NOVARTIS

Clinical Development

BYL719/alpelisib

BYL719A2201 / NCT01923168

A phase II randomized, double-blind placebo controlled, study of letrozole with or without BYL719 or buparlisib, for the neoadjuvant treatment of postmenopausal women with hormone receptor-positive HER2-negative breast cancer

Statistical Analysis Plan (SAP) Amendment 1

Author:	[redacted]
Document type:	SAP Documentation
Document status:	Final
Release date:	7-Feb-2017
Number of pages:	72

Document History – Changes compared to previous final version of SAP

Version	Date	Changes
Initial version - Final	10-Jun-2014	N/A – Initial approved version
Amendment 1 - Final	7-Feb-2017	Summary of changes: alignment with protocol amendments #2 to #7, new Novartis SAP template language, new Novartis guidelines for safety analyses, new Oncology Standard Outputs v3.0 for safety, new Novartis guideline for biomarkers analysis. Major changes were the following ones: Section 1 Introduction: mentioned that content of the SAP was based on protocol CBYL719A2201 Amendment 7 and that all decisions regarding final analysis, as defined in the SAP document, were made prior to database lock and unblinding of the study data, as per the new SAP template. Section 2 Study objectives and study design: updated to align with protocol amendments #2 and #5, especially: - Updated details on study design, randomization and number of patients enrolled due to the permanent stop of the accrual in the buparlisib/buparlisib-placebo treatment arms; - Mentioned new dosing schedule of buparlisib; - Changed ORR from secondary to primary endpoint; changed the assessment of the anti-tumor activity of buparlisib into an exploratory objective; - Removed central review for pathological response. - Mentioned the safety review done by an internal DMC Section 3.1 Definitions: deleted the possibility to analyze one cohort earlier as per protocol amendment #5; added definitions of windows for multiple assessments and last contact date. Section 3.2 Analysis sets: - Removed pre-screened patients set and clarified screened patients set (correction based on information collected in the CRF); - Updated definitions of Safety set and actual treatment received as per protocol amendment #5 and new safety guidance; - Revised per-protocol set based on updated Protocol deviations defined for the study; - Corrected definition of alpelisib and buparlisib PAS; - Updated buparlisib FPAS as per protocol amendment #2 and all the FPASs as per protocol amendment #5;

Version	Date	Changes
		- Mentioned that all listings were to be produced by cohort and treatment groups; - Added management of data collected after withdrawal of informed consent. Section 3.3 Implementation of RECIST criteria: mentioned that BOR was to be determined without restriction to on-treatment assessments; clarified that applicable new antineoplastic therapies were medications and radiotherapies. Section 3.4 Patient disposition: corrected information summarized as per the data collected in the eCRF page. Section 3.5 Analysis sets: added display by stratum as per new OSO. Section 3.7 Background and demographic characteristics: added summaries of age groups by sex, and race in the safety set as per new OSO; added information for description of stratification factors; added relevant variables for diagnosis and extent of cancer; deleted summary tables for antineoplastic therapies since discontinuation of study treatment Section 3.8 Study treatment: added definitions of last date of exposure, planned cumulative dose and average daily dose; revised categories for exposure and cumulative dose for buparlisib intermittent regimen; clarified definition of dose reductions for some specific situations; deleted cumulative exposure. Section 3.9 Prior and concomitant medications: clarified the period considered for summaries; added listing of concomitant medications. Section 3.10 Primary objective: - As per protocol amendment #5, updated primary objectives and endpoints details for ORR, added details for PoC on ORR and updated statistical analysis details to remove buparlisib from the PoC assessment. - Mentioned that 80% and 95% credible intervals and a plot were to be provided for bayesian posterior difference between treatment groups. - Added 80% and 95% confidence intervals on observed difference between treatment groups using Chan and Zhang (1999) exact method, and 95% confidence intervals by treatment arm based on Clopper-Pearson (1934). - Defined handling of missing values/censoring/discontinuations for ORR as per protocol amendment #5. - Removed sensitivity analysis based on central assessment of pCR as per protocol amendment #5.

Version	Date	Changes
		Section 3.11 Secondary objectives: updated the objectives and removed ORR which was now a primary endpoint as per protocol amendment #5; added 95% confidence intervals for breast conserving surgery, and a summary on the overall population for PEPI results; added summary tables and a plot for KI67; removed analysis in the overall population for the breast conserving surgery. Section 3.12 Exploratory efficacy objectives: added similar exploratory analysis on ORR as done on pCR; added 80% and 95% confidence intervals on the observed difference versus placebo and 95% confidence intervals by treatment arm; added exploratory analysis on the efficacy of buparlisib based on the description of pCR and ORR; removed exploratory analysis using a different definition of pCR assessed centrally as per protocol amendment #5. Sections 3.13 to 3.16 on safety assessment: - Changes throughout those sections to align with new guidance for safety evaluations and new OSO recommendations, including addition of summary tables for overview of AEs, disclosure to CT.gov/EudraCT, all deaths, on-treatment deaths and SAEs with fatal outcome; reviewed the strategy to display AEs tables by SOC and/or PT, by All Grades and Grades ≥ 3 or with full detail by maximum grade as per new OSO; updated notable criteria for ECG and vital signs; - Added details on AESI definition, CRS analysis as per new safety guidance. - Added some summary tables for AEs by cohort. - Added the possibility to analyze time to first occurrence of any CTC grade ≥ 2 AESI for alpelisib. - Added display of trends over time for HbA1c, fasting glucose and fasting C-peptide, and a plot of hepatic function tests and listings for new liver event CRF pages. - Deleted shift table of overall interpretation for cardiac imaging and replaced by summary of LVEF based on CTC grade as per new OSO. Section 3.17 Mood assessments: mentioned analysis of compliance to questionnaire completion. Section 3.20 Subgroup analysis: added relevant subgroups for efficacy Section 3.21: Pharmacokinetic analysis: added $T_{1/2,\ eff}$ for buparlisib as per protocol amendment #2; added trough concentration analysis; defined primary PK parameters Section 3.22 Biomarkers: added relevant details and definitions as per the new guidance on biomarker analysis; clarified objectives applicable to

Version	Date	Changes
		this SAP as biomarkers available before the database lock; mentioned possible analysis of pCR and ORR by categorical biomarkers; added TILs biomarker analysis; updated details for IHC as per the database. Section 4 Sample size calculation: new section as per new SAP template and update sample size details as per protocol amendment #5. Section 5 Change to protocol specified analyses: new section as per new SAP template Section 6 Appendix: new section as per new SAP template in order to provide details on imputations rules, AE coding/grading, laboratory parameters derivations and statistical models Section 7 References: added Chan and Zhang (1999) to the reference list. Minor clarifications and corrections, illustration with key examples, were also made throughout the document.

Table of contents

Table of contents 6
List of tables 8
List of figures 9
1 Introduction 12
2 Study objectives and study design 12
2.1 Primary objective 12
2.1.1 Endpoints for primary objective 12
2.2 Secondary objectives 13
2.2.1 Endpoints for secondary objectives 13
2.3 Exploratory objectives 14
2.3.1 Endpoints for exploratory objectives 14
2.4 Study design 15
3 Statistical methods 21
3.1 Definitions 21
3.1.1 Study drug and study treatment 21
3.1.2 Date of first administration of study drug 21
3.1.3 Date of last administration of study drug 21
3.1.4 Date of first administration of study treatment 21
3.1.5 Date of last administration of study treatment 21
3.1.6 Study day 22
3.1.7 Baseline 22
3.1.8 On-treatment assessment/event 23
3.1.9 Screening failure 24
3.1.10 Time unit 24
3.1.11 Data included in analyses 24
3.2 Analysis sets 26
3.2.1 Screened patients 26
3.2.2 Full analysis set 26
3.2.3 Safety set 26
3.2.4 Per-protocol set 26
3.2.5 Pharmacokinetic analysis set 27
3.2.6 Patient classification 29
3.3 Implementation of RECIST criteria 30
3.3.1 Tumor assessment 30
3.3.2 Response and progression evaluation 31

3.4 Patient disposition 33
3.5 Protocol deviations 33
3.6 Analysis sets 34
3.7 Background and demographic characteristics 34
3.7.1 Basic demographic and background data 34
3.7.2 Baseline stratification factors 34
3.7.3 Diagnosis and extent of cancer 34
3.7.4 Medical history 35
3.7.5 Antineoplastic therapy 35
3.8 Study treatment 35
3.8.1 Duration of exposure to study drug 36
3.8.2 Duration of exposure to study treatment 36
3.8.3 Cumulative and average daily dose 37
3.8.4 Dose intensity and relative dose intensity 38
3.8.5 Dose reduction, interruption and permanent discontinuation 39
3.9 Prior and concomitant medication 43
3.10 Primary objective 44
3.10.1 Statistical hypothesis, model, and method of analysis 44
3.10.2 Sensitivity and other supportive analyses of the primary endpoints 46
3.10.3 Handling of missing values/censoring/discontinuations 47
3.11 Secondary efficacy objectives 47
3.11.1 Breast conserving surgery (BCS) rate 48
3.11.2 Preoperative endocrine prognostic index (PEPI) score 48
3.11.3 Ki67 49
3.12 Exploratory efficacy objectives 49
3.13 Safety evaluation 49
3.13.1 Adverse events 50
3.13.2 Dictionary coding of adverse events 50
3.13.3 Grading of adverse events 50
3.13.4 General rules for AE reporting 50
3.13.5 Adverse events summaries 51
3.13.6 Adverse events of special interest 52
3.14 Laboratory data 55
3.14.1 Grading of laboratory data 55
3.14.2 Laboratory data summary 55
3.15 Vital signs 56

3.16 Cardiac assessments 57
3.16.1 Electrocardiogram (ECG) parameters 57
3.16.2 Cardiac imaging (MUGA / ECHO) 58
3.17 Mood assessments 58
3.18 ECOG performance status 59
3.19 Other safety data 59
3.20 Subgroup analyses 59
3.20.1 Efficacy 59
3.21 Pharmacokinetic analysis 60
3.21.1 Pharmacokinetic analysis 60
3.21.2 Data handling principles 62
3.22 Biomarkers 62
3.22.1 Outline of data analysis 62
3.22.2 Exploratory biomarker objectives 63
3.22.3 Biomarker analysis set 63
3.22.4 General data handling and preprocessing 64
3.22.5 Immunohistochemistry (IHC) biomarker data 64
3.22.6 Somatic or Germline biomarker data 65
3.22.7 Other biomarker assays 66
4 Sample size calculation 66
5 Change to protocol specified analyses 67
6 Appendix 67
6.1 Imputation rules 67
6.1.1 Study drug 67
6.1.2 AE, ConMeds and safety assessment date imputation 68
6.2 AEs coding/grading 70
6.3 Laboratory parameters derivations 70
6.4 Statistical models 71
7 References 71

List of tables

Table 3-1 Patient classification based on protocol deviations 29
Table 3-2 Definition of last date of exposure of study drug 36
Table 3-3 Examples of dose reductions for alpelisib/placebo 40

Table 3-4 Examples of dose reductions for buparlisib/Placebo 41
Table 3-5 The preoperative endocrine prognostic index (PEPI) score 48
Table 3-6 AESI for alpelisib 53
Table 3-7 AESI for buparlisib 53
Table 3-8 Notable criteria for vital signs 57
Table 3-9 Notable criteria for ECG values 57
Table 3-10 Classification of severity based on depression and/or anxiety questionnaire scores 59
Table 3-11 ECOG Performance status 59
Table 3-12 PK parameters 61
Table 3-13 Biomarker summary table 63
Table 6-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS) 68
Table 6-2 Imputation of end dates (AE, CM) 69

List of figures

Figure 2-1 Assumptions for end of recruitment after protocol amendment 5 16
Figure 2-2 Study design until clinical study protocol amendment 4 18
Figure 2-3 Study design from clinical study protocol amendment 5 19

List of abbreviations

AE	Adverse event
AESI	Adverse event of specific interest
ATC	Anatomical Therapeutic Chemical
BCS	Breast Conserving Surgery
BOR	Best overall response
bpm	beats per minute
C.I.	Confidence Interval
CR	Complete response
CRF	Case Report Form
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DAR	Dosage administration record
DCR	Disease control rate
DI	Dose Intensity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case report/record form
EOT	End of treatment
FAS	Full analysis set
GPS	Global Programming & Statistical environment
IHC	Immunohistochemistry
ITT	Intent To Treat
IVR/IRT	Interactive Voice Response/ Interactive Response Technology
LSH	Life Sciences Hub
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
NMQ	Novartis MedDRA queries
ORR	Overall response rate
PAS	Pharmacokinetic analysis set
pCR	Pathological Complete Response
PD	Progressive disease
PDs	Protocol Deviations
PDI	Planned dose intensity
PIK3CA	PIK3CA Gene which encodes the p110alpha catalytic subunit
PK	Pharmacokinetic
PoC	Proof of Concept
PPS	Per Protocol Set
PR	Partial response
PS	Performance status
PT	Preferred term

QD/od	once a day
RAP	Report and Analysis Process
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
sd	Standard deviation
SDTM	Study Data Tabulation Model
SEC	Safety Event Categories
SLD	Sum of the longest diameter
SMQ	Standardized MedDRA queries
SOC	System organ class
TA	Tumor assessment
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, Listings
ULN	Upper limit of normal
UNK	Unknown
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This Statistical Analysis Plan (SAP) describes all planned analysis for the Clinical Study Report (CSR) of study CBYL719A2201 study using Novartis Clinical Data Standards in Oncology Clinical Development.

The content of this SAP is based on protocol CBYL719A2201 Amendment 7 version dated 18 October 2016. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock for the primary analysis and unblinding of the study data.

CBYL719A2201 is a multicenter phase II randomized, double-blind placebo controlled study of letrozole with or without alpelisib or buparlisib, for the neoadjuvant treatment of postmenopausal women with hormone receptor (HR)-positive HER2-negative breast cancer.

Standards for assessment of response based on RECIST 1.1 are not described in this document. They are provided in the Novartis guidance document guidelines for response assessment, which is included as an appendix of the Clinical Study Protocol (CSP).

The shells for the tables, figures and listings used for the Clinical Study Report will be inthe TFLs document. Programming specifications will be given in the Programming Dataset Specifications.

All data will be analyzed by Novartis. It is planned that the data from all the centers that participate in this protocol will be pooled. Analysis data sets and statistical outputs will be produced using the SAS system Version 9.2 or higher (UNIX environment), or in R v2.13.2 (or higher) in the global programming & statistical environment (GPS). Outputs will be stored in GPS under CBYL719A/CBYL719A2201 folder.

2 Study objectives and study design

2.1 Primary objective

The primary objective is:

To assess the anti-tumor activity of alpelisib QD plus letrozole versus letrozole alone in increasing the pathologic complete response (pCR) rate during neo-adjuvant treatment among postmenopausal patients with HR-positive, HER2-negative breast cancer for each of the two cohorts: i) *PIK3CA* mutated and ii) *PIK3CA* wild-type tumors based on tumor tissue.

and

To assess the anti-tumor activity of alpelisib QD plus letrozole versus letrozole alone in increasing the objective Response Rate (ORR) during neo-adjuvant treatment among postmenopausal patients with HR+, HER2-negative breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types based on tumor tissue.

The primary objective of the study will be considered met if either one or both of these two objectives are met in any cohort.

2.1.1 Endpoints for primary objective

The primary efficacy endpoints are:

pCR rate per investigator assessment is defined as percentage of patients with an absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes (ypT0/Tis ypN0) following 24 weeks of treatment.

and

ORR is defined as the percentage of patients with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) based on local investigator's assessment according to RECIST 1.1.

2.2 Secondary objectives

- To assess the anti-tumor activity of alpelisib QD plus letrozole versus letrozole alone in increasing the pCR rate and ORR for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types, based on ctDNA. (1)To evaluate the safety and tolerability of the combinations.
- To estimate the rate of breast conserving surgery for each of the two cohorts, namely i) PIK3CA mutated and ii) PIK3CA wild-type based on tumor tissue.
- To evaluate the association between changes in Ki67 from baseline to day 15, and from baseline to surgery, with pCR for each of the two cohorts, namely i) PIK3CA mutated and ii) PIK3CA wild-type based on tumor tissue.
- To assess centrally the Preoperative Endocrine Prognostic Index (PEPI) score for each of the two cohorts, namely, i) PIK3CA mutated and ii) PIK3CA wild-type based on tumor tissue.
- To characterize the pharmacokinetics (PK) of alpelisib/buparlisib and letrozole when given in combination

(1) Not covered in this CSR SAP as it is foreseen that ctDNA will not be available before the database lock.

2.2.1 Endpoints for secondary objectives

- pCR rate per investigator assessment and ORR per investigator assessment and according to RECIST v1.1 in PIK3CA mutated and PIK3CA wild tumor types, based on ctDNA.
- Frequency and severity of AEs, laboratory abnormalities
- Rate of breast conserving surgery defined by the percentage of patients with no mastectomy following completion of 24 weeks of treatment
- Correlation between pCR and change in Ki67 from baseline to day 15 and from baseline to surgery
- PEPI response is defined as percentage of patients with central PEPI score of 0 at the surgery
- Plasma concentration-time profiles of alpelisib and buparlisib as well as appropriate individual PK parameters (e.g. AUCtau, Cmax, Tmax and other PK parameters if deemed appropriate)
- Plasma concentration-time profiles of letrozole and appropriate individual PK parameters (e.g. AUCtau, Cmax, Tmax and other PK parameters if deemed appropriate)

2.3 Exploratory objectives

- To assess the anti-tumor activity of buparlisib (QD continuous or QD 5 days on/2 days off) plus letrozole versus letrozole alone in increasing the pCR rate during neo-adjuvant treatment among postmenopausal patients with HR+, HER2-negative breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types based on tumor tissue and ctDNA.

  and

  To assess the anti-tumor activity of buparlisib (QD continuous or QD 5 days on/2 days off) plus letrozole versus letrozole alone in increasing the objective response rate during neo-adjuvant treatment among postmenopausal patients with HR+, HER2-negative breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types based on tumor tissue and ctDNA.
- To assess the anti-tumor activity of alpelisib QD plus letrozole and buparlisib (QD or QD 5 days on/2 days off) plus letrozole versus letrozole alone in increasing pCR rate during neo-adjuvant treatment among postmenopausal patients with HR-positive, HER2-negative breast cancer regardless of PIK3CA mutational status (overall patient population)
- To assess the anti-tumor activity of a PI3K inhibitor when added to letrozole (alpelisib QD plus letrozole and buparlisib QD or QD 5 days on/2 days off) plus letrozole - both arms pooled together) versus letrozole alone in increasing the pCR rate during neo-adjuvant treatment among postmenopausal patients with HR-positive, HER2-negative breast cancer for the overall patient population (regardless of PIK3CA mutational status)

[redacted]

- To explore the change in cell proliferation and cell death in the context of letrozole treatment alone versus letrozole treatment in combination with alpelisib or buparlisib

[redacted]

2.3.1 Endpoints for exploratory objectives

- pCR per investigator assessment following 24 weeks of treatment and ORR per investigator assessment according to RECIST v1.1.
- [redacted]
- Ki67 and other markers of cell death [redacted]
- [redacted]

[redacted]

2.4 Study design

This is a multicenter phase II randomized, double-blind placebo controlled, study comparing safety and efficacy of letrozole to letrozole with alpelisib or with buparlisib, for the neoadjuvant treatment of postmenopausal women with HR-positive HER2-negative breast cancer.

Patients will be assigned to one of the two cohorts (i.e. PIK3CA mutated and PIK3CA wild-type).

Until protocol amendment 5, patients were randomized to one of the following treatment arms in a 1:1:1 ratio within each cohort of PIK3CA mutated and PIK3CA wild-type patients:

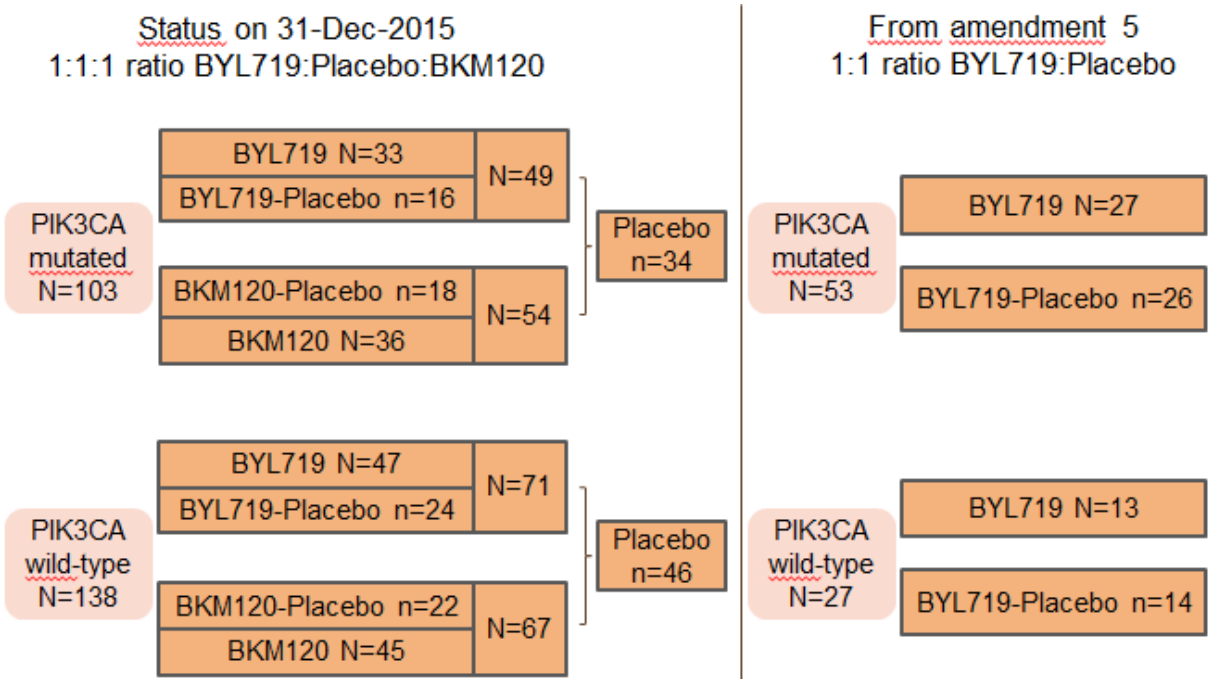
- Alpelisib + letrozole
- Buparlisib + letrozole
- Placebo + letrozole: within the placebo+letrozole arm, half the patients received matching alpelisib or buparlisib placebo.

From protocol amendment 5 following the termination of enrollment in buparlisib/buparlisib placebo arms, newly randomized patients were randomized to one of the following treatment arms in a 1:1 ratio within each cohort of PIK3CA mutated and PIK3CA wild-type patients:

- Alpelisib + letrozole
- Placebo + letrozole: where all patients received matching alpelisib placebo.

Overall approximately 320 patients will be randomized in the study so that 60 patients would be randomized to alpelisib and placebo within each cohort. This is based on status at the time of the stop of the enrollment to buparlisib/buparlisib placebo, and assuming a 2:1 ratio for number of patients randomized to alpelisib : alpelisib placebo and to buparlisib : buparlisib placebo: see Figure 2-1.

Figure 2-1 Assumptions for end of recruitment after protocol amendment 5



Note: Number of patients randomized by cohort and by blinded treatment group alpelisib/alpelisib placebo or buparlisib/buparlisib placebo are known, whereas numbers of patients randomized to alpelisib / buparlisib / alpelisib placebo or buparlisib placebo are assumptions.

Within each cohort, randomization will be stratified according to Ki67% (<14% vs. ≥14%, as measured by Novartis designated central lab) and lymph node status (positive or negative).

Note: It was discovered in the course of the study that the stratification was not performed within each cohort as planned, but on the overall population. This issue has been corrected when the randomization scheme was modified to remove buparlisib/buparlisib placebo arms following protocol amendment 5.

pCR and ORR per RECIST1.1, as assessed by local investigator's review are the primary endpoints in this study.

The primary analysis will be performed after all patients in each cohort (i.e. PIK3CA mutated and PIK3CA wild-type) have completed 24 weeks of treatment and have pCR evaluation available or have discontinued study treatment due to any reason.

No formal interim efficacy analysis is planned in this study. An internal DMC will monitor safety data by blinded treatment group, or semi-blinded upon their request, every 6 months during the conduct of the trial since protocol amendment 5.

A sample from the diagnostic biopsy (slides or core) will be required for all patients for assessment of the PIK3CA status prior to randomization in order to evaluate the effect of the letrozole+alpelisib and letrozole+buparlisib vs. letrozole+placebo according to PIK3CA mutation status.

Study treatment should be started as soon as possible and no later than 3 days after the randomization of the patient.

Figure 2-2 Study design until clinical study protocol amendment 4

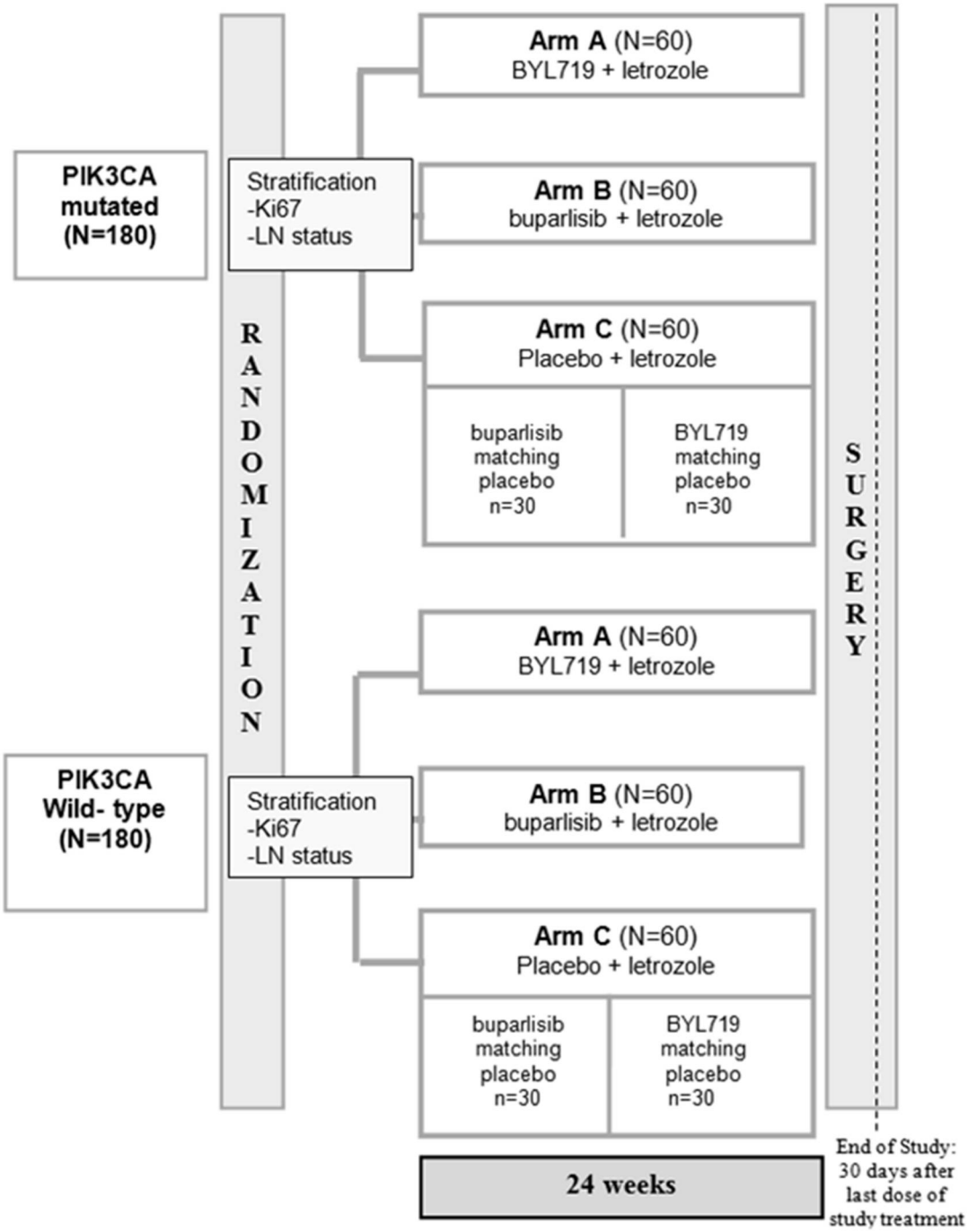
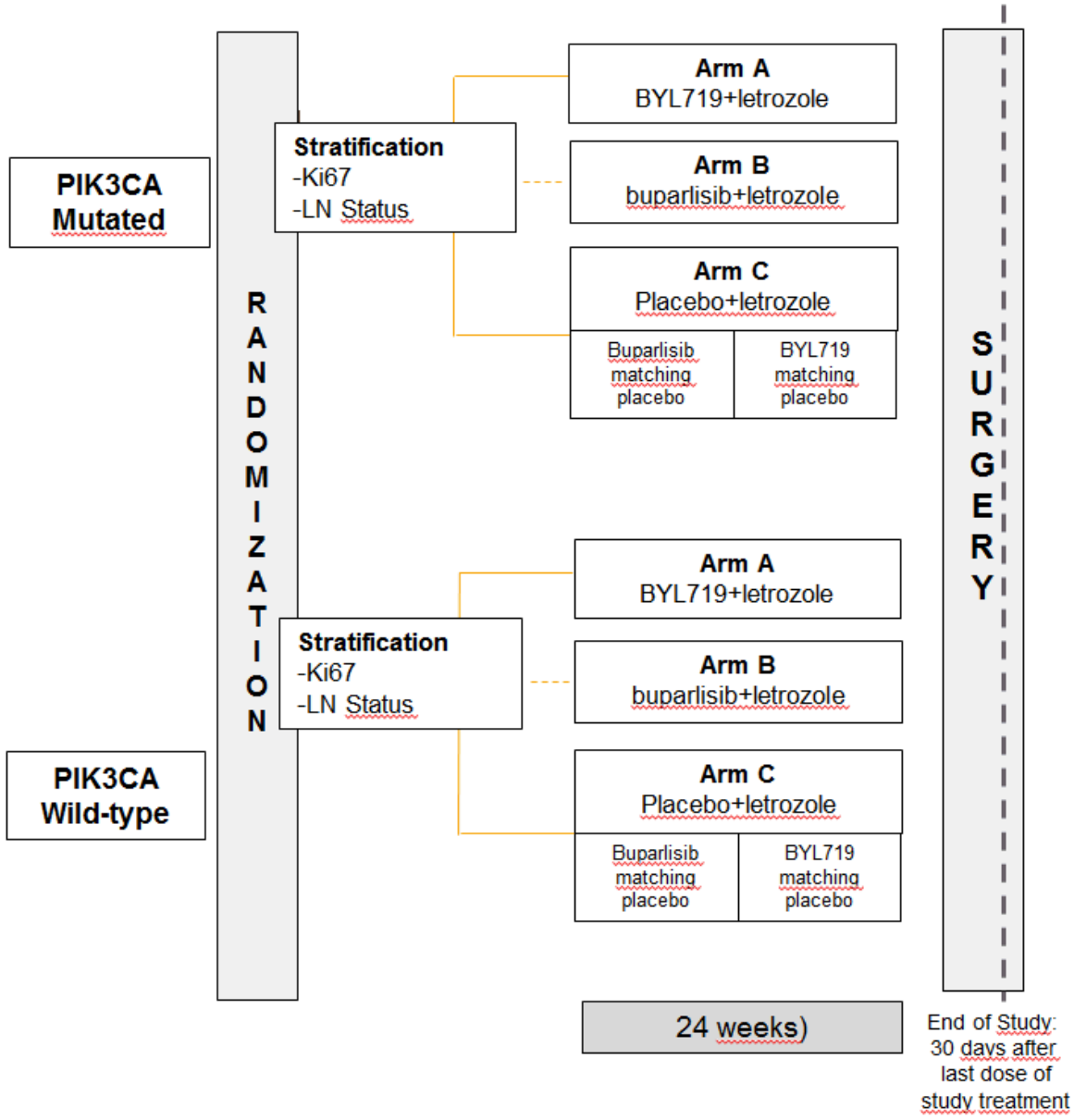


Figure 2-3 Study design from clinical study protocol amendment 5



Patients received buparlisib 100 mg QD dose or matching placebo, given once daily continuously starting from Cycle 1 Day 1 until protocol amendment 2 which introduced 100 mg 5 days on / 2 days off as a starting dose; or alpelisib 300 mg QD or matching placebo given once daily continuously starting from Cycle 1 Day 1. In addition, letrozole 2.5 mg QD was administered continuously starting at Cycle 1 Day 1.

A core biopsy (14 to 16 gauge recommended) will be performed in all patients at the end of second week of treatment to assess Ki67 status and additional biomarkers as described in Section 7.2.4 of the study protocol.

Patients will be treated for a maximum of 24 weeks or until surgery, or progression, or unacceptable toxicity or discontinuation from the study treatment for any other reason.

Tumor evaluations will be performed at baseline, at cycle 4 day 1 (with a window of +/ - 7 days) and at maximum of 7 days before surgery. Disease progression should always be documented radiologically, if needed adding earlier than planned time point for tumor evaluation.

Patients who discontinue letrozole without progression (e.g. because of toxicity attributed to letrozole or at the discretion of the investigator) will be allowed to continue alpelisib/alpelisib placebo or buparlisib/buparlisib placebo until treatment is completed or until surgery or discontinued due to progression or unacceptable toxicity and vice versa. Patients will be followed up for safety to 30 days post treatment. End of study is defined when the treatment phase and safety follow up is completed for all patients. No follow up other than safety follow up for 30 days after treatment discontinuation will be done.

After patients have completed 24 weeks of therapy, surgery will be performed as early as possible but not more than 14 days after the last dose of study treatment. In the case that surgery is not immediately performed after the last dose of alpelisib/placebo or buparlisib/buparlisib placebo, letrozole will be continued until the day of surgery. Surgery is not considered as a study assessment.

Adjuvant treatment after surgery (endocrine therapy, chemotherapy or radiotherapy) is left to the judgment of the investigator and is outside the scope of this study.

Surgical specimen will be assessed for Ki67 and molecular alterations as described in Section 7.2.4 of the study protocol.

.

3 Statistical methods

3.1 Definitions

3.1.1 Study drug and study treatment

Study treatment refers to alpelisib + letrozole, alpelisib matching placebo + letrozole, buparlisib + letrozole and buparlisib matching placebo + letrozole

Study drug can refer to alpelisib/alpelisib matching placebo and buparlisib/buparlisib matching placebo or letrozole. Study drug may also be referred to as components of study treatment.

Alpelisib matching placebo or buparlisib matching placebo will be referred to as "placebo" in the remainder of this document.

3.1.2 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a non-zero dose of study drug (alpelisib/buparlisib/placebo or letrozole) is administered as per the Dosage Administration Case Report Form (CRF). For the sake of simplicity, the date of first administration of study drug is referred to as **start date of study drug**. Start date of study drug is defined for each drug which is part of study treatment.

The date of first administration for alpelisib/buparlisib/placebo and letrozole is recorded on the corresponding "Dosage Administration Record" (DAR) eCRF page.

3.1.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug is administered. This date will also be referred to as **last date of study drug.** Last date of study drug is defined for each drug which is part of study treatment.

The date of last administration for alpelisib/buparlisib/placebo and letrozole is recorded on the corresponding "DAR" eCRF page.

3.1.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of the study treatment (alpelisib /buparlisib/placebo or letrozole) is administered as per the Dosage Administration (e)CRF. For the sake of simplicity, the date of first administration of study treatment will also be referred to as **start date of study treatment**.

For example: if the 1st dose of alpelisib/placebo is taken on the 15MAR2014, and the 1st dose of letrozole is taken on the 14MAR2014, then the date of first administration of study treatment is 14MAR2014.

3.1.5 Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of study treatment (alpelisib/buparlisib/placebo or letrozole) is administered as per Dose Administration (e)CRF. For the sake of simplicity, the date of last administration of study treatment will also be referred as the **last date of study treatment**.

For example: if the last dose of alpelisib/placebo is taken on the 30NOV2014, and the last dose of letrozole is taken on the 05DEC2014, then the date of last administration of study treatment is on 05DEC2014.

3.1.6 Study day

The study day describes the day of the event or assessment date, relative to the reference start date (randomization date or start date of study treatment).

The reference start date is designated as Study Day 1. Study Day –1 is the day that precedes Day 1. Study Day 0 is not defined.

The reference start date for all safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, PK etc.) will be start date of study treatment.

The reference start date for all efficacy assessments (e.g. pCR surgery date, tumor assessment, disease progression, and tumor response) will be the randomization date. For any non-safety screening assessments or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease), or for any safety assessment which would be also described as part of demographics (e.g. ECOG), that occurred prior to randomization the reference start date will be also the randomization date.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Study day is not to be used in numerical computations, for example in calculating exposure.

The study day will be calculated as:

- The date of the event (visit date, onset date of an event, assessment date etc.) minus reference start date + 1 if event is on or after the reference start date.
- The date of the event (visit date, onset date of an event, assessment date etc.) minus reference start date if event precedes the reference start date.

Example for safety assessments: if start of study treatment is on 05-Jan-2014 and start date of an adverse event is on 09-Jan-2014 then the study day of the adverse event onset is 5. For safety assessments before start of study treatment, the study day is negative and derived by date of event – start date of study treatment. For example: if start of study treatment is on 05-Jan-2014 and date of lab measurement is on 02-Jan-2014 then the study day of the laboratory abnormality is -3. Note, the day of start of study treatment is day 1, and the day before the date of first study treatment is day – 1, not day 0

3.1.7 Baseline

Baseline is the result of an investigation describing the “true” uninfluenced state of the patient.

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as “baseline” value or “baseline” assessment. In the context of baseline definition, the efficacy evaluations also include performance status.

For safety evaluations, the last non-missing assessment, including unscheduled assessments on or before the day of start of study treatment, is defined as "baseline" value or "baseline" assessment.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: if values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

If patients have no value as defined above, the baseline value will be missing.

Note: Deviations from the above rules for particular assessments, e.g. biomarkers are detailed in the relevant sections.

3.1.8 On-treatment assessment/event

The overall observation period will be divided into three mutually exclusive segments:
1. ***pre-treatment period***: from day of subject's first informed consent to the day before first administration of study treatment

2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date for on-treatment adverse events, excluding start date for other safety parameters)

3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

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

However, all safety data (including those from the pre and post-treatment period) will be listed and those collected during the post-treatment period will be flagged.

An on-treatment adverse event is defined as any adverse event reported in the following time interval (including the lower and upper limits):

- date of first administration of study treatment; to date of last administration to study treatment + 30 days;

This rule is consistent with the definition of treatment emergent AEs (TEAE) given in the protocol, i.e. AEs that started or worsened during the on-treatment period (see protocol Section 10.5.3.2).

An on-treatment assessment is defined as any assessment performed after the date of first administration of study treatment i.e. assessments performed in the following time interval (including the lower and upper limits):

- date of first administration of study treatment + 1; date of last administration to study treatment + 30 days;

Furthermore, assessments collected post-dose on the date of first administration of study treatment are on-treatment assessments.

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

3.1.9 Screening failure

Screening failures are patients who have signed main informed consent and/or pre-screening informed consent and failed screening criteria in the study, based on the "Screening phase disposition" eCRF page with a subject status other than "completed". These patients are not randomized.

Patients who are randomized, but never received any study drug, are not screening failures.

The following information is collected for screening failures:

- Reason for not completing screening phase
- Data on serious Adverse Events/Death

3.1.10 Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25 / 12). If duration is to be reported in months, duration in days is divided by 30.4375. If duration is to be reported in years, duration in days will be divided by 365.25.

3.1.11 Data included in analyses

Periodic review of safety data aggregated by blinded treatment group (alpelisib/buparlisib/placebo) will be performed and results will be shared with study steering committee (until protocol amendment 5) or with an internal Data Monitoring Committee.

The analysis cut-off date for the primary and final analysis will be established after all patients randomized have completed 24 weeks of treatment or have discontinued study treatment and have completed the safety follow-up and the pCR response is reported (if relevant). The study will end when the treatment phase and follow-up for safety period have ended for all patients.

All statistical analysis will be performed using all data collected in the clinical database up to the data cut-off date. A cut-off date will be defined and will be specified in the outputs. Only data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in such an analysis. For example, if the cut-off date is 15 June 2014 then an AE starting on 13 June 2014 will be reported, whereas an AE with start date on 17 June 2014 will not be reported. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with a start date either before or on the cut-off date and an end date after the cut-off date will be reported as 'ongoing' (the end date will be missing in the listings). The same rule will be applied to events starting either before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in listings.

If it is required to impute an end date to be able to perform a specific analysis, the missing end date is imputed with the cut-off date and is displayed and flagged in the listings

3.1.11.1 Windows for multiple assessments

In order to summarize labs parameters as applicable, collected over time (including unscheduled visits), the assessments will be time slotted.

Table 3-1 Time windows for labs

Assessment (1)	Target day of assessment	Time Interval
Baseline		*≤ Day 1*
Cycle 1 Day 8	*8*	*Day 2 to day 11*
Cycle 1 Day 15	*15*	*Day 12 to day 18*
Cycle 1 Day 22	*22*	*Day 19 to day 25*
Cycle 2 Day 1	*29*	*Day 26 to day 35*
Cycle 2 Day 15	*43*	*Day 36 to day 49*
Cycle 3 Day 1	*57*	*Day 50 to day 70*
Cycle 4 Day 1	*85*	*Day 71 to day 98*
Cycle k Day 1 (k≥5)	*d=(k-1)*28+1*	*Day d-14 to day d+13*
End of Treatment		*Assessment taken at the end of treatment visit*

(1) HbA1c is measured on-treatment at Cycle 3 Day 1 and EOT and same rule applies.

For laboratory parameters, all scheduled/unscheduled assessments should be assigned to time windows. In case of multiple values per window, the one closest to the planned visit date should be used. If 2 values are equidistant to the planned visit date, the selection should be made by selecting the one assessed by central (if any) and otherwise - for multiple central assessments equidistant to the planned visit - the last value.

3.1.11.2 Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

- Assessment dates (e.g. laboratory, vital signs, ECOG performance status, PHQ-9, GAD-7, ECG, cardiac imaging, tumor imaging, PK assessment, EOT completion, surgery date etc.).
- Medication and procedures dates including study medication, concomitant medications, surgical and medical procedures, antineoplastic therapies administered after study drug discontinuation (with non-missing medication/procedure term).
- Adverse event start and end dates (with non-missing verbatim AE term present)
- Study treatment start/end date (Non-missing dose. Doses of 0 are allowed).
- Randomization date

The last contact date is defined as the latest complete date from the above list or the cut -off date, whichever comes first. The cut-off date will not be used for last contact date, unless the patient

was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

3.2 Analysis sets

The following analysis sets will be used in this study.

3.2.1 Screened patients

Screened patients are all patients who completed the "Screening phase disposition" eCRF page and have signed the pre-screening informed consent or main informed consent.

3.2.2 Full analysis set

The Full Analysis Set (FAS) comprises of all randomized patients in the study. Following the intent to treat (ITT) principle, patients will be analyzed according to the treatment, cohort (PIK3CA mutant or PIK3CA wild-type) and strata they have been assigned to during the randomization procedure.

The FAS will be the main population for analyses of patient disposition, demographics and other baseline characteristics. The FAS will be the primary population for the efficacy analyses.

3.2.3 Safety set

The Safety Set will comprise all patients who received at least one dose of study treatment. Subjects will be analyzed according to the treatment actually received.

The actual treatment received corresponds to:

- the randomized treatment if patients took at least one dose of that treatment.
- the first treatment received if the randomized treatment was never received

3.2.4 Per-protocol set

The per-protocol set (PPS) comprises all patients in the FAS who are compliant with requirements of the CSP (i.e. do not have any protocol deviations that could confound the interpretation of the primary analyses conducted on the FAS).

The following list of protocol deviations will lead to exclusion of the patient from the Per-Protocol Set:

Inclusion / exclusion criteria not met

- Patient was not an adult (INCL01)
- Patient does not have histologically and/or cytologically confirmed diagnosis of breast cancer (INCL02)
- Patient was not postmenopausal as defined in the protocol (INCL03)
- Patient does not have [T1c-T3, any N, M0] operable breast cancer (INCL04)
- Patient does not have measurable tumor (INCL05)

- Patient does not have diagnostic biopsy available (INCL06)
- Patient does not have [estrogen-receptor and/or progesterone positive] breast cancer (INCL07)
- Patient does not have HER2 negative breast cancer (INCL08)
- Patient does not have PIK3CA mutation status known (PIK3CA mutated or wild-type), as defined by a Novartis designated laboratory (INCL09)
- Patient does not have ECOG performance status < or = to 1 which the investigator believes is stable at the time of screening (INCL11)
- Patient is not able to swallow and retain oral medication (INCL12)
- Patient was not a female (INCL19)
- Patient has locally recurrent or metastatic disease (EXCL01)
- Patient has inflammatory breast cancer (EXCL02)
- Patient has a concurrent malignancy or malignancy within 3 years (EXCL04)
- Patient has received any systemic therapy or radiotherapy for current breast cancer disease before study entry (EXCL05)
- Patient is concurrently using other approved or investigational antineoplastic agent (EXCL27)

Treatment not taken as per protocol

- Patient was given different treatment than originally randomized to (TRT02)
- Patient randomized but did not take study treatment (TRT36)
- Patient randomized in the wrong cohort (TRT40)

Use of prohibited concomitant medications

- Concurrent other anti-cancer therapy, or investigational therapy while on study (COMD03)

Additional criteria (not PDs) leading to exclusion from pCR PPS

- Patients treated with study treatment for less than 16 weeks
- Surgery not performed within 28 days after discontinuation of study treatment

3.2.5 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who received at least one dose of alpelisib, buparlisib or letrozole and have at least one evaluable post-treatment concentration PK data.

3.2.5.1 Alpelisib Pharmacokinetic Analysis Set (BYL PAS)

The BYL PAS will include all patients who received at least one dose of alpelisib and had at least one evaluable post-treatment alpelisib concentration measurement.

3.2.5.2 Alpelisib Full Sampling Pharmacokinetic Analysis Set (BYL FPAS)

The BYL FPAS will include the subset of the patients in the BYL PAS who:

- received all planned doses of alpelisib for the last consecutive 3 days preceding full PK profile assessment on Cycle 4 Day 1
- did not vomit within 4 hours of alpelisib and/or letrozole dosing on the day of full PK profile assessment (Cycle 1 Day 1 and Cycle 4, Day 1)
- received all planned doses of letrozole for the last consecutive 7 days and received ≥ 70% of all planned doses preceding full PK profile assessment Cycle 4, Day 1
- had an evaluable full PK profile on the day of full PK assessment (C1D1 and C4D1)

3.2.5.3 Buparlisib Pharmacokinetic Analysis Set (BKM PAS)

The BKM PAS will include all patients who received at least one dose of buparlisib and had at least one evaluable post-treatment buparlisib concentration measurement.

3.2.5.4 Buparlisib Full Sampling Pharmacokinetic Analysis Set (BKM FPAS)

The BKM FPAS will include the subset of the patients in the BKM PAS who:

- received all planned doses of buparlisib on 10 days out of 14 days (including cycle 4 day 1) preceding full PK profile assessment on Cycle 4, Day 1
- did not vomit within 4 hours of buparlisib and/or letrozole dosing on the day of full PK profile assessment (Cycle 1 Day 1 and Cycle 4, Day 1)
- received all planned doses of letrozole for the last consecutive 7 days and received ≥ 70% of all planned doses preceding full PK profile assessment Cycle 4, Day 1.
- had an evaluable full PK profile on the day of full PK assessment (C1D1 and C4D1).

3.2.5.5 Letrozole Pharmacokinetic Analysis Set (LZ PAS)

The LZ PAS will include all patients who received at least one dose of letrozole and had at least one evaluable post-treatment letrozole concentration measurement.

3.2.5.6 Letrozole Full Sampling Pharmacokinetic Analysis Set (LZ FPAS)

The LZ FPAS will include the subset of the patients in the LZ PAS who:

- received all planned doses of letrozole for the last consecutive 7 days and received ≥ 90% of all planned doses preceding full PK profile assessment Cycle 4, Day 1.
- did not vomit within 4 hours of letrozole dosing on the day of full PK profile assessment (Cycle 1 Day 1 and Cycle 4, Day 1)
- had an evaluable full PK profile on the day of full PK assessment

3.2.6 Patient classification

All protocol deviations will be reviewed and entered into the database before database lock. Patients may be excluded from the analysis sets defined above based on the protocol deviations entered in the database and/or on specific patient classification rules.

Table 3-1 Patient classification based on protocol deviations

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety set	No written inform consent No dose of study treatment	Not applicable
Per-protocol set	See definition of PP set	Patient not in the FAS
pCR Per-protocol set	Not applicable	Patient not in the Per-protocol set Patients treated with study treatment for less than 16 weeks Surgery not performed within 28 days after discontinuation of study treatment
BYL PK Analysis set	No written inform consent	No dose of alpelisib No evaluable post-treatment alpelisib concentration measurement
BKM PK Analysis set	No written inform consent	No dose of buparlisib No evaluable post-treatment buparlisib concentration measurement
LZ PK Analysis set	No written inform consent	No dose of letrozole No evaluable post-treatment letrozole concentration measurement
Full PK Analysis Set	No written inform consent	See definition of alpelisib, buparlisib and letrozole FPAS

Efficacy analyses will be performed on the FAS. Safety analyses and exposure to study treatment will be performed on the Safety set.

The listings will be provided for the FAS unless otherwise specified. They will be produced by cohort and treatment group.

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

Additional data for which there is a separate informed consent, e.g. PK, biomarker etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

3.3 Implementation of RECIST criteria

Response and progression evaluation in solid tumors are determined according to the Response Evaluation Criteria In Solid Tumor (RECIST) Novartis guidelines version 3.0 (based on RECIST v1.1), provided as Appendix 2 (Section 14.2) of the CSP.

In general, the definitions and the details regarding the derivations are provided in the guideline and are not detailed here again.

The Sections below give instructions and study level conventions to be implemented.

3.3.1 Tumor assessment

3.3.1.1 Data and determination of adequate tumor assessment

Lesion measurements and overall lesion response based on local radiological assessment are collected on the RECIST eCRF pages.

Details on adequate tumor assessments (TAs) are given in protocol Section 14.2.24 of RECIST Novartis guidelines which are based on RECIST version 1.1 (Eisenhauer et al 2009).

3.3.1.2 Determination of missing adequate tumor assessments

The term ‘missing adequate tumor assessment’ is defined as a tumor assessment not done or tumor assessment with overall lesion response ‘Unknown’. For the sake of simplicity, a ‘missing adequate tumor assessment’ will also be referred to as a ‘missing assessment’

An exact rule to determine whether there is no, one or two missing TAs is therefore needed. This rule is based on the interval between the last adequate tumor assessment date and the event date. Two thresholds are defined: D1 and D2

In this study, the first tumor assessment is planned 12 weeks after randomization (+/- 7 days) and the subsequent assessment is planned maximum 7 days before the surgery (planned no more than 2 weeks after the treatment period of 24 weeks).

If the first post-baseline tumor assessment (12 weeks ± 7 days post randomization) is missing:

- If the interval is greater than D1=91 days (12 weeks*7+7) and is less than or equal to D2=182 days (24 weeks* 7+14) then the number of missing assessments is 1.
- If the interval is greater than D2=182 days (24 weeks* 7+14) then the number of missing assessments is ≥ 2.

If the first post-baseline tumor assessment (12 weeks ± 7 days post randomization) is not missing:

- If the interval is greater than D1=98 days (12 weeks*7+7*2) and is less than or equal to D2=182 days (24 weeks* 7+14) then the number of missing assessments is 1.

If the interval is greater than D2=182 days (2*12 weeks* 7+7*2) then the number of missing assessments is ≥ 2.

3.3.1.3 Change of imaging modality

Details are given in protocol Section 14.2.5.

In particular it is described that "A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis-calculated unknown response may be accepted from the investigator if a definitive response assessment can be justified based on the available information."

3.3.1.4 Other screening methods

Not applicable

3.3.2 Response and progression evaluation

3.3.2.1 Overall lesion response

Details are given in the protocol Section 14.2.14.

The overall lesion response at a given assessment will be provided from different sources:

- Reported overall lesion response by the investigator, which is used for efficacy analyses.
- Calculated overall lesion response based on individual lesion measurements from the investigator, which is used only for validation purposes (queries and data cleaning process).

3.3.2.2 Best overall response (BOR)

Details are given in protocol Section 14.2.16.

The best overall response will be determined from all response assessments without any restriction to on treatment assessments. TAs performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic medications or radiotherapy) will be considered in the BOR determination.

The start dates of further antineoplastic therapies are identified; from the date collected on all antineoplastic therapy eCRF pages i.e.; antineoplastic therapy since discontinuation of study treatment – medication or radiotherapy

Continuation of letrozole monotherapy as 1st new anti-neoplastic therapy after end of treatment without prior PD and collected in the 'antineoplastic therapy since discontinuation of study

treatment- Medication' eCRF, will not be considered as an anti-neoplastic therapy for the assessment of BOR.

The best overall response date will be derived based on the protocol Section 14.6.25 from the 'RECIST target lesion response', 'RECIST non-target lesion assessment' and 'RECIST new lesion' eCRF pages.

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

- CR = one determination of CR prior to progression
- PR = one determination of PR prior to progression (and not qualifying for a CR)
- SD = at least one SD assessment (or better) > 5 weeks after randomization (and not qualifying for CR or PR).
- PD = progression ≤ 26 weeks after randomization (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for CR or PR and without SD after more than 5 weeks or early progression within the first 26 weeks)

3.3.2.2.1 Complete or partial response

No confirmation of complete and partial response (CR or PR) is required; please refer to the protocol Section 10.4.1.

3.3.2.2.2 Progressive disease

Details are given in the protocol Section 14.2.16.

Only objective progression per RECIST 1.1 i.e. PD identified using objective tumor assessment method (e.g. CT scan/MRI, etc.) is considered.

In particular, discontinuation due to PD or death due to study indication without supporting radiological evidence will not be considered as PD in the BOR determination.

3.3.2.2.3 Unknown response

Patients with 'unknown' BOR will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- Stable disease (SD) too early
- PD too late

Note 1: A SD is considered as 'a SD too early' if the SD is documented within the first 6 weeks (i.e. 6*7 – 7=35), i.e. up until Study Day 36.

Note 2: A PD is considered as 'a PD too late' if the first documentation of PD is recorded more than D2 days after the reference start date with no valid post-baseline assessment in between.

Note 3: Special (and rare) cases where BOR is 'unknown' due to both too early SD and too late PD will be classified as 'SD too early'.

3.4 Patient disposition

The number and percentage of patients included in the FAS will be presented overall and by treatment group. The number and percentage of patients who are still on treatment, who discontinued the study treatment phase and the reason for discontinuation will also be presented.

The following summaries will be provided (% based on the total number of FAS patients):

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on 'DAR' eCRF page not completed for any study treatment component)
- Primary reason for not being treated (based on "End of Treatment Phase Completion" eCRF page)
- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered)
- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Phase Completion' eCRF page not completed)
- Number (%) of patients who discontinued the study treatment (based on the 'End of Treatment Phase Completion' eCRF page completed)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase Completion' eCRF page completed)

All the above summaries will be repeated for the PIK3CA mutated subpopulation and PIK3CA wild type subpopulation by treatment group in the FAS.

The number (%) of screened and not-randomized patients, the number and percentage of patients completing or not screening phase, and the primary reason for not completing screening phase will be presented on a separate output.

3.5 Protocol deviations

The number and percentage of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the Study Specification Document) overall and by treatment group.

Reasons for exclusion from analysis sets (including protocol deviations) will be tabulated separately overall and by treatment group. All protocol deviations will be listed.

All the above summaries will be repeated for each cohort (PIK3CA mutated subpopulation, PIK3CA wild-type subpopulation) by treatment group in the FAS.

3.6 Analysis sets

The number and percentage of patients in each analysis set will be summarized overall by treatment group. Summaries will be also displayed by cohort, treatment group and stratum.

3.7 Background and demographic characteristics

The FAS will be used for all baseline and demographic summaries and listings. Summaries will be reported by treatment arm and for all patients, overall and by PIK3CA cohort, and listings will be reported by cohort and treatment arm to assess baseline comparability. No inferential statistics will be provided.

3.7.1 Basic demographic and background data

Descriptive statistics (e.g. mean, median, standard deviation, minimum and maximum) will be presented for continuous variables (e.g. age). The number and percentage of patients in each category will be presented for categorical variables e.g. age groups, race, ethnicity, ECOG performance status). The number and percentage of patients with missing data will also be provided.

All summaries will be presented for the full population, PIK3CA mutant subpopulation and PIK3CA wild type subpopulation by treatment group in the FAS.

In addition, summaries of age groups by sex, and race will be presented in the Safety set.

Biomarker assessment characteristics (archival tumor and its source) will also be presented.

Other data collected at baseline will be summarized or listed as appropriate.

Inclusion/exclusion criteria not met for screened patients will be summarized and listed.

3.7.2 Baseline stratification factors

The number (%) of patients in each stratum (Lymph Node status (Positive, Negative) & KI67 ($\leq$ 14%, > 14%)) based on data obtained from the IRT system will be summarized overall and by treatment group, for the FAS overall and by PIK3CA cohort. Discordances between the stratum recorded in IRT at the time of randomization and the actual stratum recorded in the clinical database through the data collected on eCRF or biomarkers will be summarized overall and by PI3KCA cohort and listed.

3.7.3 Diagnosis and extent of cancer

Summary statistics will be tabulated for the full population, PIK3CA mutated subpopulation and PIK3CA wild type subpopulation by treatment group in the FAS for diagnosis and extent of cancer.

Categorical data will include primary site of cancer, details of predominant histology/cytology, histological grade, stage (primary tumor, lymph node, metastases) at study entry, presence/absence of target and non-target lesions, HER2 receptor status, estrogen receptor (ER) status, progesterone receptor (PgR) status and hormone receptor (ER and/or PgR) status, and multicentric disease.

Time since initial diagnosis of primary site will be summarized in months.

ER status and Ki67 assessed centrally will also be summarizedThis event time (in months) is defined as:

[(reference start date) – (date of initial diagnosis of primary site) + 1]/30.4375

Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites (if any) will be based on diagnosis page.

3.7.4 Medical history

Medical history and ongoing conditions including cancer-related conditions and symptoms will be summarized overall and by treatment group and listed in the FAS. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT).

Medical history/current medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting the study will be specified in the CSR and as a footnote in the related tables and listings (if possible). The latest version available at that time of the analyses will be used.

Medical history will be summarized for the full population, PIK3CA mutated subpopulation and PIK3CA wild type subpopulation by treatment group.

3.7.5 Antineoplastic therapy

Prior anti-neoplastic surgery will be listed.

Anti-neoplastic therapies (medication, radiotherapy, surgery other than the surgery to assess pCR) since study treatment discontinuation will be listed by treatment group in FAS.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. The MedDRA and WHO-DD version used for reporting the study will be specified in the CSR and as a footnote in the related outputs (if possible). The latest version available at that time of the analyses will be used.

3.8 Study treatment

The following parameters will be listed and summarized in the full population, PIK3CA mutated subpopulation and PIK3CA wild type subpopulation by treatment group for the Safety set.

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm, separately for each component of study treatment. The duration of exposure will also be presented for the study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions, interruptions and discontinuations, with the corresponding reasons, will be summarized by treatment group.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

3.8.1 Duration of exposure to study drug

Duration of exposure to study drug (for alpelisib/buparlisib/placebo and letrozole) is defined as outlined below:

Duration of exposure (days) = (last date of exposure to study drug) – (date of first administration of study drug) + 1.

The duration includes the periods of temporary interruption.

Note 1: If the last record in DAR CRF page is a zero dose, this record will not be used in the analysis of duration of exposure.

Note 2: For patients who have ongoing treatment and had one (or more than one) last dosing record(s) of interruption for study drug at the time of the cut-off date, duration of exposure of study drug will be calculated using the end date of last non-zero dose prior to dose interruption, and this interruption will not be counted.

The definition of last date of study drug exposure for alpelisib/buparlisib/placebo or letrozole is defined in Table 3-2.

Table 3-2 Definition of last date of exposure of study drug

Scenario	Definition of last date of exposure of study drug	Example
Daily/intermittent schedule	Date of last administration of a non-zero dose of the study drug.	A patient had a permanent discontinuation of the study drug on 06Jan2013 after being put on a temporary interruption since 01Jan2013. In this case the last date of exposure is 31Dec2012.

The categorical summaries of exposure will use weeks and the continuous summaries (i.e. mean, standard deviation etc.) will use days.

The categories of exposure to study drug will be ≤ 8 weeks, > 8 - ≤ 16 weeks, > 16 - ≤ 24 weeks, > 24 weeks.

3.8.2 Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to its each drug component:

Duration of exposure (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1,

The last date of exposure to study treatment is the latest of the last dates of exposure to alpelisib/buparlisib/placebo and letrozole (see Table 3-2).

The categories of exposure to study treatment will be ≤ 8 weeks, > 8 - ≤ 16 weeks, > 16 - ≤ 24 weeks, > 24 weeks. Summaries (i.e. mean, standard deviation etc.) based on continuous variable will be displayed in days.

3.8.3 Cumulative and average daily dose

Cumulative dose is defined as the total dose given during the study drug exposure and is summarized for each study drug separately.

The planned cumulative dose for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The planned cumulative dose is not summarized / listed. It is used for relative dose intensity calculations.

Note: For buparlisib/buparlisib placebo, the planned starting dose will be either "100 mg daily" or "100 mg 5 days out of 7". This will be determined from the first entry in the DAR page with dose 100 mg and no dosing error ticked.

The actual cumulative dose refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

For patients who do not receive any study drug, the cumulative dose is equal to zero. Cumulative dose should be reported in the same units as the prescribed dose.

For continuous dosing, for alpelisib/alpelisib placebo, letrozole and buparlisib/buparlisib placebo when applicable, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, for buparlisib/buparlisib placebo when applicable, the actual cumulative dose is defined based on the days when the subject is assumed to have taken a non-zero dose during dosing periods.

For instance for buparlib or buparlisib placebo administered at X mg /day and dosing schedule of 5 days on 2 days off: the Actual cumulative dose (mg) is calculated as: X(mg)*5*W + X(mg)*min(D,5),

where W = integer part of (intermittent dosing period on X(mg)) which represents the number of full weeks the subject is on this dosing period prior to the last week o f this dosing period, and D = (duration of the intermittent dosing period on X(mg) – 7*W), which is the number of remaining days the subject is on this X(mg) intermittent dosing in the last week.

The planned cumulative dose in this setting would be defined in similar manner except that it would be based on the planned starting dose instead of the actual dose over the non -zero dosing days as shown above. The examples below illustrate the derivation of the actual and planned cumulative dose under different scenarios of dosing.

Subject 1: A subject's assigned dose is 100mg/d daily and duration of exposure is 15 days at the assigned dose. In this case the planned and the actual cumulative dose is 100*15=1500 mg.

Subject 2: A subject's assigned dose is 100mg/d, intermittent schedule 5 days on 2 days off and duration of exposure is 15 days at the assigned dose. For this scenario, W=2 and D=1 and

therefore the actual cumulative dose = 2*5*100 + 100*min(1,5) = 1100 mg. The planned cumulative dose is the same as the actual cumulative dose.

Subject 3: A subject's assigned dose is 100mg/d daily and duration of exposure is 15 days. During this dosing period the subject has been treated with 100 mg/day on days 1–7, zero dose on days 8-9 and 100 mg/day (intermittent dosing 5 days on 2 days off) on days 10-15. For the daily dosing period the actual cumulative dose = 100*7 = 700 mg. For the intermittent dosing period (6 days), W=0 and D=6 and therefore the actual cumulative dose = [(100*5*0) + (100*min(6,5)]= 500 mg. Therefore the total actual cumulative dose = 1200 mg. The planned cumulative dose is 100*15=1500 mg.

Subject 4: A subject's assigned dose is 100mg/d intermittent schedule 5 days on 2 days off and duration of exposure is 15 days. During this dosing period the subject has been treated with 100 mg/day (5 days on 2 days off) on days 1–8, and 80 mg/day (5 days on 2 days off) on days 9-15. For the 100 mg intermittent dosing period (8 days), W=1 and D=1 and therefore the actual cumulative dose = 1*5*100 + 100*min(1,5) = 600 mg. For the 80 mg intermittent dosing period (7 days), W=1 and D=0 and therefore the actual cumulative dose = 1*5*80 = 400 mg .Therefore the total actual cumulative dose = 1000 mg. For the total planned cumulative dose over the entire dosing period W=2, D=1 and is therefore calculated as: 2*5*100 + 100*min(1,5) = 1100 mg.

The cumulative dose is calculated from the DAR eCRF pages and is expressed in mg for alpelisib/buparlisib and letrozole:

- The sum of 'dose administered' (mg/d) during the exposure to buparlisib
- The sum of 'dose administered' (mg/d) during the exposure to alpelisib
- The sum of 'dose administered' (mg/d) during the exposure to letrozole

Average daily dose = [Cumulative dose (mg) / Number of dosing days], drug free day(s) are not counted.

Note: the number of dosing days is the duration of exposure to study drug minus the periods of temporary interruption.

Note: There might be subjects in the Safety Set who did not take one component of study treatment and the cumulative dose for that component would be zero.

3.8.4 Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg/day) = Actual cumulative dose (mg) / Duration of exposure (day).

Considering the example of subject 3 in the previous section:

DI (mg/day) = Actual Cumulative dose (mg) / Duration of exposure (day)

= 1200 (mg) / 15 (Day) = 80 (mg/day)

For patients who did not take any drug the DI is equal to zero.

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients as per protocol in the same dose unit and unit of time as that of the Dose Intensity.

PDI (mg/day) = Planned Cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/day) / PDI (mg/day).

DI and RDI will be summarized separately for each study drug, using the individual exposure duration for each study drug.

3.8.5 Dose reduction, interruption and permanent discontinuation

The number (%) of patients with dose reductions or interruptions and permanent discontinuations and associated reasons, will be summarized separately for each study drug.

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions and permanent discontinuations, respectively. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

Dose administered (mg) and dosing frequency from the DAR eCRF pages will be used to determine the dose reductions. Fields with zero dose administered will be used to determine interruptions.

3.8.5.1 Dose interruption

An interruption is defined as a zero dose administered on one or more days, followed by resumption of dosing.

The number (%) of dose interruptions along with the reasons will be summarized.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Note 1: The last zero dose of alpelisib/buparlisib or letrozole (followed by permanent discontinuation) is not considered as a dose interruption.

Note2: Two consecutive zero doses of alpelisib (e.g. in the sequence 300 mg daily, 0 mg, 0 mg, 300 mg daily) or buparlisib/letrozole will be counted as one interruption if the reasons for these two consecutive dose interruption are the same.

Note 3: For buparlisib dose administered at 100 mg 5 days out of 7 days, an interruption is defined as a zero dose on the scheduled 5 days.

3.8.5.2 Dose reduction

A reduction is defined as a decrease in dose from the protocol planned starting dose or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. Any dose change to correct a dosing error will not be considered a dose

reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change. For example:

- A decrease in dose from the protocol planned starting dose or a decrease from the previous non-zero dose will be counted as a dose reduction even if this decrease has been directly preceded by an interruption: see example 3 in Table 3-3.
- For buparlisib, a dose reduction is defined as a decrease in dose from the protocol planned starting dose (e.g. 100 mg daily to 80 mg daily or "100 mg 5 days out of 7" to "80 mg 5 days out of 7") or a change in dosing frequency (i.e. from 80 mg daily to 100 mg 5 days out of 7), even if the dose decrease or change in dosing frequency has been directly preceded by an interruption: see examples 3, 4 and 7 in Table 3-4.
- If the dose decrease is followed by an interruption, with the dose resuming at the same level prior to the interruption, the second dose decrease or change in dosing frequency will not be counted as dose reduction: see example 1 in Table 3-3 and example 1 in Table 3-4.
- If, due to a dosing error, a patient receives higher than protocol planned starting dose and moves down to the planned starting dose then this is not a dose reduction: see example 14 in Table 3-3 and example 21 in Table 3-4. However if the change is directly from a higher than planned starting dose down to a lower than protocol planned starting dose, then this is a dose reduction: see example 15 in Table 3-3 and example 22 in Table 3-4.
- If, due to a dosing error, a patient receives lower than previous non-zero dose and resumes later at the protocol specified dose reduction, then lower dose received due to dosing error and protocol specified dose reduction are dose reductions: see example 7 in Table 3-3 and example 14 in Table 3-4.
- If, due to a dosing error, a patient receives lower than previous non-zero dose and resumes later at lower than previous non-zero dose, then 2 dose reductions will be counted: see example 10 in Table 3-3 and example 12 in Table 3-4.
- For buparlisib/buparlisib placebo, the protocol planned starting dose was "100 mg daily" until protocol amendment 1 and then "100 mg 5 days out of 7" for patients enrolled after protocol amendment 2 (or later amendments). Since the information of the amendment on which the patient was enrolled is not collected, for patients enrolled under protocol amendment 1 and starting at "100 mg 5 days out of 7" by error, it is assumed that this will be ticked as a dose change with dose change reason 'Dosing error" and this will be counted as a dose reduction: see example 23 in Table 3-4. Otherwise, it will be assumed that the starting dose is correct and this will not be counted as a dose reduction: see example 4 in Table 3-4.

Table 3-3 Examples of dose reductions for alpelisib/placebo

Example	Sequence	Reduction
With dose change		

Example	Sequence	Reduction
1	300 mg daily - 250 mg daily – 0 mg - 250 mg daily	1 reduction (the 1st 250 mg)
2	300 mg daily – 300 mg daily – 0 mg - 250 mg daily	1 reduction (250 mg)
3	300 mg daily – 0 mg – 250 mg daily	1 reduction (250 mg)
With interruption		
4	300 mg daily – 0 mg - 300 mg daily	0 reduction
With dosing error		
5	300 mg daily – 250 mg daily – 200 mg daily*	2 reductions (250 mg, 200 mg)
6	300 mg daily – 200 mg daily* - 300 mg daily	1 reduction (200 mg)
7	300 mg daily – 200 mg daily* - 250 mg daily	2 reductions (200 mg, 250 mg)
8	300 mg daily – 400 mg daily* - 350 mg daily*	0 reduction since 400 mg and 350 mg are higher doses than planned
9	300 mg daily – 150 mg daily* - 300 mg daily	1 reduction (150 mg)
10	300 mg daily – 150 mg daily* - 100 mg daily*	2 reductions (150 mg and 100 mg)
With dosing error at the 1st administration		
11	150 mg daily* - 300 mg daily	1 reduction (150 mg)
12	150 mg daily* - 0 mg – 150 mg*- 300 mg daily	1 reduction (150 mg)
13	150 mg daily* - 300 mg daily – 0 mg - 250 mg daily	2 reductions (150 mg and 250 mg)
14	350 mg daily* – 300 mg daily – 0 – 250 mg daily	1 reduction (250 mg)
15	350 mg daily* – 250 mg daily – 0 – 200 mg daily	2 reduction (250 mg and 200 mg)

*dosing error

Table 3-4 Examples of dose reductions for buparlisib/Placebo

Example	Sequence	Reduction
With dose change		
1	100 mg od – 80 mg od- 0 mg- 80 mg od	1 reduction (the 1st 80 mg od)

Example	Sequence	Reduction
2	100 mg od – 100 mg od – 0 mg – 80 mg od	1 reduction (80 mg od)
3	100 mg od – 0 mg – 80 mg od	1 reduction (80 mg od)
4	100 mg 5 days out of 7 – 0 mg – 80 mg 5 days out of 7	1 reduction (80 mg 5 days out of 7)
5	100 mg 5 days out of 7 – 0 mg – 80 mg 5 days out of 7 – 0 - 60 mg 5 days out of 7	2 reductions (80 mg 5 days out of 7 and 60 mg 5 days out of 7)
With dose frequency change		
6	100 mg od – 80 mg od – 80 mg 5 days out of 7 – 80 mg od	2 reductions (80 mg od, 80 mg 5 days out of 7)
7	100 mg od – 100 mg 5 days out of 7 – 0 mg -100 mg 5 days out of 7	1 reduction (the 1st 100 mg 5 days out of 7)
With dose change & dose frequency change		
8	100 mg od – 0 mg – 80 mg od – 0 mg -100 mg 5 days out of 7	2 reduction (80 mg od, 100 mg 5 days out of 7)
9	100 mg od – 0 mg – 80 mg od – 0 mg -100 mg 5 days out of 7 – 0 mg- 80 mg 5 days out of 7	3 reductions (80 mg od, 100 mg 5 days out of 7, 80 mg 5 days out of 7)
10	100 mg od – 0 mg – 80 mg od – 0 mg – 100 mg 5 days out of 7 – 0 mg - 80 mg 5 days out of 7 – 70 mg* 5 days out of 7 – 0 mg – 80 mg 5 days out of 7	4 reductions (80 mg od, 100 mg 5 days out of 7, the 1st 80 mg 5 days out of 7, 70 mg 5 days out of 7)
With interruption		
11	100 mg od- 0 mg -100 mg od	0 reduction
12	100 mg 5 days out of 7 – 0 mg -100 mg 5 days out of 7	0 reduction
With dosing error		
13	100 mg od – 80 mg od – 70 mg od* – 60 mg od*	3 reductions (80 mg od, 70 mg od and 60 mg od)
14	100 mg od – 70 mg od* – 100 mg od	1 reduction (70 mg od)
15	100 mg od – 70 mg od* – 80 mg od	2 reductions (70 mg od, 80 mg od)
16	100 mg od – 300 mg od* – 250 mg od*	0 reduction since 300 mg od and 250 mg are dosing errors (i.e higher dose than planned)
17	100 mg od – 200 mg od* – 100 mg od	0 reduction since 200 mg od is a dose escalation not reduction
18	100 mg od – 50 mg od* – 100 mg od	1 reduction (50 mg od)
With dosing error at the 1st administration		

Example	Sequence	Reduction
19	50 mg od* – 100 mg od	1 reduction (50 mg od)
20	50 mg od* – 0 mg – 50 mg* – 100 mg od	1 reduction (50 mg od)
21	50 mg od* – 100 mg od – 0 mg – 80 mg od	2 reductions (50 mg od and 80 mg od)
22	150 mg od* – 100 mg od - 0 mg – 80 mg od	1 reduction (80 mg od)
23	150 mg od* – 80 mg od - 0 mg – 100 mg 5 days out of 7	2 reduction (80 mg od and 100 mg 5 days out of 7)
24	100 mg 5 days out of 7* - 0 mg - 80 mg 5 days out of 7	2 reduction (100 mg 5 days out of 7 and 80 mg 5 days out of 7)

* dosing error

Since there is no planned dose reduction for letrozole – so no reason for letrozole dose reduction is planned to be collected in the eCRF.

The number (%) of dose reductions along with reasons will be summarized.

3.8.5.3 Permanent discontinuations

"Dose permanently discontinued" ticked box from the DAR eCRF page will be used to determine the permanent discontinuations. Reasons for permanent discontinuation from the study drug will be summarized for the study drug.

3.9 Prior and concomitant medication

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the WHO-DD; Surgical and medical procedures will be coded using MedDRA. The MedDRA and WHO-DD version used for reporting the study will be specified in the CSR and as a footnote in the related tables (if possible). The latest version available at that time of the analyses will be used.

Concomitant medications, procedures and significant non-drug therapies taken concurrently with study treatment will be listed and will be summarized by lowest Anatomical Therapeutic Chemical (ATC) class and preferred term/SOC and preferred term using frequency counts and percentages.

These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any prior medications, procedures and significant non-drug therapies starting and ending prior to the start date of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

The Safety set will be used for all tables and listings. Summary tables will only include on treatment assessments. All data collected later than last treatment +30 days will only be listed.

Summaries will be tabulated for the full population, PIK3CA mutated subpopulation and PIK3CA wild-type subpopulation by treatment group in the safety set.

3.10 Primary objective

The primary objective is:

To assess the anti-tumor activity of alpelisib QD plus letrozole versus letrozole alone in increasing the pCR rate as assessed locally by the investigator during neo-adjuvant treatment among postmenopausal patients with HR-positive, HER2-negative breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types based on tumor tissue.

and

To assess the anti-tumor activity of alpelisib QD plus letrozole versus letrozole alone in increasing the Objective Response Rate during neo-adjuvant treatment among postmenopausal patients with HR+, HER2-negative breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types based on tumor tissue.

The primary objective of the study will be considered met if either one or both of these two objectives are met in any cohort.

The primary efficacy endpoints are:

pCR defined as percentage of patients with an absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of 24 weeks of treatment by local assessment (ypT0/Tis ypN0). Patients who experience progression of disease while undergoing neoadjuvant therapy, or who do not receive surgery for any reason, or receive antineoplastic treatment other than study drug(s) before surgery will be considered as non-responders for the calculation of pCR rate.

and

ORR defined as the percentage of patients with a BOR of Complete Response or Partial Response based on local investigator's assessment according to RECIST 1.1. It is defined in greater details in section 3.3.2.2

3.10.1 Statistical hypothesis, model, and method of analysis

The primary objective of this study is to assess the treatment effect of alpelisib plus letrozole vs. letrozole alone on pCR rate and ORR in each of the following two cohorts of HR-positive, HER2-negative breast cancer patients: (i) PIK3CA mutated and (ii) PIK3CA wild type based on tumor tissue.

These comparisons will be performed separately for PIK3CA mutated and PIK3CA wild type tumors. There is no formal plan to compare the alpelisib and buparlisib combination arms.

Since this study is double-blinded with respect to placebo but not whether a patient is on alpelisib or buparlisib, some patients in the control arm of letrozole will receive letrozole plus alpelisib-matching placebo and some patients will receive letrozole plus buparlisib-matching placebo. Letrozole plus alpelisib placebo and letrozole plus buparlisib placebo will be combined together within a cohort for all analyses.

Pathologic Complete Response

Based on published results, the pCR rate with letrozole is expected to be 5% or less. A 10% absolute improvement in the pCR rate to 15% is considered clinically meaningful among HR-positive patients. Therefore a Proof of Concept (PoC) about efficacy of treatment based on pCR will be declared if both of the following conditions are met for any cohort:

- Posterior probability that the difference in the pCR rate is more than 0 is > 90% and
- Estimated mean difference of the pCR rate between combination arm and letrozole is at least 10%

Overall Response Rate

Based on published results, the ORR with letrozole is expected to be around 45%. A 20% absolute improvement in the ORR is considered clinically meaningful among hormone receptor-positive patients. Therefore a PoC about efficacy of treatment based on ORR will be declared if both of the following conditions are met for any cohort:

- Posterior probability that the difference in the ORR is more than 0 is > 90% and
- Estimated mean difference in the ORR between combination arm and letrozole is at least 20%

Proof of concept will be declared in a given cohort if the PoC criteria are met for pCR or ORR.

Each comparison will be performed separately using Beta-binomial model as follows:
Let us assume that y_{is} out of n_{is} patients have a response in treatment for arm i and strata s. Where i= 1 (alpelisib plus letrozole), 2 (letrozole alone) and s= 1 (PIK3CA mutated), 2 (PIK3CA wild tumor). The likelihood function is

$$y_{is} \sim \text{Bin}(n_{is}, p_{is})$$

where p_{is} denote response rate for arm i and strata s . Assume p_{is} follows a beta prior distribution:

$$[p_{is}] \sim \text{Beta}(a_{is}, b_{is}), \text{ where } a_{is} > 0 \text{ , } b_{is} > 0$$

The posterior distribution of p_{is} is therefore (Spiegelhalter et al 2004)

$$[p_{is} \mid y_{is}] \sim \text{Beta}(a_{is} + y_{is}, b_{is} + n_{is} - y_{is})$$

The posterior distribution of treatment Difference is

alpelisib plus letrozole vs letrozole alone: $[\delta_{1s}] = [p_{1s} \mid y_{1s}] - [p_{2s} \mid y_{2s}]$

As a prior a minimally informative unimodal Beta(0.05/0.95,1) distribution (Neuenschwander 2008) will be used for pCR and Beta(0.45/0.55,1) distribution will be used for ORR. The prior parameters are chosen so that the prior mean for pCR rates is equal to 5% and the prior mean for ORR is 45%. To determine the PoC, the posterior distribution of the $[\delta_{1s}]$ will be used.

The posterior distribution of the treatment difference $[\delta_{1s}]$ is not tractable analytically. Therefore a simulation approach will be considered by drawing 100,000 random samples from each of the posterior distribution $[p_{is} \mid y_{is}]$ on treatment and control arms to calculate the difference δ_{1s} for each simulation. Both PoC criteria will be determined using this empirical distribution of δ_{1s}. The 80% credible interval (based on 10^{th} and 90^{th} percentiles) and 95% credible interval (based on 2.5^{th} and 97.5^{th} percentiles) will also be provided.

The primary analysis will be performed based on full analysis set (FAS).The FAS comprises all patients who are randomized to study treatment. According to the intent to treat principle, patient will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

A plot for the posterior distribution of difference in PCR rates and ORR between alpelisib and placebo will also be provided by cohort.

There is no formal plan to compare the alpelisib and buparlisib combination arms. The pCR rates and ORR will be summarized by cohort with descriptive measures including 80% and 95% confidence intervals by treatment arm using Clopper and Pearson (1934) exact method , along with the observed difference in response rates versus placebo and its 80% and 95% CI confidence intervals using Chan and Zhang (1999) exact method. The Disease Control Rate (DCR: CR+PR+SD) will also be reported.

The following information will be also summarized with number of patients (%) in each category: surgery performed (Yes / No / Unknown if the surgery page has not been filled out for any reason), residual tumor classification, post-treatment pathologic tumor stage, lymph nodes stage and tumor grade.

Reasons for “Unknown” BOR

Patients with ‘unknown’ BOR will be summarized by reason for having unknown status for each of the cohort.

3.10.2 Sensitivity and other supportive analyses of the primary endpoints

As a sensitivity measure, primary efficacy analysis for pCR and ORR will be repeated using the PPS in a given cohort if the PoC is established, and if the PPS and FAS are considered different in this cohort. Other supportive analyses may be conducted if necessary.

3.10.3 Handling of missing values/censoring/discontinuations

Patients with no pCR evaluation will be considered non-responders.

Patients who experience progression of disease while undergoing neoadjuvant therapy, or who do not receive surgery for any reason, or receive antineoplastic treatment other than study drug(s) before surgery will be considered as non-responders for the calculation of pCR rate. If a surgery was performed after the start of a new antineoplastic therapy, then the corresponding results will not be summarized in the pCR/surgery summary table (e.g. surgery performed will be considered as unknown and surgery results as not applicable).

Only tumor assessments performed on or before the start of antineoplastic treatment other than study drug(s) will be considered in the assessment of BOR. Patients with unknown best overall response will be considered as non-responders for the calculation of ORR.

Patients with no baseline tumor assessment

If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'.

For the computation of ORR, these patients will be included in the FAS analysis and will be counted as 'failures'. Similar approaches are followed for any response rate.

Patients with no post-baseline tumor assessment

If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown", unless progression was reported.

For the computation of ORR, these patients will be included in the FAS analysis and will be counted as 'failures'.

Patients with PR or CR

Partial or Complete Responses reported prior to any additional antineoplastic therapy will be considered for ORR computation irrespective of the number of missed assessments before response.

Missing Dates

All dates must be complete. For any incomplete dates, the imputation rules described in protocol Section 14.2.34 are followed.

3.11 Secondary efficacy objectives

All secondary efficacy analyses will be reported for PIK3CA mutated subpopulation and PIK3CA wild type subpopulation by treatment groups. Analysis will be based on the FAS unless otherwise specified.

As described in Section 2.2, the secondary efficacy objectives are

- To assess the anti-tumor activity of alpelisib QD plus letrozole versus letrozole alone in increasing the pCR rate and ORR for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types, based on ctDNA (1).

- To estimate the rate of breast conserving surgery for each of the two cohorts, namely i) PIK3CA mutated and ii) PIK3CA wild types based on tumor tissue.
- To evaluate the association between changes in Ki67 from baseline to day 15, and baseline to surgery, with pCR for each of the two cohorts, namely i) PIK3CA mutated and ii) PIK3CA wild types based on tumor tissue.
- To assess centrally the Preoperative endocrine prognostic index (PEPI) score for each of the two cohorts, namely, i) PIK3CA mutated and ii) PIK3CA wild types based on tumor tissue.
  (1) Not covered in this CSR SAP as it is foreseen that ctDNA will not be available before the database lock.

3.11.1 Breast conserving surgery (BCS) rate

Rate of breast conserving surgery (BCS) is defined as the percentage of patients with no mastectomy following completion of 24 weeks of treatment. Descriptive statistics (N, percentage, two-sided 80% and two-sided 95% confidence intervals using Clopper & Pearson (1934) method) will be used to summarize the BCS rate by treatment group and cohorts based on tumor tissue. The number and proportion of patients who undergo breast conserving surgery, mastectomy, and no surgery will be reported.

3.11.2 Preoperative endocrine prognostic index (PEPI) score

PEPI score is related to risk of relapse and is a prognostic model that incorporates standard pathological staging variables and "on-treatment" biomarker values.

The total PEPI score assigned to each patient is the sum of the risk points derived from the pT stage, pN stage, Ki67 level, and ER status of the surgical specimen. The total risk point score for each patient is the sum of all the risk points accumulated from the four factors in the model (please see Table 14-10 in protocol section 14.3).

Table 3-5 The preoperative endocrine prognostic index (PEPI) score

Pathology, biomarker Status	RFS Points	BCSS Points
Pathological tumor size		
T1/2	0	0
T3/4	3	3
Node status		
Negative	0	0
Positive	3	3
Ki67 level		
0% – 2.7% (0 – 1†)	0	0
>2.7% – 7.3% (1 – 2 †)	1	1
>7.3% – 19.7% (2 – 3 †)	1	2
>19.7% – 53.1% (3 – 4 †)	2	3
>53.1% (>4 †)	3	3
ER status, Allred score		
0 – 2	3	3

Pathology, biomarker Status	RFS Points	BCSS Points
3 – 8	0	0

† The natural logarithm interval corresponding to the percent Ki67 values on the original percentage scale. (Ellis 2008)

Summary statistics as well as the number of patients (%) with a score of 0 will be presented for PEPI score by treatment group separately for PIK3CA mutated cohort and PIK3CA wild type cohort based on tumor tissue, and by treatment group regardless of PIK3CA mutational status.

3.11.3 Ki67

The association between changes in Ki67 with pCR will be evaluated by summarizing (e.g. with arithmetic mean, geometric mean, median, SD, coefficient of variation CV (%), geometric mean CV (%), minimum and maximum) the changes from baseline to day 15 and changes from baseline to surgery in Ki67, as well as by summarizing the number of patients (%) in each of the KI67 categories used for the PEPI score, by responders / non-responders. This will be done by treatment group and by cohort based on tumor tissue, and by treatment group regardless of PIK3CA mutational status. The response will be based on ORR from RECIST 1.1 and pCR if a sufficient number of responders are observed.

Some plots of KI67 percent change from baseline at C1D15 by cohort based on tumor tissue, and by treatment group will also be provided.

3.12 Exploratory efficacy objectives

Analysis will be based on the FAS unless otherwise specified.

Exploratory objectives are described in Section 2.3.

The pCR rates and ORR will be summarized regardless of the PIK3CA mutational status (overall patient population) for the three treatment arms, as well as for the pool of alpelisib and buparlisib (Pi3K inhibitors) vs placebo. Descriptive measures including 80% and 95% confidence intervals by treatment arm using Clopper and Pearson (1934) exact method will be provided, along with the observed difference in response rates versus placebo and its 80% and 95% CI confidence intervals using Chan and Zhang (1999) exact method.

Exploratory analyses will be performed to assess the anti-tumor activity of buparlisib versus letrozole alone in increasing the pCR rate and the ORR as assessed locally by the investigator during neo-adjuvant treatment among postmenopausal patients with HR+, HER2-negative breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild tumor types based on tumor tissue. Descriptive measures including 80% and 95% confidence intervals by treatment arm using Clopper Pearson (1934) exact method will be provided, along with the observed difference in response rates versus placebo and its 80% and 95% CI confidence intervals using Chan and Zhang (1999) exact method.

3.13 Safety evaluation

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

Profiling Plan will mainly be analyzed by frequency of events; further exploratory analyses may be performed as appropriate. The latest version of the SPP and Case retrieval Strategy (CRS) available at the time of an analysis will be used.

All safety outputs will use the Safety set and be presented by treatment group on pooled cohorts' data. Some key safety outputs will be also provided by treatment group and cohort in the safety set.

On treatment period

The safety summary tables include only on-treatment assessments/events (refer to Section 3.1.8 for definition). All safety assessments are listed and those collected outside of the on-treatment period are flagged.

3.13.1 Adverse events

3.13.2 Dictionary coding of adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and will be reported by primary system organ class (SOC) and preferred term (PT), by Standard MedDRA Queries (SMQs) and Novartis MedDRA Queries (NMQs) (for safety topics of interest). The MedDRA version used for reporting the study will be specified in the CSR and as a footnote in the related tables (if possible). The latest version available at that time of the analyses will be used.

3.13.3 Grading of adverse events

Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version v4.03. In case of an update of the CTC criteria and for legacy studies using an older version of CTC some mapping may be necessary when data need to be pooled.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event although there is not necessarily proportionality among grades (a grade 2 is not twice as bad as a grade 1).

If CTCAE grading does not exist for an adverse event, grades 1 – 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE grade 5 (death) is not used; If an AE results in death it is documented in the outcome ("fatal").

3.13.4 General rules for AE reporting

The number and percentage of patients reporting any on-treatment AEs will be summarized by system organ class (SOC) and/or preferred term (PT). Additional summaries will be provided by severity and relationship to study treatment.

If the patients reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If the patients reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

Summary will be provided for study treatment related adverse events, death, serious adverse events, grades 3 and 4 adverse events, other significant adverse events leading to discontinuation, adverse events requiring additional therapy and adverse events leading to dose adjustment and/or study treatment interruption.

3.13.5 Adverse events summaries

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs, e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings. AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational arm alpelisib + letrozole.

The following adverse event summaries will be produced by treatment group: overview of adverse events and deaths *(number and % of subjects who died, with any AE, any SAE, any dose reductions/interruptions)*, AEs by SOC and PT, summarized by relationship *(all AEs and AEs related to study treatment)*, seriousness *(SAEs and non-SAEs)*, leading to treatment discontinuation, *leading to dose interruption/adjustment, requiring additional therapy* and leading to fatal outcome. In addition, a summary of serious and non-serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term) as per EudraCT requirements.

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by treatment group, system organ class and preferred term.

All deaths will be listed for the safety set; post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

The following summaries will be provided by treatment group

- Overview of AEs (All grades and Grades ≥ 3)
- AEs, regardless of study treatment relationship by PT (All grades and Grades ≥ 3)
- AEs, regardless of study treatment relationship, by SOC (All grades and Grades ≥ 3)
- AEs, regardless of study treatment relationship by primary SOC, PT, maximum CTCAE grade
- AEs suspected to be related to the study treatment by primary SOC and PT (All grades and Grades ≥ 3)
- AEs suspected to be related to the study treatment by PT (All grades and Grades ≥ 3)

- On-treatment deaths, by primary SOC, PT
- On-treatment deaths and serious adverse events with fatal outcome, by PT
- All deaths, by primary SOC and PT
- Serious adverse events (SAEs), regardless of study treatment relationship, by PT (All grades and Grades ≥ 3)
- Serious adverse events (SAEs), regardless of study treatment relationship, by primary SOC and PT (All grades and Grades ≥ 3)
- SAEs suspected to be related to the study treatment, by primary SOC and PT(All grades and Grades ≥ 3)
- AEs leading to discontinuation, regardless of study treatment relationship, by primary SOC and PT (All grades and Grades ≥ 3)
- AEs leading to discontinuation, regardless of study treatment relationship, by PT (All grades and Grades ≥ 3)
- AEs suspected to be related to the study treatment and leading to discontinuation, by primary SOC and PT (All grades and Grades ≥ 3)
- AEs requiring dose adjustment or study treatment interruption, regardless of study treatment relationship, by primary SOC and PT (All grades and Grades ≥ 3)AEs requiring additional therapy, regardless of study treatment relationship, by primary SOC and PT (All grades and Grades ≥ 3)
- Non-serious AEs with occurrences
- SAEs and deaths with occurrences.

The following summaries will be provided by treatment group and by PIK3CA cohort:

- AEs, regardless of study treatment relationship by primary SOC and PT (All grades and Grades ≥ 3)
- AEs suspected to be related to the study treatment by primary SOC and PT (All grades and Grades ≥ 3)
- AEs leading to discontinuation, regardless of study treatment relationship, by primary SOC and PT (All grades and Grades ≥ 3)
- On-treatment deaths and serious adverse events with fatal outcome, by PT
- Serious adverse events (SAEs), regardless of study treatment relationship, by SOC and PT (All grades and Grades ≥ 3)

Deaths and SAEs will also be listed for screening failures.

3.13.6 Adverse events of special interest

Specific groupings of Adverse Events of Special Interest (AESI) will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with alpelisib or buparlisib treatment (i.e. where alpelisib / buparlisib may influence a common mechanism of action

responsible for triggering them) or AEs which are similar in nature (although not identical). The groups are defined according to the MedDRA terms defined in the program Case Retrieval Strategy (CRS) documents for alpelisib and buparlisib and will be summarized. The latest versions of the CRS documents available at the time of the analyses will be used.

All AESI groupings are defined through the use of Preferred Terms (PT), High Level Terms (HLT) or System Organ Classes (SOC) or through a combination of these three components. An Excel file with the exact composition of the AEs groupings is to be used to map reported AEs to the AESI groupings. This file may be updated (i.e. it is a living document) based on review of accumulating trial data. Note that certain AEs may be reported within multiple groupings. Final deliverables will be aligned with the final excel file. A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

Table 3-6 AESI for alpelisib

AESI grouping	Definition*
Hyperglycemia	SMQ Hyperglycaemia /new onset diabetes mellitus (narrow)
Rash	Rash [BYL719] NMQ
Pneumonitis	SMQ Interstitial lung disease (narrow)
Nausea, Vomiting, Diarrhea	HLT Diarrhoea (excl infective)
	HLT Nausea and Vomiting symptoms

* At the time of the analyses, MedDRA-defined (SMQ) or Novartis-defined (NMQ) groupings described in the latest version of the CRS document available for alpelisib will be used

Table 3-7 AESI for buparlisib

AESI grouping	Definition*
Hyperglycemia	Hyperglycaemia /new onset diabetes mellitus (SMQ, narrow)
Mood disorders	Mood disorders and disturbances NEC (HLGT),
	Personality disorders and disturbances in behaviour (HLGT),
	Suicidal and self-injurious behaviours NEC (HLGT),
	Psychiatric and behavior symptoms NEC (HLGTs)
Hypersensitivity, Rash (including DRESS, photosensitivity)	Hypersensitivity/Allergy (SMQ, narrow)
	HLT Photosensitivity conditions and photodermatosis conditions
	HLT Eosinophilic disorders
	PTs Eosinophilic count increased, Eosinophil count abnormal, Eosinophil percentage increased,
	Eosinophil percentage abnormal
Liver toxicity	SMQs (narrow):
	Cholestasis and jaundice of hepatic origin; Hepatic failure, fibrosis and cirrhosis and other liver
	damage-related conditions; Hepatitis, non-infectious; Liver related investigations, signs and symptoms
Posterior Reversible Encephalopathy Syndrome (PRES)	HLT Encephalopathies NEC

AESI grouping	Definition*
Asthenia, Fatigue	HLT Asthenic conditions
Nausea, Vomiting, Diarrhea	HLT Diarrhoea (excl infective)
	HLT Nausea and Vomiting symptoms
Pneumonitis	SMQ Interstitial lung disease (narrow).

* At the time of the analyses, MedDRA-defined (SMQ) or Novartis-defined (NMQ) groupings described in the latest version of the CRS document available for buparlisib will be used

For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on-treatment period will be summarized. This will be done also by PIK3CA cohort.

Summaries of all AESIs for alpelisib and some of the AESIs for buparlisib (i.e. Hypersensitivity, Rash (including DRESS, photosensitivity) , Liver toxicity, Mood disorders and hyperglycemia) will be provided by treatment group (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, fatal outcome, etc.). If sufficient number of events occurred, analysis of time to first occurrence of any CTC grade ≥ 2 AESI for alpelisib will be applied.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.
All AEs in a given AESI will be listed.

Time to first occurrence of any CTC grade ≥ 2 AESI for alpelisib

Time to onset of CTC grade ≥ 2 events will be summarized using the Kaplan-Meier method. Median time to onset and 95% CI will be provided. In addition, ascending Kaplan-Meier plots will be generated.

Time to onset of CTC grade ≥ 2 event is defined as the time from the start of treatment to the start date of the first incidence of an event of CTC grade ≥ 2 i.e. time in days is calculated as (start date of first occurrence of the event) – (date of first dose of study treatment) +1.

A patient will be censored if:

The patient discontinues from the study treatment without experiencing any CTC grade ≥ 1 event during the on-treatment period.

The patient dies without experiencing any CTC grade ≥ 2 event.

The patient receives a new antineoplastic therapy (with the exception of letrozole monotherapy) before experiencing any CTC grade ≥ 2 event.

The censoring date will be the earliest of the following dates: death date, new anticancer antineoplastic therapy start date, end date of on-treatment period (end of study treatment + 30 days) or withdrawal of informed consent date.

3.14 Laboratory data

3.14.1 Grading of laboratory data

Laboratory data grades will be converted into Standard International (SI) units and will be derived programmatically according to the Common Terminology Criteria for Adverse Events (CTCAE) version v4.03. The calculation of CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in "Novartis internal criteria for CTC grading of laboratory parameters". The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

A severity grade of 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be applicable. 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.

Laboratory values with missing units or normal range may not be able to be graded or included in laboratory tables.

3.14.2 Laboratory data summary

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date.

The summary of laboratory evaluations will be presented by treatment group for two groups of laboratory tests: hematology (including coagulation) and biochemistry.

The following summaries will be produced for the laboratory data (by laboratory parameter and treatment):

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

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

Trends of lab parameter values over time (baseline and selected on-treatment timepoints) may be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points: HbA1c, fasting glucose and fasting C-peptide.

The following listings will be produced for the laboratory data:

- 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 reference ranges
- Listing of patients with CTC grade 3 or 4 laboratory toxicities.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values in the following categories will be summarized:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- ALP > 1.5xULN• TBIL > 1.5xULN• ALT or AST > 3xULN & TBIL > 2xULN (without time window)
- ALT or AST > 3xULN & TBIL > 2xULN & ALP < 2xULN (without time window)

Potential Hy's Law events (candidates) are defined as those subjects with AST or ALT > 3xULN and TBIL > 2xULN and ALP < 2xULN at any visit during the on-treatment period. Further medical review has to be conducted to assess potential confounding factor such as liver metastases, liver function at baseline etc.

Additional categories may be added to the above list based on any updates to the internal guidelines on collection, analysis, and presentation of liver safety data.

A figure displaying time course of hepatic function tests (ALT, AST, TBIL, ALP) in patients with potential Hy's law cases will be displayed.

3.15 Vital signs

Vital sign assessments are performed in order to characterize basic body functions. The following parameters were collected: height (cm), weight (kg), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Vital signs collected during on-treatment will be summarized. Values measured during the post-treatment period will be flagged in the listings.

The following summary table will be produced by parameter:

- The number and percentage of patients with notable vital signs values (High / Low) will be presented by treatment group. Notable criteria are provided in Table 3-8 below.

The following listing will be produced by treatment group:

- A listing of all vital sign assessments will be produced by treatment group and notable values will be flagged.
- Separate listing of only the subjects with notable vital sign values

In the listings, the assessments collected during the post-treatment period will be flagged.

Table 3-8 Notable criteria for vital signs

Vital Sign (unit)	Notable high value	Notable low value
Weight (kg)	increase >= 10% from baseline	decrease >= 10% from baseline
Systolic blood pressure (mmHg)	≥ 180 and increase from Baseline of ≥ 20	≤ 90 and decrease from Baseline of ≥ 20
Diastolic blood pressure (mmHg)	≥ 105 and increase from Baseline of ≥ 15	≤ 50 and decrease from Baseline of ≥ 15
Pulse Rate (bpm)	≥ 100 and increase from Baseline of >25%	≤ 50 and decrease from Baseline of >25%

3.16 Cardiac assessments

The summary tables will include only on-treatment assessments in the Safety set. All assessments will be listed and those collected outside of the treatment period will be flagged.

3.16.1 Electrocardiogram (ECG) parameters

As recommended in the FDA guidance on Clinical Evaluation of QT/QTc interval prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, the number and percentage of patients having notable ECG interval values will be summarized by treatment group.

The following summary table will be produced by parameter:

- Number and percentage of patients with notable ECG values will be presented by treatment group.

Notable ECG criteria are provided in Table 3-9.

Table 3-9 Notable criteria for ECG values

ECG parameter (unit)	Clinically notable criteria
QTcF (ms) and QT (ms)	New value of > 450 ms and ≤ 480 ms
	New value of > 480 ms and ≤ 500 ms
	New value of > 500 ms
	Increase from Baseline > 30 ms to ≤ 60 ms
	Increase from Baseline > 60 ms
PR duration (ms)	Increase > 25% from Baseline and to a value>200 ms
	New value of > 200 ms
QRS duration (ms)	Increase > 25% from Baseline and to QRS duration >120 ms
	New values of QRS > 120 ms
Heart Rate (bpm)	decrease from Baseline of >25% and to a value < 50 bpm
	increase from Baseline of >25% and to a value > 100 bpm

Baseline is defined as the average of available sequential ECG measurements taken at pre-dose on Cycle 1 Day 1. The percentage of patients having notable ECG interval values is based on the total number of patients in the Safety set.

The following listing will be produced by treatment group:

- A listing of all ECG assessments will be produced by treatment group and notable values will be flagged.
- Patients with at least one notable ECG value

In the listings, the assessments collected during the post-treatment period will be flagged.

3.16.2 Cardiac imaging (MUGA / ECHO)

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

For left ventricular ejection fraction (LVEF) a shift table using CTC grades for 'Ejection fraction - decrease' as defined per CTCAE version v4.03 to compare baseline to the worst on-treatment value will be provided.

All data will be listed and those occurring more than 30 days after last study treatment will be flagged.

3.17 Mood assessments

This section is applicable to buparlisib/buparlisib placebo part only. Mood assessment includes two self-rating patient questionnaires, the GAD-7 and PHQ-9 scales.

The primary variable for the analyses of the mood questionnaires will be the study-derived total scores from the PHQ-9 and GAD-7. Analysis will be performed based on the Safety set. For each scale, a total score will be derived by adding column scores. Categorization will be performed as described in the protocol Section 14.4 to assess severity.

In case of a missing answer to at least one item, the total score value will be missing except if available answers translate into a severe score (for example: a patients fills in PHQ-9 questionnaire as followed: for questions from 1 to 7, the answer is "nearly every day" (3) and the questions 8 and 9 are not answered. The total score is unknown but equal to 21 or more. The toxicity is severe.)

Number and percentage of patients will be described at each time point according to PHQ-9 total score categories (0-4, 5-9, 10-19, 20-27). Shift tables (from Baseline to worst post-baseline total score) based on the classification above will be produced. Similar analysis will be performed to report answer to question 9 of PHQ-9 questionnaire.

Number and percentage of patients will be described at each time point according to GAD-7 total score categories (0-4, 5-9, 10-14, ≥15). Shift tables (from baseline to worst post-baseline total score) based on the classification above will be produced.

Compliance will be analyzed using a ratio of the number of completely responded assessments (i.e., no missing answer or no missing evaluation) and the number of planned assessments. Compliance will be described by time point.

If a patient has more than one assessment at the same visit, the worst total score will be used.

Table 3-10 Classification of severity based on depression and/or anxiety questionnaire scores

PHQ-9 (depression)		GAD-7 (anxiety)	
Score	Severity	Score	Severity
0-4	None	0-4	None
5-9	Mild	5-9	Mild
10-19	Moderate	10-14	Moderate
20-27	Severe	≥ 15	Severe

3.18 ECOG performance status

ECOG Performance status (PS) is assessed to attempt to quantify the impact of disease on daily life activities of patients.

ECOG PS scale is used to assess physical health of patients, ranging from 0 (most active) to 5 (least active).

Table 3-11 ECOG Performance status

Score	Description
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

ECOG PS will be listed. The analysis will be performed on the safety set.

3.19 Other safety data

Other safety data (e.g. pulmonary function test, slit lamp exam, Liver event – imaging, Liver Event - History of Alcohol Use 6 Weeks prior to Liver Event, Liver Event - Drugs of Abuse History, Liver Event – Pathology) will be listed in the safety set.

3.20 Subgroup analyses

3.20.1 Efficacy

Summaries of primary endpoints will be performed based on below subgroups in an exploratory manner in a given cohort if the PoC is established in that cohort:

- Age (<65 years vs ≥65 years)
- Race (Caucasian, Asian vs others)
- ER status (positive or negative)
- PR status (positive or negative)
- Estrogen receptor and Progesterone receptor status (++/+-/-+)

Subgroup analysis based on stratification factors will be performed in the FAS by cohort and on the overall population:

- Ki67 status (<14% vs ≥14%)
- Lymph node status (positive or negative)

In each of the subgroup, the pCR rates and ORR in each of the treatment groups will be summarized by cohort using descriptive measures including 80% and 95% confidence intervals by treatment arm using Clopper and Pearson (1934) exact method, along with the observed difference in response rates versus placebo and its 80% and 95% CI confidence intervals using Chan and Zhang (1999) exact method. Efficacy analyses in subgroups will be purely exploratory and are intended to explore the consistency of overall treatment effect.

3.21 Pharmacokinetic analysis

In general, the pharmacokinetic analysis set (PAS) will be used for all tables and figures while the full analysis set will be used for all listings in all pharmacokinetic data analyses unless otherwise is specified.

3.21.1 Pharmacokinetic analysis

The plasma concentration of the patients included in the FPAS (BKM FPAS, BYL FPAS and LZ FPAS) will be used to generate derived PK parameters using a non-compartmental approach. The aim of this PK analysis is to have a preliminary PK assessment of any potential impact of letrozole on the pharmacokinetics of alpelisib/buparlisib.

The concentration-time profiles (treatment arms) will be presented by tabulating descriptive statistics : n (number of values to be reported), m (number of non-zero values to be reported), arithmetic mean, geometric mean, median, SD, coefficient of variation CV (%), geometric mean CV (%), minimum and maximum by time point and by plotting geometric and arithmetic mean (SD) concentration-time profiles, for alpelisib, buparlisib and letrozole for both the linear and semi-log view at each occasion (Cycle 1 Day 1 and Cycle 4 Day 1). Trough concentration will be reported for the PAS, and PK profile concentrations will be reported separately and by visit for the FPAS. Descriptive graphical plots of individual plasma concentration by-time profiles will also be generated for alpelisib, buparlisib and letrozole for the semi-log view for the full analysis set.

Descriptive statistics: n (number of values to be reported), arithmetic mean, geometric mean, median, SD, coefficient of variation CV (%), geometric mean CV (%), minimum and maximum will be presented for subjects in the FPAS for the PK parameters for buparlisib, alpelisib and letrozole at cycle 1 day 1: Tmax, Cmax, AUCinf, AUClast, AUC0-24, CL/F, Vz/F and T1/2 (only for alpelisib as T1/2 cannot be properly estimated for buparlisib due to its long half-life).

Descriptive statistics: n (number of values to be reported), arithmetic mean, geometric mean, median, SD, coefficient of variation CV (%), geometric mean CV (%), minimum and maximum will be presented for subjects in the FPAS for the PK parameters for buparlisib, alpelisib and letrozole at cycle 4 day 1: Tmax, Cmax, AUClast, AUC0-24, CLss/F, T1/2 (for alpelisib), effective half-life T1/2,eff (for buparlisib only) and Racc.

Primary PK parameters will be Tmax, Cmax, AUClast and AUC0-24. For all compounds Clast and Tlast will be listed but not summarized. Trough concentrations will be listed.

Pharmacokinetic parameters listed in Table 3-12 will be determined using non-compartmental method(s) by the pharmacokineticist and transferred to the database.

Listing will be provided for all concentrations and PK parameters mentioned below for the full analysis set.

PK parameters on Cycle 4 Day 1 will be compared between letrozole treatment arms using an ANOVA model in the letrozole FPAS. An ANOVA model will be fitted to the log-transformed PK parameters (AUC0-24 and Cmax) of letrozole including study treatment (letrozole alone, letrozole + alpelisib, letrozole + buparlisib) as a fixed effect. The treatment difference between letrozole + alpelisib and letrozole alone and between letrozole + buparlisib and letrozole alone will be calculated. A point estimate and corresponding 90% confidence interval for the treatment difference (letrozole + alpelisib and letrozole alone and between letrozole + buparlisib and letrozole alone) will be calculated. This will be back transformed to obtain the point estimate and the 90% CI for the ratio of the geometric means on the original scale.

Table 3-12 PK parameters

Term	Definition
Cmax	The maximum (peak) observed plasma drug concentration after single dose administration [ng × ml^{-1}]
Tmax	The time to reach Cmax [hr]
Tlast	The time to last measurable concentration sampling [hr]
Clast	The last measurable concentration [ng x ml^{-1}]
AUClast	The area under the concentration-time curve from time zero to the last measurable concentration sampling time (Tlast) [ng × hr × ml^{-1}]
AUC0-24	The area under the concentration-time curve from time zero to 24 hours post dose [ng x hr x ml^{-1}]
AUCinf	The area under the plasma concentration-time curve from time zero to infinity [ng x hr x ml^{-1}]
AUCex[1]	The area under the plasma concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC (%)
CL/F	Apparent oral total drug clearance calculated from AUCinf after a single oral dose [L x hr^{-1}]
CLss/F	Apparent oral total drug total plasma clearance calculated from stead-state exposure data [L x hr^{-1}]
Vz/F	The apparent volume of distribution during terminal phase (associated with lambda_z) [L]
T1/2	Elimination half-life associated with the terminal slope (λ_z) of a semi logarithmic concentration-time curve time
RAcc	Accumulation ratio calculated as $AUCtau_{,SS}/AUCtau_{,dose1}$ where tau is the dosing interval
Rsqadj[1]	Square of the correlation coefficient associated with lambda_z

[1] AUCex and Rsqadj will be used in the interpretation of the primary PK parameters and therefore will be included in the listings only.

3.21.2 Data handling principles

3.21.2.1 Analysis sets

The plasma samples will be assayed for alpelisib or buparlisib and letrozole concentrations by Novartis or subcontractor using validated LC-MS/MS methods described in the [Laboratory Manual].

BYL, BKM and LZ FPAS will be used in the non-compartmental analysis (NCA) of selected patient subpopulation and BYL, BKM and letrozole PAS will be used to assess trough levels within all patients.

For plasma alpelisib, buparlisib and letrozole, the LLOQ is 5.0 ng/mL, 1.0 ng/mL and 2.0 ng/mL, respectively. All concentrations below the LLOQ will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and omitted for data analysis.

3.21.2.2 Basic Tables, Figures and Listings

Descriptive statistics (arithmetic mean, standard deviation, CV%, geometric mean, geometric CV% median, minimum and maximum) will be presented for all parameters by analyte, treatment arm and study day. When a geometric mean is presented, it will be stated as such. Only median, minimum and maximum will be given for Tmax. Similarly descriptive statistics will be presented for concentration by analyte, treatment arm, study day and scheduled sampling time-point.

Descriptive graphical plots of individual plasma concentration by time will be generated, as will mean concentration time profiles for alpelisib, buparlisib and letrozole.

3.22 Biomarkers

As a project standard, Novartis Oncology BDM will analyze only biomarkers collected in the clinical database. [redacted]

There may be circumstances when a decision is made to stop a sample collection, or not perform or discontinue the analysis of blood / archival tumor samples / fresh tumor biopsies / fine needle aspirates due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

3.22.1 Outline of data analysis

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. These analyses may include but are not limited to the meta-

analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the RAP or in a stand-alone analysis plan document, as appropriate.

The analyses of biomarkers will be reported in the CSR if data are available at the time of clinical database lock and CSR preparation. Otherwise, the results may be reported in a separate report document.

3.22.2 Exploratory biomarker objectives

The exploratory biomarker objectives covered in this CSR SAP are the following ones:

- [redacted]
- To explore the change in cell proliferation and cell death in the context of letrozole treatment alone versus letrozole treatment in combination with alpelisib or buparlisib
- [redacted]
- [redacted]
- [redacted]

3.22.3 Biomarker analysis set

The FAS will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

3.22.3.1 List of biomarkers evaluated and the collection time points

Table 3-13 Biomarker summary table

Biomarker	*Time point*	*Sample*	*Method*	*Dataset*
PI3K Activation Status				
PIK3CA mutation	*Baseline*	*Archival tumor sample* *Fresh tumor biopsy (if archival not available)*	*PCR*	*B1(Y7 for stratification data)*
[redacted]				
[redacted]				

[redacted]				
ER	*Baseline, EOT*	*Fresh tumor biopsy* *Archival sample can be used in place of baseline tumor biopsy if fresh tumor biopsy tissue is limited or unavailable*	*Immunohisto-chemistry*	*B1*
[redacted]				

3.22.4 General data handling and preprocessing

Data preprocessing and transformations are described in detail in the Programming Dataset Specifications document.

3.22.4.1 Definition of baseline and summarizing replicate data values

The screening assessment will be used as the baseline assessment. In case several results would be available, the last non-missing assessment on or before the date of randomization will be taken as "baseline"

For PIK3CA mutational status at baseline, archival tumor biopsy will be used or else fresh tumor biopsy if archival is not available. For other assessments performed in tumor biopsies, fresh biopsy results will be used for baseline when both archived and fresh tumor samples are available.

When more than one biomarker data value are available for a subject at any time point, the mean of the replicate values will be used for all statistical analyses.

3.22.5 Immunohistochemistry (IHC) biomarker data

3.22.5.1 Handling of IHC data: Computation of H scores

Immunohistochemistry (IHC) data reported from the lab will include quantitative data such as percent tumor and percent positive cells and H-scores (ranging between 0 and 300 and calculated by the lab based on percent cells showing slight (1+), moderate (2+), or strong (3+) staining in a specific compartment). [redacted]

Ki67 is reported using the % of positive cells and for practicality, only the field (1+) (CELLOC1C=1, 4 or 7) is reported. When only the field (1+) is populated (CELLOC1C=1, 4 or 7) the lab will be consulted to confirm that the % of positive cells, and not the H-Score, is reported.

Derivation of Change and Percent Change Variables

Absolute and relative change (percent change) and fold change from baseline will be calculated for each subject and or treatment group.

Percent change is computed as ((visit i – baseline) / baseline) * 100. To compute the average percent change from baseline is to compute the average expression level at each time point and then compute the percent change using the average values. Please note the number of subjects for the average of percent change from baseline might vary due to potential missing values at respective timepoints.

3.22.5.2 IHC summary statistics

When an expression status is being reported by the lab [redacted], expression status will be summarized using counts and percentages.

For each IHC assay (e.g. % positive cells, H-scores), the mean, standard deviation, %CV, median, minimum, maximum, inter-quartile range, number and percent of the H-score values for each treatment group at each time point, for change from baseline and percent change from baseline at each timepoint, will be reported. Interquartile range is the number of data points between the 25^{th} and 75^{th} percentile. The expression status and/or the H-scores will be listed for each subject for all time points and ordered by cohort and the treatment group.

3.22.6 Somatic or Germline biomarker data

3.22.6.1 Handling of Somatic or Germline biomarker data

Overall, somatic mutation status (wild type or mutant) will be derived from the mutational status of the interrogated exons for any of the genes. These may be non-exclusive and the presence of mutation across more than one exon will be reported in separate categories.

The mutation status of PIK3CA will be assessed in all patients in the study.

3.22.6.2 Mutation summary statistics

3.22.6.2.1 Somatic mutations

All somatic mutation data will be reported using counts and percentages by the mutation type in the form of contingency tables with the rows containing the different mutations assayed, (grouped by the gene) and the treatment groups in the columns.

All the mutation categories for a gene will also be aggregated into mutant, wild type or missing/unknown groups and counts/percentages will be reported by these three categories as well.

If somatic mutations are analyzed in multiple samples from a subject (e.g. biopsy) fresh and/or frozen sample, the patient may be considered having a mutation if a mutation is observed in at least one of the samples.

pCR and ORR may be summarized by treatment group and categorical biomarker at baseline (e.g. [redacted], if a sufficient number of patients is available per category).

All the mutation data will be listed for each subject ordered by cohort and treatment group.

3.22.7 Other biomarker assays

Summary statistics will be provided for TILs by responders / non-responders. The response will be based on ORR from RECIST 1.1 and pCR if a sufficient number of responders is observed. Further description may be considered by tumor area (resected vs core needle biopsies) depending on the number of patients per categories.

TILs data will be listed by cohort and treatment group.

4 Sample size calculation

A total of approximately 320 patients will be randomized. Patients will be assigned to one of the two cohorts, and within each cohort patients will be randomized to one of the three arms (i.e. alpelisib+letrozole, buparlisib+letrozole, or placebo+letrozole). Following the permanent stop of the enrollment in the buparlisib arm, the target number of 60 patients per arm in each cohort remains unchanged for the alpelisib+letrozole and placebo+letrozole arms. However a lower number of patients will be randomized to buparlisib+letrozole.

Within the placebo+letrozole arm, patients will receive matching alpelisib (or buparlisib placebo, respectively only before amendment 5). The placebo groups within each cohort will be pooled together providing a total of 60 patients in placebo+letrozole within each cohort.

With 60 patients in the two arms alpelisib+letrole and placebo+letrozole within each cohort, the assessment of the PoC for alpelisb will have the following operating characteristics, using the PoC criteria described in Section 4.7.1 and assuming a pCR rate of 5% and an ORR of 45% in the letrozole arm:

True Treatment Effect on pCR (absolute increase in %)	True Treatment Effect on ORR (absolute increase in %)	Probability that PoC is declared on pCR or ORR
0	0	0.014
	0.2	0.484
	0.25	0.684
	0.3	0.861
0.05	0	0.119
	0.2	0.520
	0.25	0.718
	0.3	0.875
0.1	0	0.437
	0.2	0.692
	0.25	0.823
	0.3	0.921
0.15	0	0.759

True Treatment Effect on pCR (absolute increase in %)	**True Treatment Effect on ORR (absolute increase in %)**	**Probability that PoC is declared on pCR or ORR**
	0.2	0.870
	0.25	0.926
	0.3	0.966
0.2	0	0.933
	0.2	0.963
	0.25	0.978
	0.3	0.990

5 Change to protocol specified analyses

The following main changes have been made as compared to the protocol specified analyses:

- Definition of the Per Protocol Set will not be restricted to patients who have completed 24 weeks of therapy as it would lead to exclusion of all patients who have progressed prior to 24 weeks, which is too restrictive. Also, it will not exclude patients with no post-baseline RECIST assessment, and those patients will be considered as non-responders in the per-protocol set analysis.
- For biomarkers, analysis of ORR and pCR by PIK3CA cohort based on ctDNA (secondary objective of the protocol) or analysis of NGS data (exploratory objective) is not covered in this SAP for the CSR, since it is foreseen that those data will not be available before the database lock. Depending on the feasibility of the assay, they will be described in a separate report.
- All exploratory analyses planned only on pCR (such as analysis regardless of PIK3CA mutational status, or assessment of the anti-tumor activity of a PI3K inhibitor) will be repeated on ORR as well.

6 Appendix

6.1 Imputation rules

All imputation rules will be provided in full details in the PDS and the most updated rules as mentioned in the PDS will be followed.

6.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record

Use the start date of that record.

Subjects with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

6.1.2 AE, ConMeds and safety assessment date imputation

Table 6-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 6-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

6.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment 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 the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. 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.

6.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

6.3 Laboratory parameters derivations

Grade categorization of lab 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. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE 4.03, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as ‘<X’ (i.e. below limit of detection) or ‘>X’, prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

6.4 Statistical models

Proof of concept

The methodology is described in section 3.10.1.

Confidence interval for binary endpoint rate (e.g. Breast Conserving Surgery)

Responses will be summarized in terms of percentage rates with two-sided 80% and 95% confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

Confidence interval for response rate difference (e.g. ORR or pCR)

The difference in proportions response will be computed as alpelisib – placebo or buparlisib – placebo.

The two-sided 80% and 95% confidence intervals of the difference of proportions between two groups will be estimated by the exact unconditional confidence limits using the score statistic [Chan and Zhang 1999]. It will be implemented via SAS procedure FREQ with the TABLES statement and RISKDIFF option in the EXACT statement.

The SAS syntax is specified as follows:

```
PROC FREQ DATA = <input_dataset>;
  TABLES <treat_var> * <response> / riskdiff(cl=(exact));
  EXACT RISKDIFF(method=FMSCORE);
RUN;
```

7 References

Allison PD (2000). Survival analysis using the SAS system. Cary, NC, SAS Institute Inc.

Chan, I. S. F. and Zhang, Z. (1999). Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 55, 1202-1209

Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26, 404-413.

Ellis MJ, Tao Y, Luo J, et al. (2008). Outcome prediction for estrogen receptor – positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst 100, 1380-1388.

FDA (2007). Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, US Department of Health and Human Services.

International Conference on Harmonization. E9: Statistical Principles for Clinical Trials.

Neuenschwander B, Branson M, Gsponer T (2008). Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine 27, 2420-2439.

Spiegelhalter DJ, Abrams KR, Myles JP (2004). Bayesian approaches to clinical trials and health-care evaluation. Chichester: Wiley.