIK3CA CDx test for alpelisib or the CE-IVD QIAGEN *therascreen*® PIK3CA RGQ PCR test can continue the screening, and no central confirmation will be required. All participants from countries without a health authority approved test for alpelisib must be tested centrally. The PIK3CA mutation status must be documented in the source documents before the participant can be consented for screening. Tumor sample or slides must still be provided to determine PTEN expression status by a Novartis designated central laboratory. The results will be communicated to the site.

Participants with the following pre-screening biomarkers results will be considered as screen failure patients:

- PIK3CA non mutant and PTEN normal
- unknown PIK3CA mutation and unknown PTEN expression
- unknown PIK3CA mutation and PTEN loss (Part A/B2)
- unknown PIK3CA mutation and PTEN normal

Patients who fail the molecular pre-screening cannot be re-screened.

If a tumor block or new biopsy is provided, the remaining tissue from screen failure samples will be returned to the site. If a participant is enrolled, the remaining block will be sent to a Novartis-designated vendor. Only if the site requests the sample to be returned, a few slides will be cut out prior to sending the remaining block back to the site.

Main Screening

Main screening assessments can begin once a participant has been confirmed to meet the molecular pre-screening criteria and has signed the main study ICF. The main screening assessments consist of all eligibility assessments except for molecular assessment to determine

the PIK3CA and PTEN status. Those main screening assessments, must be performed within 28 days of first dose of study treatment to confirm participant's eligibility with the exception of the central serum pregnancy test and selected assessments that must be conducted within 14 days prior to start of study treatment as per Table 8-2 and Table 8-3 . It is highly recommended to send the serum pregnancy sample to the central laboratory no later than 7 days prior the start of study treatment in order to receive the result prior to participant's randomization/enrollment.

For participants who may have had procedures previously performed as part of the participant's routine disease care (prior to signing the main study informed consent), the following procedures can be used providing a proper documentation in participant's file is available:

- Any imaging assessments within 28 days of start of study treatment (Cycle 1 Day 1) (within 42 days for the whole body bone scan)

A participant who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the retest result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within 28 days of screening period. In this case, the participant will not be required to sign another ICF, and the original participant ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 28 days of screening period or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant will be considered a screen failure.

A new informed consent form must be signed if the investigator chooses to re-screen a participant after he/she screen failed.

Re-screening of participant is only allowed once per participant if the participant was not registered as entering the treatment phase before (i.e. IRT randomization/treatment assignment). In this case a new participant number will be generated, and a specific rescreen form will be added in the eCRF, to collect the original participant number. This data will be used to link the two participant numbers for reporting and validation.

All required screening activities that were performed at initial screening and which made the patient screen failed must be repeated when the participant is re-screened to satisfy the window requirements defined in Table 8-2 and Table 8-3. The molecular pre-screening PIK3CA/PTEN testing does not need to be repeated once a participant is re-screened.

Once the number of participants screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the participants who screen failed will not be permitted to re-screen.

8.1.1 Eligibility screening

Following IRT registration at molecular pre-screening and main screening, participant eligibility will be checked according to study inclusion and exclusion criteria as described in Section 5 once all screening procedures are completed. A list of procedures to be performed during the screening period is summarized in Table 8-2 and Table 8-3. Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to start study treatment of each participant to ensure that all inclusion and exclusion criteria have been satisfied. When all screening procedures are completed and the participant's eligibility is confirmed (i.e. all inclusion/exclusion criteria have been verified), the key

eligibility criteria checklist embedded in the IRT system will be completed prior to the first dose of study drug. Please refer to Section 6.3.2 and as well as comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign the informed consent form and subsequently are found to be ineligible prior to enrollment/randomization will be considered a screen failure.

This includes participants who has signed the molecular pre-screening ICF and do not continue to the screening period (e.g. as they do not meet the molecular eligibility criteria) or those who are found not eligible after signing the main study consent. The data for these two cases of screening failures will be handled in the same manner.

The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, local PIK3CA mutation and inclusion/exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3). For participants who fail the molecular pre-screening, only SAEs possibly related to a study procedure will be reported.

If the participant is a molecular pre-screening failure or fails to be randomized or enrolled, the IRT must be notified within 2 days.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristics data will be collected on all enrolled/randomized participants:

- Demography information (gender, age, race and ethnicity as allowed by local regulations) is collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities).

- Medical History/current medical conditions (including BRCA mutation and PD-L1 expression status, if available) present before signing the informed consent. Investigators will have the discretion to record abnormal test findings on the appropriate eCRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

- Disease baseline characteristics including diagnosis, history, extent of cancer, prior antineoplastic therapy
- Prior/concomitant therapy: all medications and significant non-drug therapies taken within 30 days prior to first dose of study treatment
- Blood sample for biomarkers
- Tumor biopsy for biomarkers (unless archival biopsy provided as per Section 8.5.3)
- Quality of life questionnaires (EORTC QLQ-C30, BPI-SF and EQ-5D-5L)

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

- Vital signs including body temperature, blood pressure and pulse
- ECOG performance status
- ECG
- Cardiac imaging
- Tumor evaluation
- Laboratory evaluations
- Complete physical examination
- Stratification factors

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

8.3 Efficacy

8.3.1 Imaging tumor assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.2 (Section 16.1) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 8-4.The local investigator's assessment will be used for treatment decision making.

With protocol amendment 02, the central collection of the imaging data, information via the Baseline Clinical Form and Cytology Form stops and the BIRC assessment will not be performed for any participant enrolled in the study.

All known lesions (measurable, non-measurable) should be accounted for at screening within 28 days before Cycle 1 Day 1 when assessing objective tumor status. Imaging assessments for response evaluation will be performed every 8 weeks (+/-7 days) after randomization during the first 18 months and every 12 weeks (+/- 7 days) thereafter. The 8-week (or 12-week) interval should be respected regardless of whether study treatment is temporarily withheld or unscheduled assessments are performed. Assessment modality must remain the same throughout the study (e.g. contrast CT or MRI scan) using RECIST v1.1 criteria. Local assessments will be used for the primary analysis.. Tumor assessments will continue as clinically indicated upon completion of Part A primary analysis.

If participants start on new antineoplastic therapy before documented disease progression, every effort should be made to continue local collection of tumor assessments until all participants have completed 6 months of study treatment or have been discontinued from study treatment.

Assessment of survival will be performed every 3 months after study treatment discontinuation or upon termination of the efficacy follow-up phase until all participants have completed 6 months of study treatment or have been discontinued from study treatment.

Table 8-4 Imaging Assessment Collection Plan

Procedure	Screening/Baseline[2]	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Every 8 weeks (+/- 7 days) during the first 18 months and every 12 weeks (+/- 7 days) thereafter until disease progression, end of treatment[1], death, withdrawal of consent, or lost to follow-up[3]
Brain CT or MRI	Mandated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis[3]
Whole body bone scan	Mandated, within 42 days (6 weeks) prior to randomization	As clinically indicated
Localized bone CT, MRI, or x-ray	Mandated for skeletal abnormalities identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis[3]
Color photography (with scale/ruler)	Mandated if any skin lesions present at screening	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis[3]
CT or MRI of other metastatic sites (e.g. neck)	Mandated if suspected lesion at screening	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis[3]

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

[2] Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatment or within 42 days for the whole body bone scan, including before signing the main study ICF, can be considered as the baseline images for this study.

[3] Imaging assessments will continue as clinically indicated once all participants have completed 6 months of study treatment or have been discontinued from study treatment.

Baseline imaging assessments

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

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

- Chest, abdomen, and pelvis CT or MRI
- Brain CT or MRI
- 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 at screening
- CT or MRI of other metastatic sites (e.g. neck), if suspected lesion at screening

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

Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

A whole body bone scan should be performed per institutional standard of care [e.g. Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET), or sodium fluoride (NaF) PET]. 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. Further guidance on photography will be outlined in the Imaging Vendor Manual.

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.

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

Post-baseline imaging assessments

Imaging assessments as described in Table 8-4 should be performed at the timepoints specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-2 and Table 8-3). Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) during the first 18 months, and every 12 weeks (+/- 7 days) thereafter until disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples. Imaging assessments should be scheduled using the randomization date as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed. Once all participants have completed 6 months of study treatment or have been discontinued from study treatment, imaging assessments will continue as clinically indicated.

All participants who discontinue from study treatment due to disease progression must have their progression clearly documented according to RECIST v1.1. If a participant did not discontinue study treatment due to disease progression per investigator, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples to efficacy follow-up,

then tumor assessments should continue to be performed according to the planned schedule until disease progression (per investigator), death, lost to follow-up or withdrawn withdrawal of consent/ opposition to use data/biological samples for efficacy follow-up.

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

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

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

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Section 16.1).

If a participant starts on a new antineoplastic therapy before documented disease progression, every effort should be made to continue to collect tumor assessment according to the planned schedule until all participants have completed 6 months of study treatment or have been discontinued from study treatment.

8.3.2 Blinded independent review committee (BIRC) assessment

With the decision to halt recruitment in Part A and to not initiate Part B2, no BIRC assessments will be made for any participants enrolled in the study.

8.3.3 Appropriateness of efficacy assessments

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

8.4 Safety

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

Safety will be monitored by assessing physical examination, vital signs, performance status (refer to Table 8-5 and Table 8-6), ECG, cardiac function evaluation by MRI/Echocardiogram (ECHO)/MUGA scan, laboratory testing (hematology, coagulation, serum chemistry, and urinalysis) as well as routine safety monitoring of AEs and SAEs. For details on adverse event collection and reporting, refer to Section 10.

CTCAE version 4.03 will be used throughout the study to allow pooling of safety data at the alpelisib program level. As per Section 4.6, during a Public Health emergency as declared by

Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-5 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination will be completed at screening, C2D1 and EOT. A short physical exam will be performed at Day 1 of each cycle starting at C3D1 as indicated in Table 8-2 and Table 8-3 during treatment except where a complete physical examination is required. It will include at least the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). If indicated based on symptoms, additional exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event (see Section 10).
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-2 and Table 8-3

The performance status will be assessed according to the ECOG Performance status scale as described in Table 8-6 following the schedule given in Table 8-2 and Table 8-3.

Table 8-6 ECOG performance status

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

8.4.1 Laboratory evaluations

Clinical laboratory analyses (hematology, biochemistry, coagulation, fasting lipase, fasting amylase, fasting lipid panel, fasting glucose, insulin level, HbA1C 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 8-2 and Table 8-3.

All laboratory assessments will be performed by the local laboratory once all participants have completed 6 months of study treatment or have been discontinued from study treatment.

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 these particular situations, 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. In addition, if participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits. If participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

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 worse than the one reported by the central lab, or
- There are no concomitant central results available
- Local lab results after all participants have completed 6 months of study treatment or have been discontinued from study treatment

For assessment of participants' eligibility to the study, only laboratory results from the central laboratory will be used, with the exception of Follicle-stimulating hormone (FSH) and plasma estradiol levels to determine menopausal status (see Section 8.4.3).

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

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 eCRF. 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 eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a participant has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is

responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance.

Table 8-7 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, *(absolute value preferred, percentages are acceptable*)
Fasting Chemistry (Full)	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase (fasting), Lipase (fasting), Glucose (fasting)
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]), Partial thromboplastin time (PTT) or Activated partial thromboplastin time (APTT)
Additional tests	HbA1c, Insulin level
Pregnancy Test For women of child-bearing potential only	Serum (central laboratory at screening, EOT and 30 days safety follow-up), serum (local laboratory at Day 1 of each cycle)

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual. All laboratory assessments will be performed by the local laboratory once all participants have completed 6 months of study treatment or have been discontinued from study treatment.

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The QTcF must be used for clinical decisions e.g., at the Screening visit (as applicable) to assess eligibility. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

Single 12 lead ECGs are collected with ECG machines available at the site. The original ECGs on non-heat-sensitive paper and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Any identifier details must be redacted e.g. participant initials, date of birth.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms) the ECG is repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the investigator or a medically

qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

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

A standard 12 lead ECG will be performed as presented in Table 8-8. Of note more frequent ECG monitoring may be considered if at increased risk for ECG abnormalities due to the use of drugs that prolong the QT interval and/or induce Torsades de Pointes

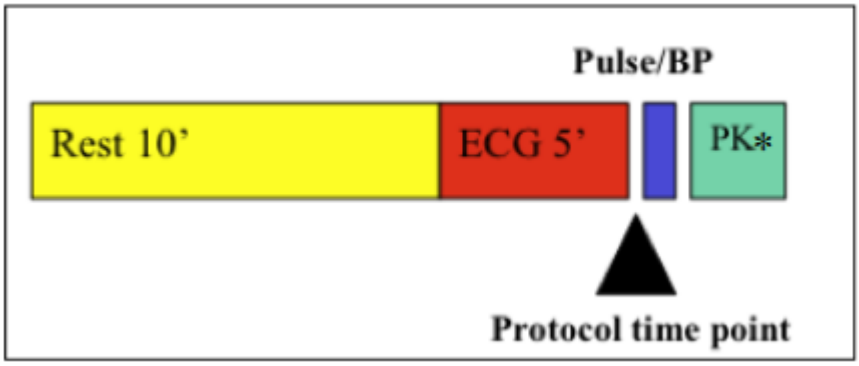
Table 8-8 ECG collection plan

Visit	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12 Lead, single
Cycle 1	1	Pre-dose (baseline ECG)	12 Lead, single
Cycle 3 and Cycle 6	1	Pre-dose	12 Lead, single
EOT	NA	Anytime	12 Lead, single
Unscheduled sample (as clinically indicated or as deemed appropriate by the investigator e.g. if the participant takes drugs that prolong the QT interval and/or induce Torsades de Pointes)	NA	Anytime	12 Lead, single

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

Please refer to Figure 8-1 for the timing of ECG study procedures.

Figure 8-1 Timing of study procedures



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

Paper ECGs should be appropriately labeled and the original kept in the source documents at the study site. If an unscheduled ECG is performed at an external medical facility, a copy of the ECG should be obtained and a copy kept in the source documents at the study site.

Clinically significant ECG abnormalities present at screening should be reported on the appropriate eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

8.4.2.1 Cardiac imaging - MRI (magnetic resonance imaging), MUGA (multiple gated acquisition) scan or echocardiogram

The left ventricular heart function will be evaluated by MRI, ECHO or MUGA at Screening to confirm eligibility and at EOT. Additional cardiac imaging during treatment is to be performed if indicated by clinical signs or symptoms. The same imaging modality should be used.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child and to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above (see exclusion criteria 24 in Section 5.2).

All women of childbearing potential as defined in the inclusion/exclusion criteria who are not surgically sterile will have serum pregnancy testing as follows.

- At screening, within 14 days of first dose of study treatment (central laboratory)
- During study treatment, on Day 1 of each cycle (local laboratory)
- At the EOT visit (central laboratory)
- During the 30 days safety follow-up visit (central laboratory)

Any local positive serum test needs to be confirmed with a central serum test. If positive, the participant must be discontinued from the study treatment.

Results will be required to be retained as source documentation.

Additional pregnancy testing might be performed if requested by local requirements.

If a positive pregnancy test is obtained in between study visits, the participant must immediately notify the investigator. Male participants must notify the investigator in case their partner becomes pregnant during the treatment period and should keep using a condom during sexual intercourse as to prevent delivery of study treatment via seminal fluid to their partner.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional Authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home (if allowed by local regulations) and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the

administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of Fertility

Medical documentation of 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile, surgical bilateral oophorectomy, hysterectomy, or bilateral tubal ligation must be retained as source documents to confirm post-menopausal status.

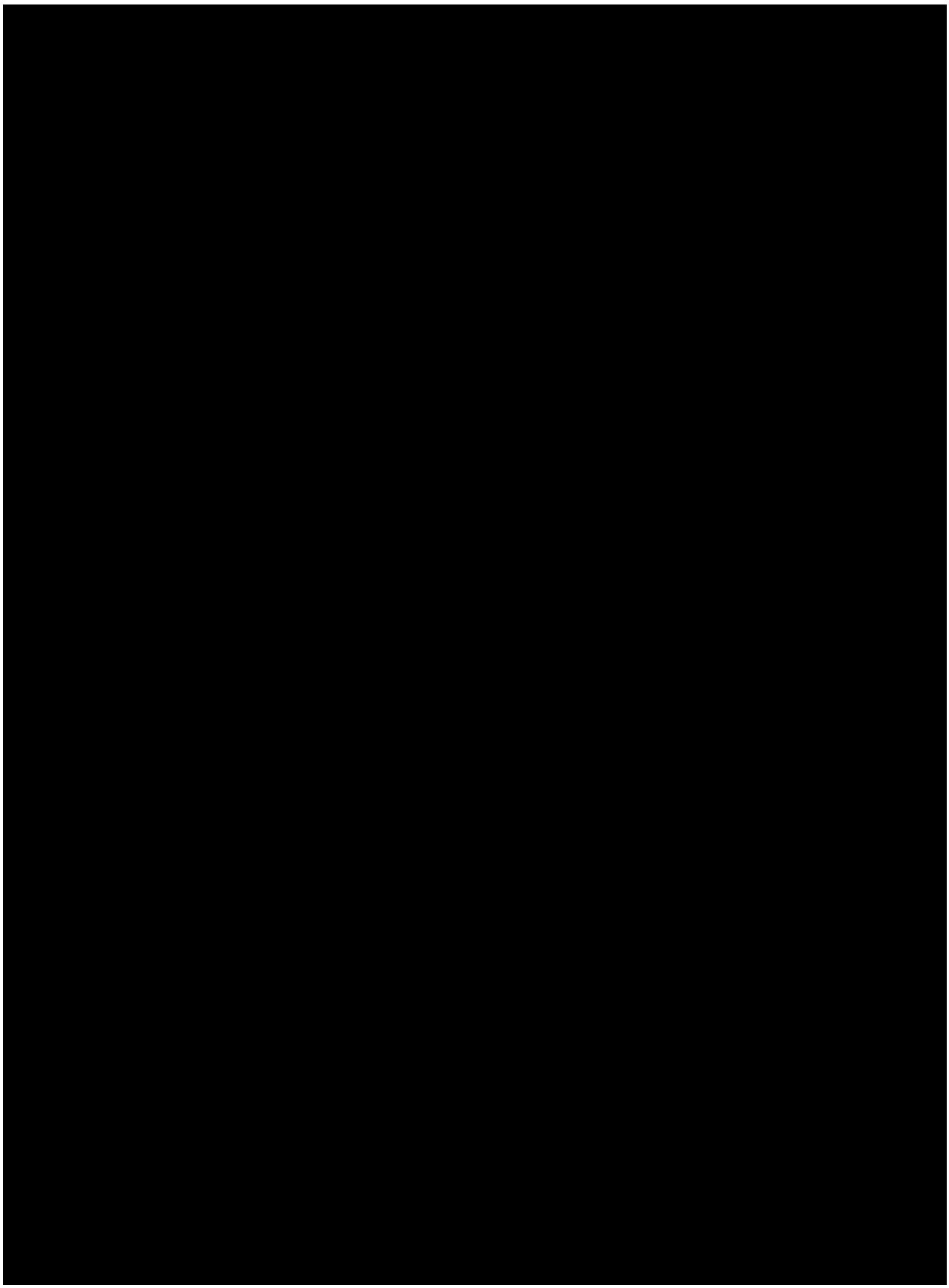
In case of oophorectomy alone, hormone level assessment (FSH, estradiol) will be done locally at screening to confirm the woman is not of childbearing potential, if applicable. Refer to Section 5.2.

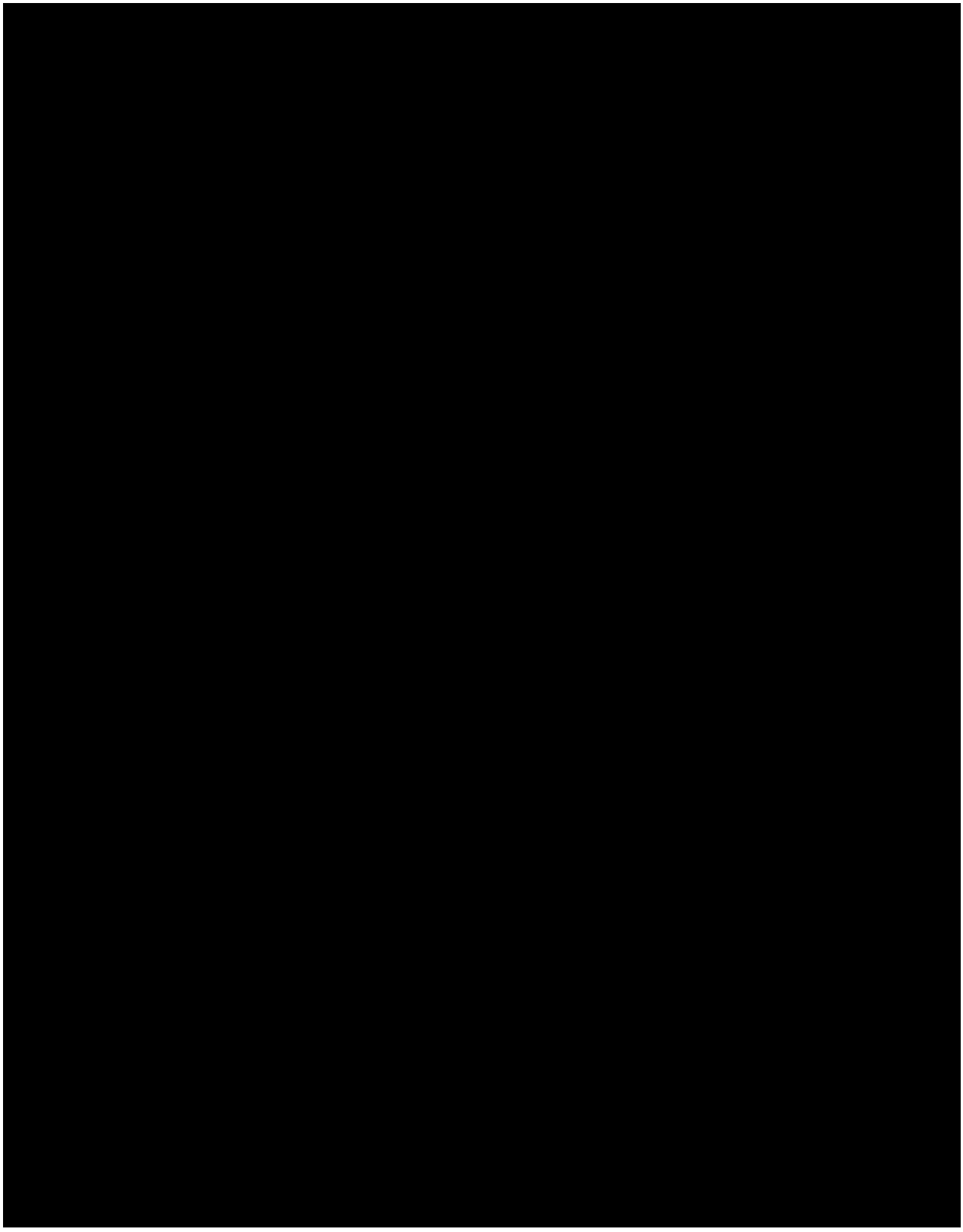
8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

[redacted]





8.5.2 Pharmacokinetics

No drug-drug interaction is anticipated between alpelisib and paclitaxel based on the known pharmacology of both drugs. The phase Ib Study CBYL719Z2101 which investigated the combination of alpelisib and solvent-based paclitaxel in participants with solid tumors confirmed no change in paclitaxel PK under repeated continuous administration of alpelisib (Rodon et al 2018).

No pharmacokinetic interactions were detected when alpelisib and nab-paclitaxel were co-administered in a phase I dose-escalation study in participants with PIK3CA-altered or wild-type, HER2-negative breast cancer (Sharma et al 2018 [CBYL719XUS06T]); though PK was only assessed after the first dose.

Thus, PK samples will be collected in a sparse manner, independent of the study Part, to primarily characterize the exposure of alpelisib in the participants with triple negative breast cancer, when administered together with nab-paclitaxel. For nab-paclitaxel, a sample will be collected in study Part [redacted] B1 at selected timepoints to characterize the maximum concentration of paclitaxel in systemic circulation when co-administered with continuous daily doses of alpelisib.

PK samples will be collected at the visits defined in Table 8-2, and Table 8-3. Follow instructions outlined in the laboratory manual and flow chart regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

Following implementation of protocol Amendment 02, PK samples collection will stop.

Alpelisib/placebo pharmacokinetic blood sampling schedules

Mandatory blood samples for sparse PK assessments of alpelisib will be collected in all participants enrolled in the study independent of study Part. In the randomized, double-blinded Part [redacted] B2 of the study, measurement of alpelisib will be performed only in participants randomized to the alpelisib arm.

Two post-dose samples will be collected at Cycle 1 Day 8 at the steady state of alpelisib (post-dose after alpelisib/placebo is started) to adequately capture both volume of distribution and clearance if population PK analysis should be conducted and to capture a concentration within the Tmax range for alpelisib.

8.5.2.1 Pharmacokinetic blood collection and handling

Complete instructions for sample collection, processing, handling and shipment will be provided in the [CBYL719H12301 Laboratory Manual] and flow chart.

For post-dose or end of infusion PK samples, only the time window specified in the blood collection log tables are allowed, while other pre-dose PK samples may be obtained within 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, blood draws in the volume specified in the blood collection log tables will be collected into tubes containing K3-EDTA (alpelisib) and Na-heparin (paclitaxel).

Both alpelisib and paclitaxel plasma samples tubes will be centrifuged to separate plasma and plasma will be immediately split and transferred into separate pre-labeled tubes as primary and backup samples. Plasma samples will be stored frozen in an upright position until shipment to the bioanalytical lab for analysis.

[redacted]

Exact dates and clock times of drug administrations and actual blood draws will be collected on the appropriate eCRF pages. The time of the meal prior to PK sampling, where post dose time points are collected for alpelisib on Day 8, should be recorded in the appropriate eCRF page. On days of PK collection and on the day of previous administration the exact time of dosing, date sample taken and actual time of sampling must be entered on the eCRF.

To ensure compliance with sampling procedures on the days of PK collection, participants will take their alpelisib/placebo doses at the clinic under the supervision of the investigator or his/her designee. Participants 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 participants 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 eCRF and on appropriate source documentation.

If vomiting occurs within 4 hrs following study-drug administration of alpelisib/placebo on Cycle 1 Day 8, 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 eCRF and on the transmittal forms, which accompany the sample. No additional study medication should be taken in an effort to replace the material that has been vomited.

If the participant 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 (preferably within 2 weeks after the last dose).

Following implementation of protocol Amendment 02, PK samples collection will stop.

[redacted]

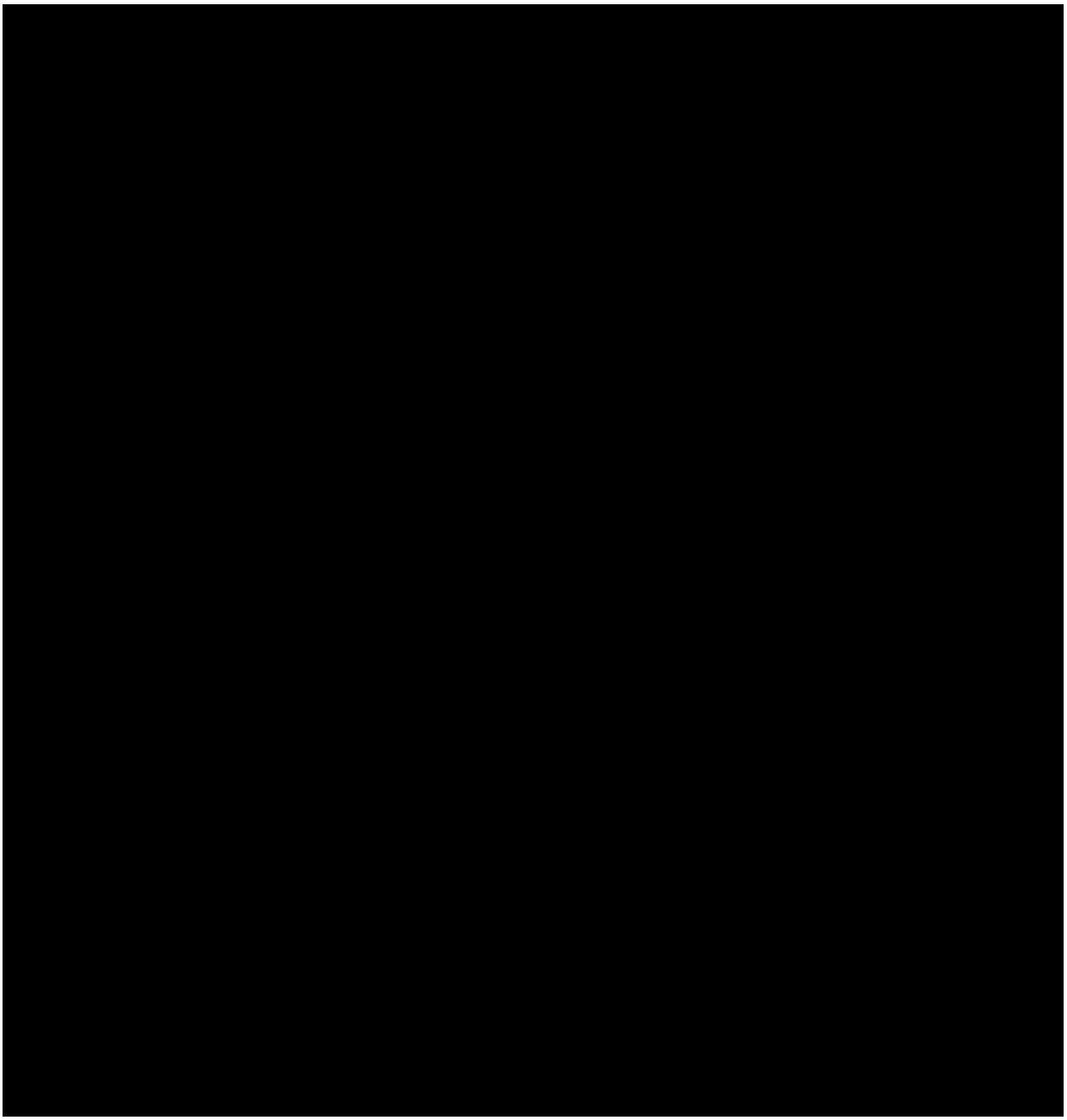


Table 8-12 Pharmacokinetic blood collection log- alpelisib/placebo - Part B2

Not applicable following protocol amendment 02.

Cycle	Day	Scheduled Time Point	Alpelisib/Placebo			
			Dose Ref. ID§		PK Sample No	Blood Volume (mL)
1	8	Pre-dose*	301	3011	301	2
1	8	1 h post dose ± 10 min	301	-	302	2

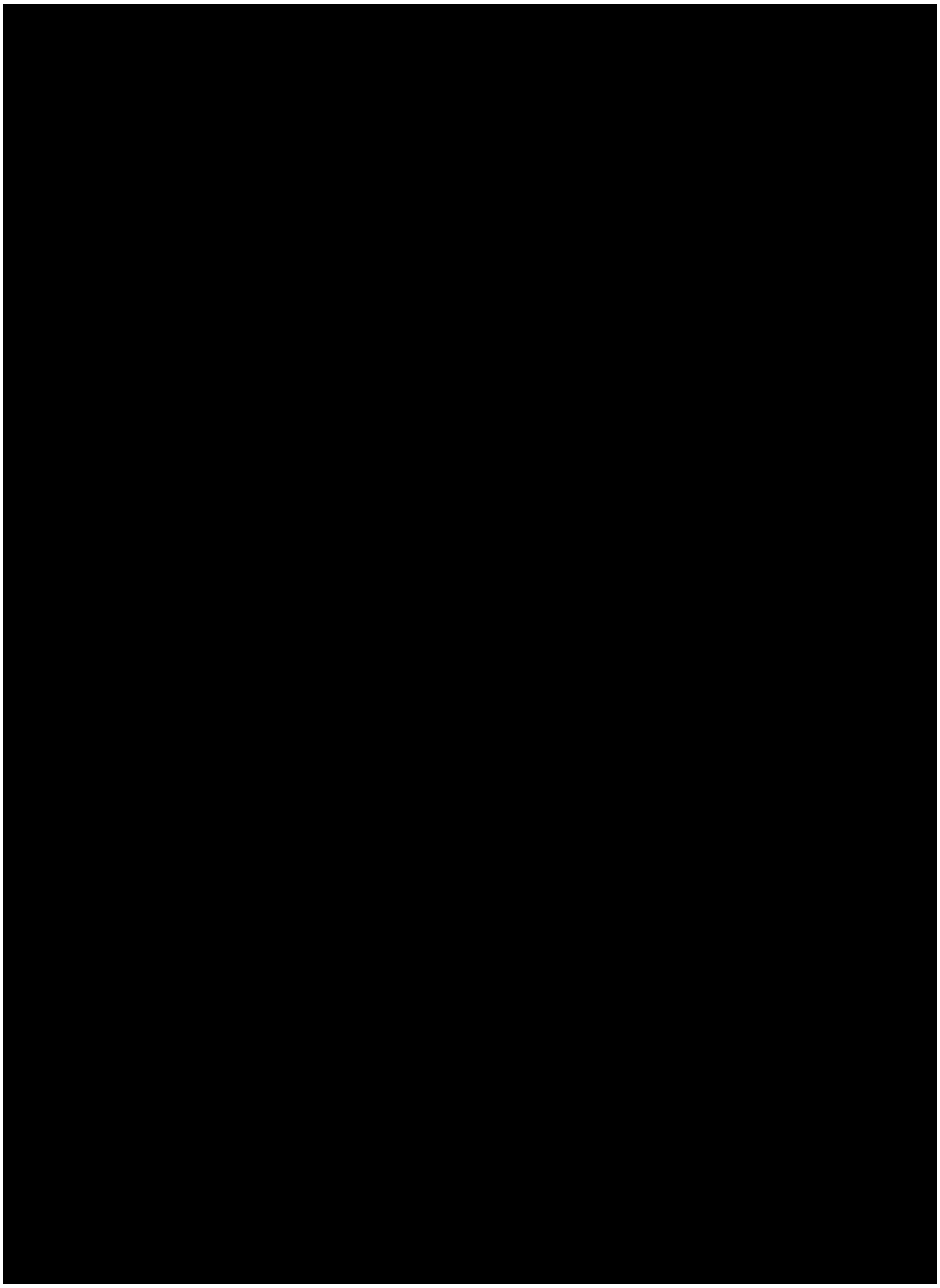
Cycle	Day	Scheduled Time Point	Alpelisib/Placebo			
			Dose Ref. ID§		PK Sample No	Blood Volume (mL)
1	8	3 h post dose + 30 min**	301	-	303	2
1	15	Pre-dose*	302	3021	304	2
2	1	Pre-dose*	303	3031	305	2
4	1	Pre-dose*	304	3041	306	2
6	1	Pre-dose*	305	3051	307	2
Anytime		Unscheduled			3001+	2

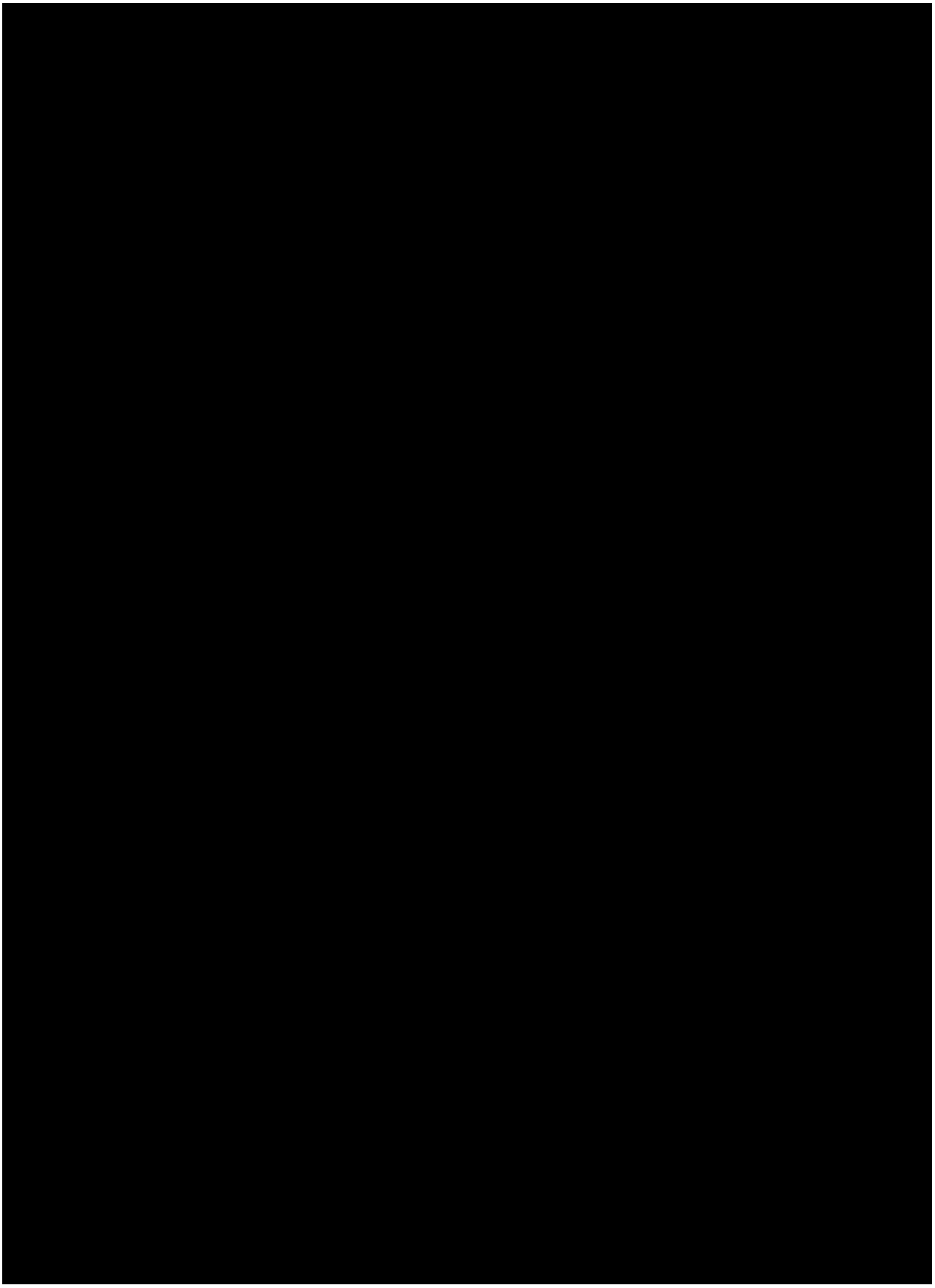
* Take sample prior to study treatment dose; at days of PK evaluation oral treatment doses should be taken at the clinical site
** Sample should be collected within 30 min after recommended scheduled timepoint of 3 hours, not before
+ Refer to Lab manual for naming conventions
§ Four digit dose reference ID for pre-dose samples ending on 1 refers to the dose taken before the PK sample (last dose information)

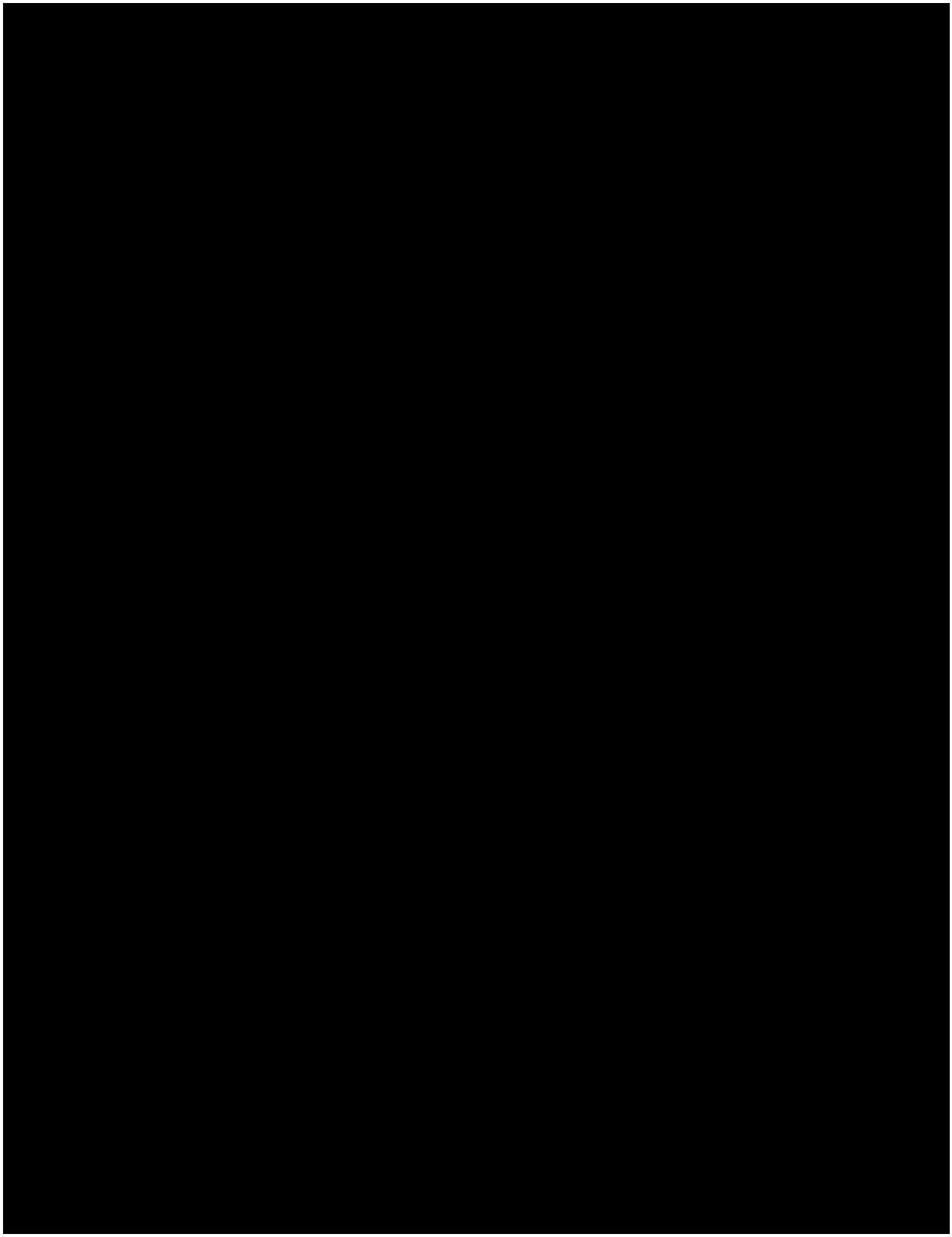
[redacted]

8.5.2.2 Analytical method

Plasma concentrations of alpelisib and paclitaxel 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 both alpelisib and paclitaxel. 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.







9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason and can be initiated by either the participant or the investigator. Nab-paclitaxel and alpelisib may be discontinued independently of each other for unacceptable toxicities.

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

Study treatment must be discontinued under the following circumstances:

- Adverse event or laboratory abnormalities requiring permanent discontinuation of study treatment as per Section 6.5.1
- Progressive disease per RECIST 1.1 as per investigator's assessment (see Section 8.3)
- Protocol deviation that results in significant risk to participant’s safety
- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 6.2.2)
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding
- Study terminated by sponsor

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

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

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

After discontinuation from study treatment for reasons other than documented progressive disease per RECIST v1.1, death, lost to follow-up, or withdrawal of consent/ opposition to use data/biological samples, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New antineoplastic therapy, if applicable
- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to details in the Emergency breaking of treatment code in Section 6.6.2.

For participants who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/ opposition to use data/biological samples, tumor assessments must continue to be performed every 8 weeks during the first 18 months and every 12 weeks thereafter until documented disease progression (per investigator), death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, irrespective of initiation of new antineoplastic therapy.

9.1.2 Discontinuation from study

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

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

9.1.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent/ exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent exercise data privacy rights should be made as detailed in the assessment table (refer to Section 8).

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

9.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), for regulatory or medical reasons or decision based on recommendations from applicable board(s) after review of safety and efficacy data. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (instructions will be provided to the investigator for contacting the participant, when the participant should stop taking drug and when the participant should come for a final visit) and treated as a participant who discontinued from study treatment (see Section 9.1.1). The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

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

At the end of the study, every effort will be made to continue provision of alpelisib outside this study through an alternative setting to participants who in the opinion of the Investigator are still deriving clinical benefit.

Parts A and B2

The primary analysis for Parts A and B2 will occur when all participants have completed 6 months of study treatment or have been discontinued from study treatment, whichever occurs earlier (refer to Section 12.4). At this time, the primary clinical study report (CSR) will be produced. After the primary analysis, the study will remain open for participants who benefit from study treatment, as assessed by the investigator, until a PTA mechanism is available. Participants still being followed on the study after the primary analysis timepoint will continue as per the schedule of assessments.

Conduct of Parts A and B2 will end once the final analysis of study data is conducted. All available data from all participants up to this cutoff date will be analyzed.

There is no analysis for Part B2 since it was never intiated.

Part B1

The primary analysis of part B1 occured when all enrolled participants have completed 6 months of study treatment or have been discontinued from study treatment, whichever occurs earlier. Six-month ORR and safety data guided the decision to not initiate Part B2. Participants still being treated/followed on the study after the primary analysis time point will continue as per the schedule of assessments.

9.2.1 Follow-up for safety evaluations

All participants who discontinue study treatment, including those who refuse to return for an EOT visit, will be contacted for safety evaluations (i.e., assessment of adverse events and/or Serious Adverse Events, concomitant medications) 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Participant whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first.

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

9.2.2 Follow-up for efficacy evaluations

Participants who discontinue study treatment for reasons other than disease progression as per RECIST 1.1, death, lost to follow-up or withdrawal of consent/opposition to use data/biological samples, should continue tumor assessment until disease progression as per RECIST 1.1, death, lost to follow-up or withdrawal of consent/opposition to use data/biological samples at the same intervals as per Table 8-4.

In Parts A and B2, PRO assessments will also be conducted following the same frequency. Tumor assessments and collection of PRO data in the efficacy follow-up will stop after all participants have completed 6 months of study treatment or have been discontinued from study treatment.

Part B2 was never initiated.

9.2.3 Follow-up after disease progression

Participants enrolled in Parts A and B2 will return to the site 8 weeks after documentation of disease progression to perform the PRO assessments (Table 8-9).

The collection of PRO data will stop after all participants have completed 6 months of study treatment or have been discontinued from the study treatment.

Part B2 was never initiated.

9.2.4 Survival follow-up

Participants will enter the survival follow-up period once they complete the safety follow-up period and efficacy follow-up period after treatment discontinuation (whichever is longer). Participants will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since study treatment discontinuation and date of progression on subsequent therapies will also be collected during these phone calls.

Additional survival assessments may be performed outside the 12 weeks follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information will be documented in the source documents and relevant eCRFs.

The collection of survival data and new antineoplastic therapies will stop after all participants have completed 6 months of study treatment or have been discontinued from the study treatment.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

For patients who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 10.1.2 and Section 10.1.3 and are reported to be causally related with study procedures (e.g. an

invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the description below (inclusive of SAEs) will be captured as adverse events.

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

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

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

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

- Dose not changed
- Dose Reduced
- Drug interrupted/withdrawn

6. Its outcome (i.e. recovery status or whether it was fatal)

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

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

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

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g. continuing at the end of the study), and assessment must be

made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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

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

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant’s general condition

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE (with the exception of progression of malignancy as described in Section 10.1.1) , regardless of causality, occurring after the participant has provided main study informed consent and until 30 days after the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

For participants who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). If the main ICF is not signed, SAE collection ends 30 days after the last study related procedure.

For participants who sign the main study ICF, SAE collection starts at time of main study informed consent whether the participant is a screen failure or not.

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

For screen failure participants, SAEs will be collected until the time the participant is deemed a screen failure.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Clinical Trial Regulation 536/2014 (if submitted under EU CTR) or EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until time period for post treatment contraception determined in Section 5.2.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he/she may learn of an SAE through spontaneous reporting.

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of

the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

For more information on AE and SAE definition and reporting requirements, please see Section 10.1.1, Section 10.1.2 and Section 10.1.3.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

Please refer to Table 16-10 in Section 16.3 for complete definitions of liver laboratory triggers and liver events.

Once a participant is exposed to study treatment, every liver event defined in Table 16-10 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Repeat liver chemistry tests (i.e. ALT, AST, Total bilirubin (TBL), PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.2.2 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be formed prior to the randomization of the first participant and will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.3 Steering Committee

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

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

11 Data Collection and Database management

11.1 Data collection

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

The investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.
Data not requiring a separate written record will be defined in the protocol and Assessment Schedule (Table 8-2 and Table 8-3) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site. Data collected by third parties (such as IRT, imaging, safety lab, [redacted] PK and PROs) will be sent electronically to Novartis.

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

11.2 Database management and quality control

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

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

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. The laboratory 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. All PRO data will be sent electronically to Novartis personnel (or a designated CRO).

Dates of pre-screening, screening, randomization, screen failure and study discontinuation as well as randomization codes and data about all study treatment (s) dispensed to the participant

and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate (at the time of Part A primary analysis), it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

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

12 Data analysis and statistical methods

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

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

Part A

The primary descriptive efficacy and safety analyses for Part A will be performed when all participants have completed 6 months of study treatment or have been discontinued from study treatment. Any additional data for participants continuing to receive study treatment past this time and for participants continuing for efficacy follow-up (PFS, OS), as allowed by the protocol, will be further summarized in the final study closeout report.

Part B1

The primary efficacy and safety analyses for Part B1 will be performed after all enrolled participants have completed 6 months treatment or have been discontinued from study treatment whichever occurs earlier. Any additional data for participants continuing to receive study treatment past this time and for patients continuing for efficacy follow-up (PFS, OS), as allowed by the protocol, will be further summarized in the final study report for Part B2 or in the CSR for Part A if Part B2 will not be initiated.

Part B2

The primary efficacy and safety analyses for Part B2 will be performed after observing approximately 192 PFS events per local assessment, should Part B2 reach the final PFS analysis. Any additional data for participants continuing to receive study treatment past this time and for participants continuing for efficacy follow-up (PFS, OS), as allowed by the protocol, will be further summarized in a study report at the time of the final OS analysis after observing approximately 197 OS events, or when statistical significance is reached at any interim OS analysis.

Part B2 was never initiated.

12.1 Analysis sets

Parts A and B2

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

The Safety Set includes all participants who received at least one dose of any study treatment (i.e. at least one dose of any component of alpelisib/placebo, nab-paclitaxel). Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

The Pharmacokinetic Analysis Set (PAS) consists of all participants who received at least one dose of study medication defined as alpelisib/placebo or nab-paclitaxel and provide at least one evaluable PK concentration.

Part B2 was never initiated.

Part B1

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

The Safety Set includes all participants who received at least one dose of any study treatment (i.e. at least one dose of any component of alpelisib or nab-paclitaxel). Participants will be analyzed according to the study treatment received, where treatment received is defined as the assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the assigned treatment was never received.

[redacted]

12.2 Participant demographics and other baseline characteristics

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

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

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

12.3 Treatments

For all Study parts:

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

The duration of exposure to alpelisib, placebo, nab-paclitaxel as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set for each study part.

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

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

12.4 Analysis supporting objectives

Part A:

The primary objective of Part A is to assess PFS for treatment with alpelisib in combination with nab-paclitaxel compared to placebo in combination with nab-paclitaxel.

Part B1:

The primary objective of Part B1 is to assess the antitumor activity of alpelisib in combination with nab-paclitaxel.

Part B2:

The primary objective of Part B2 is to determine whether treatment with alpelisib in combination with nab-paclitaxel prolongs PFS compared to placebo in combination with nab-paclitaxel. Part B2 was never initiated.

12.4.1 Definition of primary endpoint(s)

Parts A and B2

The primary endpoint (variable attribute of the primary estimand; refer to Section 2.1) 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 participant has not had an event, PFS will be censored at the date of the last adequate tumor assessment (see RECIST 1.1 in Section 16.1 for further details). Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. PFS will be assessed via a local radiology assessment according to RECIST 1.1. Censoring conventions (i.e. handling of missing values/censoring/discontinuations) are provided in Section 12.4.3.

Part B2 was never initiated.

Part B1

The primary endpoint is ORR with confirmed response at 6 months, based on local radiology assessments in participants with measurable disease at baseline. ORR is defined as the proportion of participants with best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST 1.1. If no valid post-baseline tumor assessments are available, the best overall response must be “Unknown” unless progression is reported. Participants whose BOR is unknown or missing will be determined to be non-responders. Details on the handling of missing values/discontinuations are provided in Section 12.4.3.

12.4.2 Statistical model, hypothesis, and method of analysis

Parts A

The primary efficacy analysis is to compare and summarize PFS between two treatment groups descriptively.

The primary efficacy variable, PFS (variable attribute of the primary estimand; refer to Section 2.1) will be analyzed based on the FAS according to the randomized treatment group and strata assigned at randomization. The PFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the randomization stratification factors, i.e. (i) line of therapy in advanced/metastatic setting (1st line versus 2nd line), ii) hormone receptor status at initial breast cancer diagnosis (HR+ versus HR-), and iii) prior therapy with checkpoint inhibitors (Yes/No). Given no inferential analysis will be conducted, no p-value will be calculated.

Part B1

A response rate of 35% is considered a minimum clinically meaningful improvement in this study population based on data from first and second line mTNBC patients treated with either nab-paclitaxel or paclitaxel in the PAKT study (Schmid et al 2018), the LOTUS study (Kim et al 2017), the IMpassion130 study (Schmid et al 2018), as well as information provided in the Abraxane USPI (Nab-Paclitaxel FDA label 2015) the Abraxane EU label (Nab-Paclitaxel EU label 2018). Therefore, proof of preliminary efficacy of alpelisib in combination with nab-paclitaxel will be declared if both of the following conditions are met:

- the mean of the posterior distribution of ORR is at least 35%

and

- the posterior probability that the ORR is $\geq$ 25% is at least 0.9

The posterior distribution of ORR will be derived from the prior distribution and all available data from the participants included in the FAS. A minimally informative unimodal Beta prior (Neuenschwander et al 2008) will be used for ORR (see Section 16.4 for further details). Additionally, ORR will be summarized by a two-sided exact binomial 95% confidence interval (Clopper and Pearson 1934). Waterfall graphs, which display the best percentage change from baseline in the sum of diameters of all target lesions for each participant with measurable disease at baseline, will be used to depict the anti-tumor activity of each treatment group. ORR as per blinded independent central review will be presented by treatment group, along with 95% confidence intervals.**Part B2 (**Not applicable as of protocol amendment 02)**:**

The primary efficacy analysis will be the comparison of PFS between the two treatment groups using a stratified log-rank test at an overall one-sided 2.5% level of significance for Parts A and B2 individually. The stratification will be based on the randomization stratification factors, i.e. (i) line of therapy in advanced/metastatic setting (1st line versus 2nd line), ii) hormone receptor status at initial breast cancer diagnosis (HR+ versus HR-), and iii) prior therapy with checkpoint inhibitors (Yes/No).

Assuming proportional hazards model for PFS, the following statistical hypotheses will be tested to address the primary efficacy objective:

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

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

The primary efficacy variable, PFS (variable attribute of the primary estimand; refer to Section 2.1), will be analyzed at the interim analysis and final analysis of a group sequential design, using a Haybittle-Peto boundary. Analyses will be based on the FAS according to the randomized treatment group and strata assigned at randomization. The PFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

Part B2 was never initiated.

Part B1

A response rate of 35% is considered a minimum clinically meaningful improvement in this study population based on data from first and second line mTNBC patients treated with either nab-paclitaxel or paclitaxel in the PAKT study (Schmid et al 2018), the LOTUS study (Kim et al 2017), the IMpassion130 study (Schmid et al 2018), as well as information provided in the Abraxane USPI (Nab-Paclitaxel FDA label 2015) the Abraxane EU label (Nab-Paclitaxel EU label 2018). Therefore, proof of preliminary efficacy of alpelisib in combination with nab-paclitaxel will be declared if both of the following conditions are met:

- the mean of the posterior distribution of ORR is at least 35%

and

- the posterior probability that the ORR is $\geq$ 25% is at least 0.9

The posterior distribution of ORR will be derived from the prior distribution and all available data from the participants included in the FAS. A minimally informative unimodal Beta prior (Neuenschwander et al 2008) will be used for ORR (see Section 16.4 for further details). Additionally, ORR will be summarized by a two-sided exact binomial 95% confidence interval (Clopper and Pearson 1934). Waterfall graphs, which display the best percentage change from baseline in the sum of diameters of all target lesions for each participant with measurable disease at baseline, will be used to depict the anti-tumor activity of each treatment group. ORR as per blinded independent central review will be presented by treatment group, along with 95% confidence intervals.

12.4.3 Handling of intercurrent events of primary estimand

Parts A & B2

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

1. **Discontinuation of study treatment**: tumor assessment data collected after discontinuation of study treatment will be used for the primary analysis irrespective of the study treatment discontinuation reason (treatment policy strategy).

Part B2 was never initiated.

Part B1

The primary estimand analysis of this estimand will account for the first of the following two intercurrent events to occur:

1. **Discontinuation of study treatment**: tumor assessment data collected within 30 days after discontinuation of study treatment will be used in the analysis. Tumor assessment data collected more than 30 days after discontinuation of study treatment will be excluded from the analysis (While on treatment strategy).
2. **Start of new anti-neoplastic therapy**: tumor assessment data collected after the initiation of new anti-neoplastic therapy will be excluded from the analysis (While on treatment strategy).

12.4.4 Handling of missing values not related to intercurrent event

In Parts A and B2 the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date.

PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of new cancer therapy.

If a PFS event is observed after one or more missing or non-adequate tumor assessments, the actual date of event will be used (see RECIST 1.1 in Section 16.1).

Part B2 was never initiated.

12.4.5 Supplementary analyses

Supplementary analyses will be provided in the Statistical Analysis Plan.

12.5 Analysis supporting secondary objectives

Parts A and B2

The secondary objectives in Parts A and B2 are to compare the two treatment groups with respect to overall survival (OS), and to evaluate the overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), duration of response (DOR), and safety.

OS was originally identified as the key secondary endpoint (variable attribute of the key secondary estimand) in each of Parts A and B2. With the recruitment halt and protocol amendment 02, OS was moved to be a secondary endpoint, rather than a key secondary endpoint; no formal testing for OS will be performed. Instead, similar descriptive summaries as for PFS will be provided.

Part B2 was never initiated.

Part B1

The secondary objectives in Part B1 are to evaluate additional efficacy parameters with respect to PFS, overall survival (OS), and to evaluate clinical benefit rate (CBR), time to response (TTR), duration of response (DOR), and safety.

No statistical testing of secondary endpoints in Part B1 will be undertaken.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 Key secondary estimand

Not applicable after Amendment 02.

12.5.1.2 Other secondary efficacy endpoints

OS is defined as the time from date of randomization to date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date).

OS will be analyzed in the FAS according to the treatment group and strata assigned at randomization (Parts A and B2) or at enrollment (Part B1). The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

Overall response rate (ORR) with confirmed response is defined as the proportion of participants with BOR of confirmed complete response (CR) or confirmed partial response (PR), as per local review and according to RECIST 1.1 (see Section 16.1 for details).

ORR with confirmed response will be calculated based on the FAS and according to the Intent To Treat (ITT) principle. ORR and its 95% confidence interval will be presented by treatment group.

As supplemental analyses in Parts A and B2, the following will also be calculated and presented by treatment group together with approximate 95% confidence intervals:

- ORR with confirmed response per local review for participants with measurable disease at baseline,
- ORR with unconfirmed responses per local review based on the FAS,
- ORR with unconfirmed responses per local review for participants with measurable disease at baseline

Clinical benefit rate (CBR) with confirmed response is defined as the proportion of participants with a best overall response of confirmed complete response (CR), or confirmed partial response (PR), or an overall response of stable disease (SD) lasting for a duration of at least 24 weeks. CR, PR, and SD are defined as per local review according to RECIST 1.1 (see Section 16.1 for details).

CBR with confirmed response will be calculated based on the FAS and according to the ITT principle. CBR with confirmed response and its 95% confidence interval will be presented by treatment group. In Parts A and B2, as supplemental analyses, the following will also be calculated and presented by treatment group together with approximate 95% confidence intervals:

- CBR with confirmed response per local review for participants with measurable disease at baseline,

- CBR with unconfirmed responses per local review based on the FAS,
- CBR with unconfirmed responses per local review for participants with measurable disease at baseline.

Time to response (TTR) is defined as the time from the date of randomization to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (although date of initial response is used, not date of confirmation). CR and PR are based on tumor response data as per local review and according to RECIST 1.1 (see Section 16.1 for details).

All participants in the FAS will be included in TTR calculations. participants without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e. Last Patient Last Visit (LPLV)-First Patient First Visit (FPFV)) for participants with a PFS event (i.e. disease progression or death due to any cause), or at the date of the last adequate tumor assessment for participants without a PFS event. TTR will be listed and summarized by treatment group.

Duration of response (DOR) with confirmed response only applies to participants whose best overall response is confirmed complete response (CR) or confirmed partial response (PR) according to RECIST 1.1 based on tumor response data per local review. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Participants continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment. DOR will be listed and summarized by treatment group for all participants in the FAS with confirmed BOR of CR or PR. As a supplemental analysis, DOR with unconfirmed response based on the FAS will also be listed and summarized by treatment group.

An analysis of PFS based on local radiology assessments and using RECIST 1.1 criteria for participants by PIK3CA mutation status as measured in ctDNA at baseline will be conducted using the same analytical conventions as the primary analysis.

12.5.2 Safety endpoints

For all safety analyses, each Study Part will be summarized separately and the safety set will be used. All listings and tables will be presented by treatment group.

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

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication

3. Post-treatment period: starting at day 31 after last dose of study medication.

Adverse events

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

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

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

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

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

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

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

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.

Vital signs

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

12-lead ECG

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

baseline will be presented. In addition, a listing of these participants will be produced (by treatment group).

All ECG data will be listed by treatment group, participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Cardiac Imaging

Shift tables comparing baseline to end of treatment LVEF will be provided for each Study Part. part.

If there is any change in the methodology used at EOT compared to baseline, the EOT values for which the methodology differs from baseline will be discarded.

Clinical laboratory evaluations

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

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

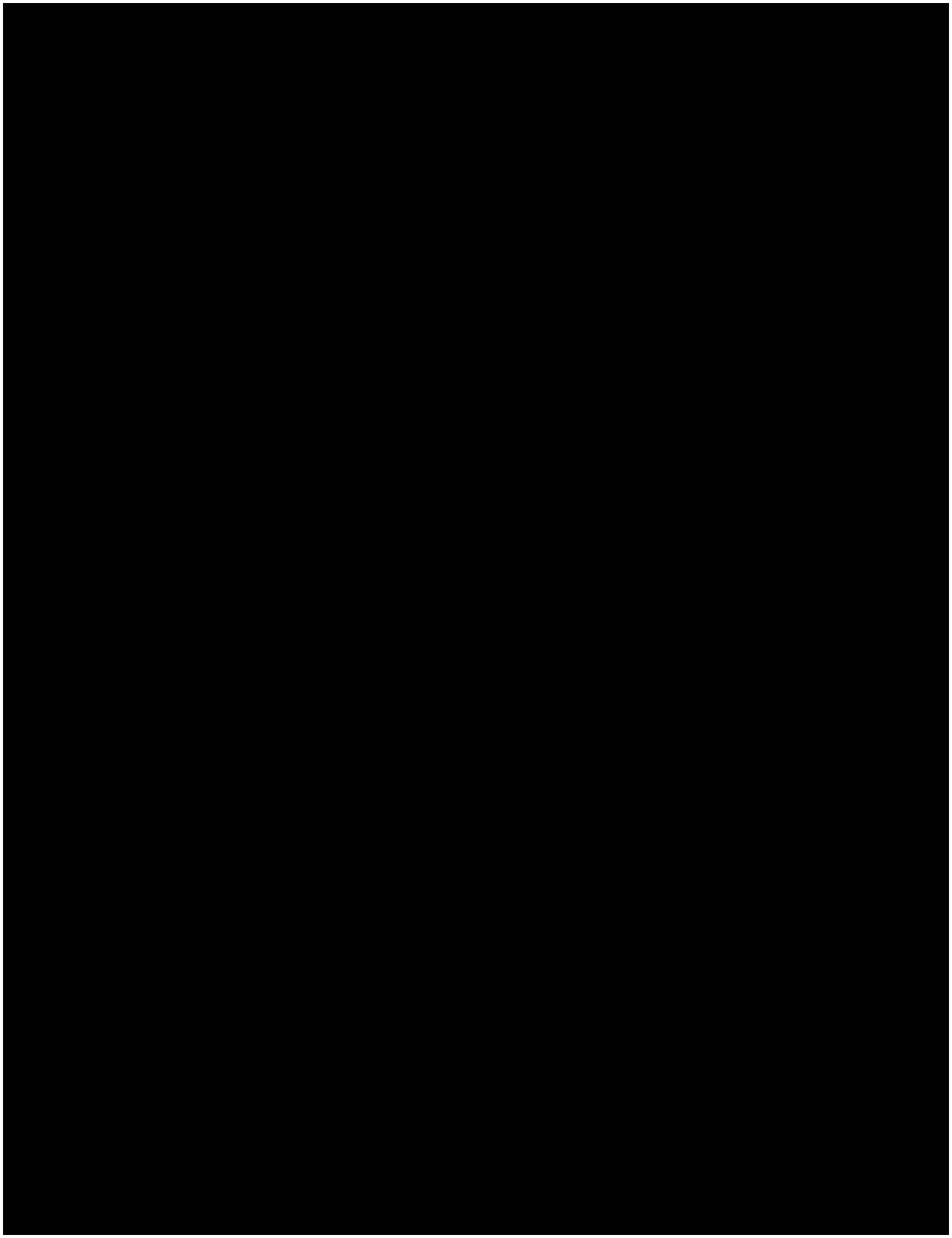
For laboratory tests where grades are defined by CTCAE v4.03:

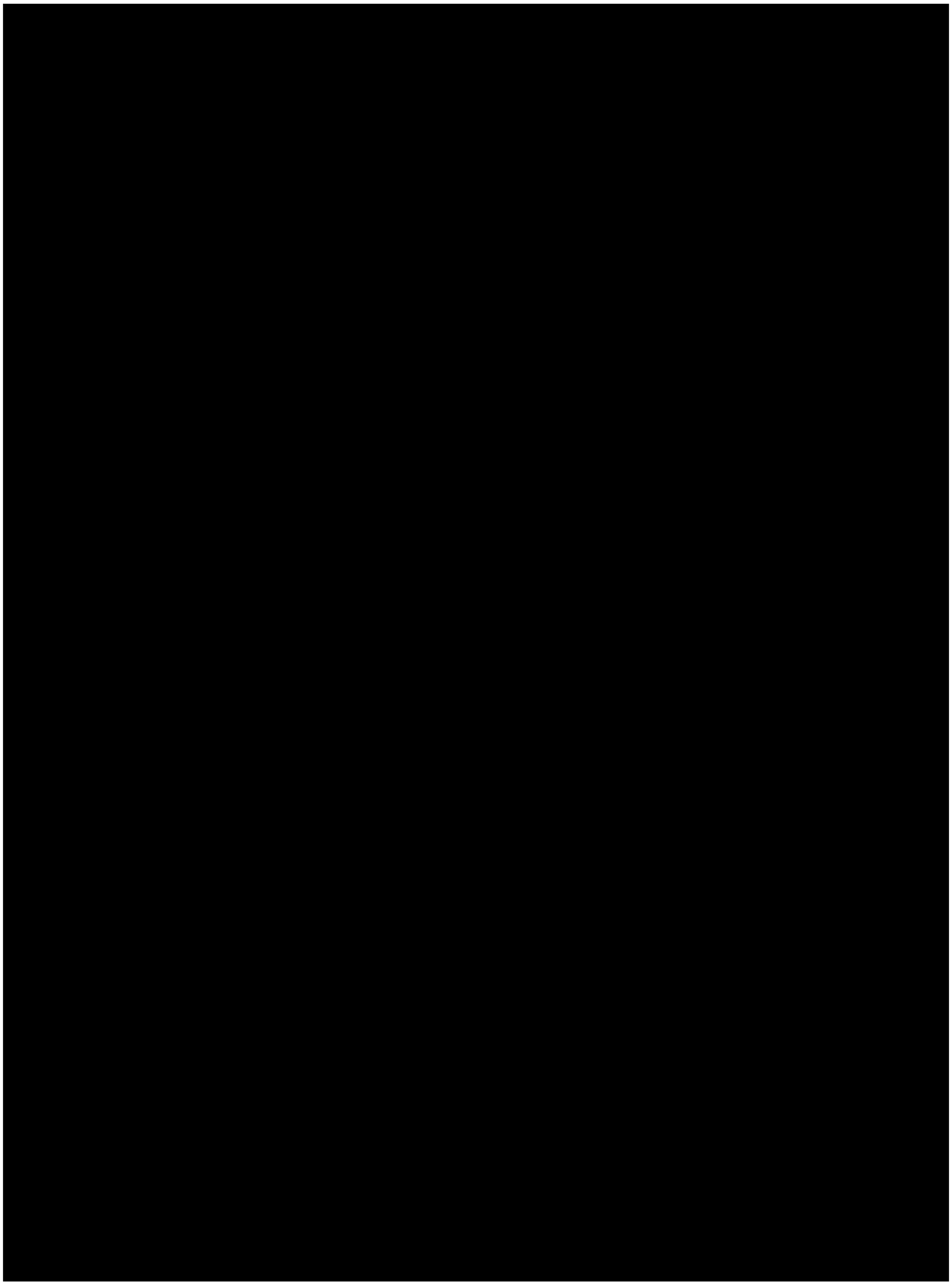
- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v4.03:

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

[redacted]





12.7 Interim analyses

Interim analyses are planned for the monitoring of safety data by DMC in all Study Parts, and will be performed approximately every 6 months during the course of the study.

Part B1

No interim efficacy analysis is planned for Part B1. The primary analysis has been performed after all participants had completed 6 months treatment or had discontinued treatment prior to 6 months, whichever was earlier.

Part A

No interim efficacy analysis will be performed for Part A. After the halt of recruitment, the primary PFS analysis for Part A will be performed when all participants have completed 6 months of study treatment or have discontinued from study treatment, whichever occurs earlier.

Part B2

Not applicable. Part B2 was not initiated based on the results from Part B1.

12.8 Sample size calculation

Note the below subsections illustrate how the original sample size was considered. Based on the decision of recruitment halt, Part A will not wait for the required number of PFS/OS events to perform the originally planned inerim/final analysis, instead similar as Part B1, the primary analysis for Part A will be descriptive only and will be undertaken when all participants have

completed 6 months of study treatment or have been discontinued from study treatment, whichever occurs earlier.

12.8.1 Primary endpoint(s)

The sample size calculation in Parts A and B2 is based on the primary variable of PFS. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

The median PFS in the control arm (placebo + nab-paclitaxel) of this study is estimated to be approximately 5 months, based on data from first and second line mTNBC patients treated with either nab-paclitaxel or paclitaxel in the PAKT study (Schmid et al 2018), the LOTUS study (Kim et al 2017), and the Impassion130 study (Schmid et al 2018).

It is expected that treatment with alpelisib plus nab-paclitaxel will result in a 40% reduction in the hazard rate for PFS, i.e. an expected hazard ratio of 0.6 (which corresponds to an increase in median PFS to 8.33 months under the exponential model assumption).

Part A

In order to ensure 90% power to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: PFS hazard ratio = 0.6, it is calculated that a total of 192 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio, and a 3-look group sequential design with a gamma spending function to define a futility rule at the 1st interim analysis and a Haybittle-Peto alpha spending function, using information fractions of (0.40, 0.85, 1).

Assuming that enrollment will continue for 29 months enrolling 3 participants/month up to month 6, 8 participants/month up to month 12 and 11 participants/month thereafter, assuming losses to follow-up for PFS of 10%, a total of 252 participants will need to be randomized to observe the targeted 192 PFS events at about 6 months after the randomization date of the last participant, i.e. 35 months after the randomization date of the first participant.

Part B2

In order to ensure 90% power to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: PFS hazard ratio = 0.6, it is calculated that a total of 192 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio, and a 3-look group sequential design with a gamma spending function to define a futility rule at the 1st interim analysis and a Haybittle-Peto alpha spending function, using information fractions of (0.40, 0.75, 1).

Assuming that enrollment will continue for 16.5 months enrolling 12 participants/month up to month 6 and 20 participants/month thereafter, assuming losses to follow-up for PFS of 10%, a total of 282 participants will need to be randomized to observe the targeted 192 PFS events at about 5.5 months after the randomization date of the last participant, i.e. 22 months after the randomization date of the first participant.

These calculations were made using the software package East 6.4.

Part B2 was never initiated.

Part B1

The sample size calculation is based on the primary variable ORR considering the statistical model, hypothesis and method of analysis detailed in Section 12.4.2. Proof of preliminary efficacy (PPE) will be declared if both of the following conditions are met:

- the mean of the posterior distribution of ORR is at least 35%

and

- the posterior probability that the ORR is ≥ 25% is at least 0.9

Approximately 32 participants will be enrolled. With 32 participants, the probability of declaring proof of preliminary efficacy (PPE) is at most 8% when ORR ≤25%. The probability of declaring PPE is at least 80% for ORR ≥ 45% (Table 12-1).

Table 12-1 Part B1 PPE Operating characteristics

True ORR	Probability of declaring PPE (≥12 responders)	Probability of missing PPE (≤11 responders)
25%	0.079	0.921
30%	0.228	0.772
35%	0.448	0.552
40%	0.675	0.325
45%	0.847	0.153

12.8.2 Secondary endpoint(s)

Part A

Per original design, OS, as the key secondary variable, will be formally statistically tested, provided that the primary variable of PFS is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in Section 12.5.1. The median OS in the control arm (placebo + nab-paclitaxel) of this study is estimated to be approximately 12 months, based on data from first and second line mTNBC patients treated with either nab-paclitaxel or paclitaxel in the PAKT study (Schmid et al 2018), the LOTUS study (Kim et al 2017), and the IMpassion130 study (Schmid et al 2018). It is hypothesized that treatment with alpelisib plus nab-paclitaxel will result in a 33.3% reduction in the hazard rate for OS, i.e., an expected hazard ratio of 0.667 (which corresponds to an increase in median OS to 18 months under the exponential model assumption). Then in order to ensure 80% power to test the null hypothesis: OS hazard ratio = 1, versus the specific alternative hypothesis: OS hazard ratio = 0.667, it is calculated that a total of 198 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio, and a 3-look group sequential design with a Lan-DeMets (O'Brien and Fleming 1979) alpha spending function using information fractions of (0.66 [if at final PFS analysis], 0.85, 1).

Based on the same number of participants that are planned to be enrolled in this study to provide sufficient power for the primary endpoint (i.e. 252 participants), and assuming losses to follow-up for OS of 10%, it is estimated that these 198 deaths will be observed approximately 66

months after the randomization date of the first participant. Therefore the cut-off date for the final analysis of OS will be approximately 31 months after the cut-off date for the final analysis of PFS. These calculations were made using the software package East 6.4.

Part B2

OS, as the key secondary variable, will be formally statistically tested, provided that the primary variable PFS is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in Section 12.5.1. The median OS in the control arm (placebo + nab-paclitaxel) of this study is estimated to be approximately 12 months, based on data from first and second line mTNBC patients treated with either nab-paclitaxel or paclitaxel in the PAKT study (Schmid et al 2018), the LOTUS study (Kim et al 2017), and the Impassion130 study (Schmid et al 2019). It is hypothesized that treatment with alpelisib plus nab-paclitaxel will result in a 33.3% reduction in the hazard rate for OS, i.e., an expected hazard ratio of 0.667 (which corresponds to an increase in median OS to 18 months under the exponential model assumption). Then in order to ensure 80% power to test the null hypothesis: OS hazard ratio = 1, versus the specific alternative hypothesis: OS hazard ratio = 0.667, it is calculated that a total of 197 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio, and a 3-look group sequential design with a Lan-DeMets (O'Brien and Fleming 1979) alpha spending function using information fractions of (0.60 [if at final PFS analysis], 0.85, 1).

Based on the same number of participants that are planned to be enrolled in this study to provide sufficient power for the primary endpoint (i.e. 282 participants), and assuming losses to follow-up for OS of 10%, it is estimated that these 197 deaths will be observed approximately 41 months after the randomization date of the first participant. Therefore the cut-off date for the final analysis of OS will be approximately 19 months after the cut-off date for the final analysis of PFS. These calculations were made using the software package East 6.4.

Part B2 was never initiated.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable

local regulations (including European Directive 2001/20/EC, or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

The protocol, protocol amendments, ICF, Investigator's Brochure, Investigational Directions For Use (IDFU) and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be also responsible for:

- Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- Informing Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

13.3 Publication of study protocol and results

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

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

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

13.4 Quality Control and Quality Assurance

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

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

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

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan, contracts.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

13.5 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

13.6 Participant Engagement

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

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Glossary

CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
eCRF	Electronic Case Report Form
FPFV	First patient first visit
ITT	Intent-to-treat
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

16.1.1 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 (Duffaud and Therasse 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.1.3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.1.2 Efficacy assessments

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

16.1.2.1 Definitions

16.1.2.1.1 Disease measurability

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

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

For participants without measurable disease see Section 16.1.3.2.9.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5 mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥ 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥ 10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions:

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

16.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the participant 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 participants be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how participants with just non-measurable disease at baseline (even if not expected as per eligibility criteria of this protocol) will be evaluated for response and also handled in the statistical analyses is given in Section 16.1.3.2.9.

16.1.2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (IV) 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 participants, 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 participant is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
    - **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 should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- **Tumor markers:** Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a participant 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.

16.1.2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.1.2.1.1
- **Nodal target:** See Section 16.1.2.1.1. A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.
- **Non-target lesions:** All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target

lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-1) and non-target lesions (Table 16-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.1.2.4.1 Follow-up and recording of lesions

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

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 participant to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

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

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

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

Nodal lesions

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

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

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

16.1.2.4.2 Determination of target lesion response

Table 16-1 Response criteria for target lesions

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

[1] SOD for CR may not be zero when nodal lesions are part of target lesions

[2] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR

[3] In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2).

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of all measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to participants who have not achieved target response of CR. For participants who have achieved CR, please refer to last bullet in this section.

- For those participants 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 eCRF 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 eCRF, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- **The measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or

central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.1.2.4.3 Determination of non-target lesion response

Table 16-2 Response criteria for non-target lesions

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

1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer prevails.
2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is CR only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. >=10 mm) the response can only be 'Non- CR/Non-PD' unless there is unequivocal progression of the non-target lesions (in which case response is PD) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable

disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.1.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a participant in which case the response should be UNK, as for any of this participant's assessment (Section 16.1.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to >= 10 mm for the first time in the study plus 5 mm absolute increase.

FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.1.2.2

16.1.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-3.

Table 16-3 Overall lesion response at each assessment

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

[1] This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2] Once confirmed PR was achieved, all these assessments are considered PR.
[3] As defined in Section 16.1.2.4

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

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

16.1.3 Efficacy definitions

The following definitions primarily relate to participants who have measurable disease at baseline. Section 16.1.3.2.9 outlines the special considerations that need to be given to participants with no measurable disease at baseline in order to apply the same concepts.

16.1.3.1 Best overall response

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

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

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

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

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

The best overall response for each participant 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 based on a 6 week tumor assessment frequency taking into account assessment windows. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A participant 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 participant has a single PR (>=30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not >=20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this participant. 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 participant 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 participant 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 overall lesion responses.

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

Overall response rate (ORR) is the proportion of participants 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 participants with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize participants 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 participants 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 participants 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 et al 2001) and counts all participants who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR, or CR. Participants 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, participants with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an intent-to-treat (ITT) approach).

16.1.3.2 Time to event variables

16.1.3.2.1 Progression-free survival

Usually in all Oncology studies, participants 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 participant 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.

16.1.3.2.2 Overall survival

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

16.1.3.2.3 Time to progression

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

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a participant has not had an event, time to progression is censored at the date of last adequate tumor assessment.

16.1.3.2.4 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

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

16.1.3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure (TTF) 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.

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'. TTF for participants who did not experience treatment failure will be censored at last adequate tumor assessment.

16.1.3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of participants: a good risk group and a poor risk group. Good risk participants tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk participants tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk participants. Less potent agents induce a response mainly in good risk participants only. This is described in more detail by (Morgan et al 1988).

It is recommended that an analysis of all participants (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all participants (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in (Ellis et al 2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-participant analysis of these endpoints are not appropriate since the status of participants throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For participants with a CR or PR (which may have to be confirmed) the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For participants with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For participants with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

16.1.3.2.7 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 16.1.3.2.6. It is recommended that an analysis of all participants (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all participants should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all participants, participants who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for participants who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the participant cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case participants have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

16.1.3.2.8 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the assessment date is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise, if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

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

Start dates

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

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred), the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if backdating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.1.3.2.8).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the participant 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 participant alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

16.1.3.2.9 Handling of participants with non-measurable disease only at baseline

It is possible that participants with only non-measurable disease present at baseline are entered into the study, because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any participants 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 participants with measurable disease at baseline, participants without measurable disease should

also be incorporated in an appropriate manner. The overall response for participants with non-measurable disease is derived slightly differently according to Table 16-4.

Table 16-4 Overall lesion response at each assessment: participants 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 16.1.2.4		

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

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

16.1.3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a participant being lost to follow-up? It is important that the protocol and SAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 16.1.3.2.8, and using the FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics 2005) as a reference, the following analyses can be considered:

Table 16-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)1 **(1) = default unless specified differently in the protocol or RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1 =Definitions can be found in Section 16.1.3.2.8.

2 =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.1.3.2.8.

3 =The rare exception to this is if the participant dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as participants without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the participant is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

16.1.4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

16.1.4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

16.1.4.2 End of treatment phase completion

Participants **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 participants 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 participant, 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.

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation

- Technical problems
- Participant/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which "*must*" lead to discontinuation of participant from trial.

16.1.4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

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

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

16.1.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

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

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

16.1.4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 16.1.3.2.8). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

16.1.4.5.3 Incomplete dates for last known date participant alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.1.4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

16.1.4.5.5 Study / project specific programming

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

16.1.4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-5)
- Death due to reason other than underlying cancer (only used for TTP and duration of response)
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.1.3.2.8. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when participants 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/opposition to use data/biological samples, loss to follow-up or alternative anti- cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

16.1.5 Reference (available upon request)

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

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

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

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

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

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

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

16.2 Appendix 2: List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or alpelisib. Please note that all lists in Appendix 2 are not comprehensive. Please refer to regular updated online sources and the label of a concomitant drug to decide whether a drug is permitted (with caution) or prohibited based on Section 6.2.2. In doubt please the contact medical monitor with any questions.

16.2.1 Permitted medication to be used with caution

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

Table 16-6 List of CYP450 substrates to be used with caution

Category	Drug Name
CYP2C9 substrates	
Narrow Therapeutic index substrates of CYP2C9	(S)-Warfarin
Sensitive substrates of CYP2C9	Benzbromarone, Celecoxib, Glimepiride, Glipizide, (R)/(S)-Ibuprofen, Lornoxicam, Meloxicam, Piroxicam, Tolbutamine, (S)-Warfarin
CYP2B6 substrates	
Narrow Therapeutic index substrates of CYP2B6	*Not applicable*
Sensitive substrates of CYP2B6	Bupropion, Efavirenz
Selected CYP3A4 substrates	
CYP3A4 substrates which are known or potential auto-perpetrators	Clarithromycin, Conivaptan, Encorafenib, Erythromycin, Diltiazem, Mifepriston, Ribociclib, Telthromycin, Troleandomycin, Verapamil
Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor. *Substrates with narrow therapeutic index (NTI):* Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsades de Pointes, QT prolongation).*CYP3A4 substrates which are auto-perpetrators:* Based on Novartis internal assessment	

Table 16-7 List of inhibitors and inducers of CYP2C8 and strong inhibitors of CYP3A to be used with caution

Category	Drug Name
Strong CYP3A Inhibitors	Ceritinib, Clarithromycin, Conivaptan, Grapefruit juice[2] (citrus paradisi fruit juice, 240 mL TID), Idealisib, Itraconazole, Ketoconazole, LCL161, Mibefradil, Mifepristone, Nefazodone, Posaconazole, Ribociclib, Telithromycin, Troleandomycin, Voriconazole
Strong and moderate CYP2C8 inhibitors	Clopidogrel (strong), Deferasirox (moderate), Gemfibrozil (strong), Letermovir, Teriflunomide (moderate),
CYP2C8 inducers	*Since all inducers are also inducers of CYP3A4 these are prohibited as of Table 16-8*

Category	Drug Name
This list of CYP inhibitors and inducers was compiled from the University of Washington's Drug Interaction Database (Dated April 2019) [1] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database.[2]Herbal product	

16.2.2 Prohibited medication

Strong inducers of CYP3A4

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

Table 16-8 List of prohibited strong inducers of CYP3A

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

Inhibitors of BCRP

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

Table 16-9 List of prohibited BCRP inhibitors

Category	Drug Name
BCRP inhibitors - Evidence for DDI potential shown in vivo	Atazanavir/ritonavir[1,2], Elvitegravir/cobicistat[1,2], Lopinavir/ritonavir[1,2], Tipranavir/ritonavir[1,2] Curcumin[1,2], Cyclosporine[1,2], Daclatasvir[1,2], Eltrombopag[1,2], Gefitinib[2], Lapatinib[1], Ledipasvir[2], Pantoprazole[1,2], Paritepravir[2], Tipranavir[2]
[1] Lee et al, 2015 [2] Novartis PK Sciences DDI List (January, 2018)	

16.3 Appendix 3: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-10 Liver event and laboratory trigger definitions

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

Table 16-11 Follow up requirements for liver laboratory triggers – ALT, AST, TBL

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

ALT	TBL	Liver Symptoms	Action
If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT > 2 x baseline AND >3x ULN			

Table 16-12 Follow up requirements for liver laboratory triggers – Isolated Hyperbilirubinemia

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

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

16.4 Appendix 4: Statistical considerations

Part B1

The primary endpoint is the overall response rate (ORR). The analysis of the primary endpoint, which is Bayesian, uses a binomial sampling and a Beta prior distribution.

The null value for the ORR was set to 25%. Moreover, a minimum ORR improvement of 10% was considered necessary to justify initiation of Protocol part B2 (see Section 12.8 for information on published data available to help elicit the 25% and 35% targets).

The two criteria to assess the proof of preliminary efficacy (PPE) in each treatment group are thus:

- Clinical relevance: posterior mean $\geq 35\%$
- Bayesian statistical significance: $\text{pr}(\text{ORR} \geq 25\% \mid \text{data}) \geq 0.90$

The first criterion is met if the posterior mean ORR is at least 35% which is the minimum ORR of clinical interest. The second criterion provides reasonable evidence that the posterior ORR is better than the null value of 25%. Both criteria need to be met in order to meet the objective of proof of preliminary efficacy.

Analysis is performed using a Beta-binomial model as follows:

Assume that y out of n patients have a response as per ORR.

The likelihood function is $y \sim \text{Bin}(n, p)$ where p denotes the ORR.

Assume p follows a beta prior distribution: $[p] \sim \text{Beta}(a, b)$, where $a > 0$, $b > 0$

The posterior distribution of p is therefore: $[p \mid y] \sim \text{Beta}(a + y, b + n - y)$

A minimally informative prior with unimodal Beta(0.35/(1-0.35),1) distribution is used. The prior parameters are chosen so that the prior mean for ORR is equal to 35%. This ensures that the clinical relevance criterion is met, if the observed ORR is exactly equal to 35%.

With the two criteria stated above the minimally required sample size is 32.

To better understand the design, operating characteristics for various true ORR were assessed using simulations as follows:

- Generate 100,000 trials with ORR results (yes / no) for n participants per treatment group, where the ORR follows a binomial distribution $y \sim \text{Bin}(n, p)$.
- Evaluate for each of these simulated trials whether the PPE criteria are met.
- The probability of declaring preliminary efficacy is the average number of trials meeting PPE over the 100,000 sampled trials.

The operating characteristics presented in Section 12.8 of the protocol consider n=32, with varying p from 0.25 to 0.45. Operating characteristics for additional sample sizes of 36 and 40 participants by treatment group were also assessed and full results are presented in Table 16-11.

Table 16-13 Part B1 Operating characteristics for ORR with 32, 36 or 40 participants in each arm

Number of participants	True ORR	Probability of declaring PPE in each arm	Probability of missing PPE in each arm
32	25 %	0.079	0.921
	30 %	0.228	0.772
	35 %	0.448	0.552
	40%	0.675	0.325
	45 %	0.847	0.153
36	25 %	0.092	0.908
	30 %	0.263	0.737
	35 %	0.507	0.493
	40%	0.738	0.262
	45 %	0.893	0.107
40	25 %	0.102	0.898
	30 %	0.296	0.704
	35 %	0.559	0.441
	40%	0.787	0.213
	45 %	0.924	0.076

Based on the Operating Characteristics the minimal sample size of 32 participants by treatment group was considered as adequate