NOVARTIS

Clinical Development

Alpelisib (BYL719)

Protocol CBYL719A2201 / 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

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List of abbreviations

ADA	American Diabetes Association
AE	Adverse Event
AI	Aromatase inhibitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
aPTT	Activated Partial thromboplastin time
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ARA	Acid Reducing Agents
b.i.d./BID	*bis in diem*/twice a day
BC	Breast cancer
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Cells Blood Count
ctDNA	Circulating tumor DNA
CDP	Clinical Development Plan
CPK	Creatine Phosphokinase
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed Tomography
CTT	Clinical Trial Team
CYP	Cytochrome P
DDI	Drug-Drug Interaction
DILI	Drug-induced liver injury
DLCO	Carbon monoxyde diffusing capacity
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EIAED	Enzyme-inducing anti-epileptic drug
EOT	End of Treatment
ER	Estrogen receptor
FAS	Full Analysis Set
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GAD-7	General Anxiety Disorder
GCP	Good Clinical Practice
GGT	Gamma-glutamyltranspeptidase
GLP	Good Laboratory Practice
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B surface Antigen

[redacted]

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High density lipoprotein
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2 negative
HFHC	High-fat high-calorie
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Hormone Receptor
HSV	Herpes Simplex Virus
i.v.	intravenous(ly)
IC50	Half maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor 1
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFLC	Low-fat low-calorie
LFT	Liver Function Tests
LLOQ	Lower Limits of Quantitation
LTED	Long Term Estrogen Deprivation
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple Gated acquisition scan
ORR	Overall Response Rate
p.o.	*per os*/by mouth/orally
pCR	pathologic complete response
PEPI	Preoperative endocrine prognostic index
PgR	progesterone receptor
PHI	Protected Health Information
PHQ-9	PHQ-9 Patient Health Questionnaire
PI3K	PI3K Phosphatidylinositol-3-kinase
PIK3CA	PIK3CA Gene which encodes the p110alpha catalytic subunit
PK	Pharmacokinetics
PLT	Platelets

[redacted]

PPS	Per Protocol Set
PTEN	Phosphatase and tensin homolog
PTT	partial thromboplastin time
QD	once a day
QTcF	Q-T interval in the ECG (corrected according to the formula of Fredericia)
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended phase two dose
SAE	Serious Adverse Event
SC	Steering Committee
TBL	Total bilirubin
UDPGA	Uridine 5'-diphospho-glucuronic acid
UGT1A4	UDP-glucuronosyltransferase 1 family, polypeptide A4
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
WNL	Within Normal Limits

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when a patient permanently discontinues study treatment for any reason;
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

[redacted]

Amendment 7 (18-Oct-2016)

As of October 14, 2016, 325 patients have been randomized in study CBYL719A2201 of these, 121 patients have been randomized to buparlisib/buparlisib-placebo arms, and 204 patients have been randomized to BYL719/BYL719 (Alpelisib)-placebo. All patients randomized to buparlisib/buparlisib-placebo arm have discontinued study treatment. 66 patients are taking study treatment in BYL719/BYL719 (Alpelisib)-placebo arm. PIK3CA wild-type cohort enrollment was completed on August 23, 2016 and 7 patients remain to be enrolled in the PIK3CA mutant cohort.

The purpose of this protocol amendment is:

- To provide more detailed treatment guidance for AE of hyperglycemia and update on AE management for skin toxicity following an advisory-board meeting recommendation
- To update the general administration guidelines for alpelisib/placebo based on a food effect and acid reducing agents (ARA) drug-drug interaction (DDI) study: alpelisib must be taken with a meal regardless of composition or overall calorie intake. A staggered approach for co-administration of alpelisib with acid reducing agents is no longer required

Amendment 7 rationale

Updated guidance for the management of hyperglycemia and skin toxicity Adverse Events

In 2016, a program-wide assessment of available data on alpelisib-induced hyperglycemia and skin toxicity was conducted and results were shared and discussed with an advisory board consisting of oncologists, endocrinologists and a dermatopathologist. The management guidelines were reviewed and more detailed guidance for the management of alpelisib induced hyperglycemia and skin toxicity has been developed. For skin toxicity of any grade, treatment with topical steroids 3-4 times daily is recommended. Oral anti-histamines are indicated in case of skin toxicity accompanied with burning, stinging or pruritus or prophylactic in case of hypersensitivity in patients' medical history, e.g. seasonal allergy, allergic asthma, drug-induced exanthema in the past. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity.

Table 6.4, Criteria for interruption and re-initiation of alpelisib/placebo treatment, has been updated to provide more detailed guidance than the previous version of the protocol.

Update of general administration guidelines for alpelisib/placebo

Based on *in vitro* solubility data, alpelisib has been administered after a light meal breakfast in most clinical trials including the first-in-man trial CBYL719X2101. The impact of food on the absorption of alpelisib was recently investigated in a clinical trial in healthy volunteers (Study CBYL719A2103) after a single 300 mg oral dose of alpelisib. Compared to the fasted state a high-fat high-calorie (HFHC) meal increased – on average – AUCinf by 73% and Cmax by 84%, and a low-fat low-calorie (LFLC) meal increased AUCinf by 77% and Cmax by 145%, confirming a positive food effect on absorption of alpelisib. No significant difference was found for AUCinf between LFLC and HFLC meals. Overall, data from study CBYL719A2103 confirmed that alpelisib must continue to be given with a meal. However as

[redacted]

neither composition nor overall calorie intake have shown an effect, the light meal restriction can be lifted, allowing also some further flexibility with regards to alpelisib intake during the day if dose administration has been forgotten in the morning.

In vitro, alpelisib demonstrates a pH-dependent solubility profile, with a >100-fold drop in thermodynamic solubility between pH 1 (> 5 mg/ml) and pH 6.8 (0.02 mg/ml). Therefore acid reducing agents (ARAs, e.g. proton-pump inhibitors, H2-antagonists and antacids) may alter the solubility of alpelisib and hence its bioavailability. Co-administration of an acid-reducing agent (ARA) in presence or in absence of a meal was investigated in the same clinical trial. The co-administration of the H2 receptor antagonist ranitidine in combination with a single 300 mg oral dose of alpelisib slightly reduced the bioavailability of alpelisib and decreased overall exposure of alpelisib. In the presence of a LFLC meal, AUCinf was decreased – on average – by 21% and Cmax by 36% with ranitidine. In the absence of food, the effect was more pronounced with a 30% decrease in AUCinf and a 51% decrease in Cmax with ranitidine compared to the fasted state without co-administration of ranitidine. As the study showed a non-clinically relevant 21% decrease in exposure of alpelisib in combination with ranitidine when given with a LFLC meal, ARAs can be administered concomitantly and do not have to be administered in a staggered manner. Hence, the restriction about the staggered administration of H2-receptor antagonists as well as the avoidance of proton-pump inhibitors has been removed.

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

Protocol Changes:

The changes are outlined as follows in order of appearance:

- List of abbreviations has been updated
- Section 2.6 Risks and Benefits has been added to the protocol
- Section 6.1.2.1 general guidelines on alpelisib/placebo dosing instructions and recommendations have been updated based on the results of a food effect and ARA DDI study for alpelisib
- Section 6.3.1.1, Table 6-4 has been updated to provide more guidance for hyperglycemia, skin toxicity management and in case of acute pancreatitis
- Section 6.3.2.3.2 has been updated per update of Table 6-4
- Section 6.3.2.3.5 has been updated per update of Table 6-4
- Section 6.4.1.3 has been updated as per approved program standard language
- Section 6.4.1.9 has been updated to reflect the changes with respect to the co-administration of acid reducing agents, lifting the restriction for the use of proton-pump-inhibitors and staggered dosing of other gastric protection agents
- Section 7.2.3 has been updated based on the results of a food effect and ARA DDI study for alpelisib
- Section 8.1.1 Adverse events Definitions and reporting has been updated to match with Novartis' updates processes
- Section 8.1.3 Adverse events of special interest has been added to the protocol

[redacted]

- Section 8.2.2 SAE reporting has been updated to match with Novartis' updates processes
- Section 8.4 Pregnancies has been added to match Novartis' protocol template language

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

IRB/IEC/HA

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

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

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

Amendment 6 (04-May-2016)

As of March 22nd, 2016, 241 patients have been randomized in the study CBYL719A2201 Of these, 121 patients have been randomized to buparlisib/buparlisib-placebo arms, and 120 patients have been randomized to BYL719/BYL719-placebo. As of this date no patients have been enrolled into amendment 5 of the trial pending local approvals.

Amendment rationale

The purpose of this protocol amendment is to correct a technical publishing issue identified in Protocol Amendment V05:

- Table 6-4 “Cardiac-QTC prolongation” adverse drug reaction text was hidden, not expanded in the PDF version. Consequently, the full wording for the dose adjustment and related management recommendations for Cardiac – QTC prolongation appeared as missing, only partial wording. This issue is corrected in Amendment 6.

Protocol Changes:

Table -6-4: Formatting error of Cardiac QTC prolongation row is corrected.

IRB/IEC/HA

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

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

Amendment 5

As of December 31, 2015, 241 patients have been randomized in the study CBYL719A2201 Of these, 121 patients have been randomized to buparlisib/buparlisib-placebo arms, and 120 patients have been randomized to BYL719/BYL719-placebo.

[redacted]

Amendment rationale

The purpose of this protocol amendment is:

- To update the clinical study protocol according to the decision made by the Sponsor on Dec 22, 2015 to stop permanently the accrual in the buparlisib/buparlisib-placebo treatment arms,
- To change the assessment of the anti-tumor activity of buparlisib/buparlisib-placebo plus letrozole into an exploratory objective.
- To change the Overall Response Rate (ORR) from being secondary to primary endpoint.
- To change the assessment of the anti-tumor activity of BYL719 plus letrozole versus letrozole alone on pCR and ORR by PIK3CA status based on circulating tumor DNA (ctDNA), from exploratory to secondary objective.
- To stop the conduct of the central review for pathological response.
- To implement regular safety review of unblinded data performed by a Data Monitoring Committee (DMC)
- To update the inclusion criteria with regards to baseline glucose metabolism parameters, potassium, and values of amylase and lipase.
- To retire the exclusion criteria related to psychiatric disorders and viral hepatitis, and update the exclusion criterion on uncontrolled medical conditions.
- To update the safety monitoring and guidance for the management of hyperglycemia, skin toxicity, and pancreatitis
- To revise and update the Appendix 14-1 "List of concomitant medications" due to a recent re-classification of drugs with QT prolongation
- To update the language of some protocol sections as part of a general update implemented across the program (e.g. safety monitoring for liver toxicity; language for Adverse Events reporting)

Rationale for stopping accrual in buparlisib/buparlisib-placebo treatment arms

As part of a program-wide assessment of Buparlisib (BKM120) in breast cancer across different indications, and considering the modest efficacy observed in the Belle-2 study (Baselga, 2015), Novartis has decided not to pursue further the development of buparlisib in early-stage breast cancer. On December 8, 2015 a pre-planned blinded pooled safety analysis of the CBYL719A2201 study (N=178) was performed for both treatment arms, i.e. Buparlisib/placebo + Letrozole and BYL719/placebo + Letrozole. Eighty-nine patients had been allocated to each of the two treatment arms. There were no new or unexpected safety findings compared with a prior analysis performed in June 2015. The results of these analyses and the decision to discontinue the development of buparlisib in early-stage breast cancer were presented and endorsed by the study Steering Committee. Ongoing patients receiving buparlisib/buparlisib-placebo and letrozole may continue the treatment based on the investigator's clinical judgement. Patients recruited under buparlisib/buparlisib-placebo will still be part of the statistical analysis. However, the assessment of the anti-tumor activity of buparlisib/buparlisib-placebo plus letrozole will now become an exploratory objective.

[redacted]

Rationale for adding ORR as a primary objective

The rationale for changing ORR from secondary to primary endpoint in this study is supported by the high clinical relevance of ORR in the neoadjuvant setting of hormone receptor-positive breast cancer (Benda 2004). In addition, in order to be aligned with the most recent neoadjuvant endocrine treatment clinical trials where ORR has been selected as the primary objective (Saura 2014, Fontein 2014), this study will now also assess ORR as primary objective. Thus, this study will now have both pCR rate and ORR as primary endpoints.

Rationale for assessing efficacy based on PIK3CA mutational status determined on ctDNA

Circulating tumor DNA is a new tool for mutation identification. A recent study demonstrated that assessments in ctDNA allowed capturing the heterogeneity and real-time status of the tumor by detecting all mutations identified in either the primary tumor or in the metastatic lesions (De Mattos-Arruda 2014). Technology evolution allows for a reliable detection of molecular alterations in ctDNA, specifically for PIK3CA mutations which were successfully detected in ctDNA from metastatic breast cancer patients (Board 2010, Higgins 2012). In addition, data reported recently suggest a relationship between PIK3CA mutations detected in ctDNA and response to BYL719 (Shah 2015).

Hence, exploring the role of ctDNA in the context of neoadjuvant treatment is critical and the previously exploratory objective of PIK3CA mutation analysis in ctDNA will now become a secondary objective in order to assess the association between ctDNA PIK3CA mutational status and clinical outcome. [redacted]

Rationale for stopping the conduct of central review for pathological response

As of Dec 31, 2015, one hundred and five patients had undergone surgery. Samples for central review of pathological response had been received for only 35 (33%) of them. In addition, the central review has been performed in 25 (24%) of the cases; in the remaining it was not possible due to insufficient material sent from the sites.

Therefore, given the substantial operational challenges encountered, the central assessment of pathological responses will no longer be conducted and the corresponding supportive analysis will not be done. The assessment of pathological response performed by the local investigator remains the primary endpoint of the study. Therefore removing the central review will not affect the primary endpoint.

Rationale for implementing a Data Monitoring Committee

Safety evaluations across the BYL719 program are regularly conducted. In order to evaluate also unblinded safety data from the current study, CBYL719A2201, a Data Monitoring Committee (DMC) will be implemented. The DMC will be composed of Novartis personnel who are not directly involved in the BYL719 program and will review ongoing safety data from the study (National Health Service [NHS]. National Patient Safety Agency. National

[redacted]

Research Ethics Service (2010): Data monitoring committees in clinical trials. Guidance for Research Ethics Committees). The recommendations of the internal DMC will be regularly shared with the study Steering Committee members.

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

An overall assessment of the incidence and potential risk factors for BYL719-induced hyperglycemia has recently been conducted across the program in more than 1000 patients treated with BYL719 at different doses, in different tumor types, and as part of different treatment regimens. A higher risk to develop grade 3/4 hyperglycemia was observed in patients with HbA1c between 6.5 and 8.0% (Novartis Internal Data). In addition, and according to the American Diabetes Association (ADA) guidelines with regards to glycemic targets in patients with diabetes mellitus, a value of HbA1c >6.5% may represent a status of not-optimally controlled diabetes. The equivalent FPG values for an HbA1c of 6.5% are around 140 mg/dl. Therefore, in an attempt to reduce the risk of BYL719-induced hyperglycemia and in alignment with ADA guidelines, the inclusion criterion #13 for FPG and HbA1c has been modified as follows: FPG ≤ 140 mg/dl and HbA1c < 6.5%

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

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

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

Therefore, in the current protocol and across the BYL719 development program, the following changes have been implemented: modification of the inclusion criteria; now including fasting amylase and lipase added to the panel of investigations at screening; frequent monitoring of amylase and lipase; and detailed dose modification guidelines in case of asymptomatic increases of amylase and/or lipase or clinical signs of pancreatitis included.

Rationale for the modification of the potassium inclusion criterion

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

[redacted]

Rationale for retiring the exclusion criteria related to psychiatric disorders and to viral hepatitis

As psychiatric disorders and viral hepatitis re-activation risk have not been observed so far in BYL719 studies (BYL719 Investigator's Brochure), and these risks were expected to be related only to buparlisib, the exclusion criteria #11 (PHQ-9 questionnaire and related score), #12 (response to question "9" on PHQ-9 questionnaire), #13 (GAD-7 questionnaire and related score), #14 (psychiatric disorders), and #15 (anxiety); and exclusion criteria #28 (screening for viral hepatitis), have been retired.

Rationale for updating the exclusion criterion related to uncontrolled medical conditions

Exclusion criteria #10 explains that patients with uncontrolled medical conditions, based on investigator's clinical judgment, are to be excluded, and some examples are given in parenthesis. Those medical situations, given as examples in parenthesis, but already outlined in individual stand-alone exclusion criteria, such as pancreatitis (exclusion criterion #28), have been deleted. For uncontrolled hypertension, a new exclusion criterion has been added (#29) to provide more clarity on the blood pressure values required for study entry.

Rationale for updating the skin toxicity management section

An overall assessment of the incidence of skin toxicity and potential preventive actions has recently been conducted across the alpelisib program. Some improvement in the severity of rash has been observed with the prophylactic use of non-sedating oral anti-histamines (Dickler 2014, Mayer 2014), however conclusive data are not yet available. Thus, the use of prophylactic oral non-sedating anti-histamines (e.g. cetirizine or equivalent), is now recommended based on investigators' clinical judgment.

Protocol Changes

Protocol summary section: Addition of ORR from secondary to primary objective and of PIK3CA ctDNA from exploratory to secondary endpoint.

Section 2.2: Addition of ORR from secondary to primary objective.

Section 2.2.1: Clarification on the material used for assessment of mutation status (tumor tissue).

Section 3, Table 3-1: Change of ORR from secondary to primary objective and related endpoint; and of PIK3CA ctDNA from exploratory to secondary objective and related endpoints. Change for safety analysis by PIK3CA cohort to safety analysis overall.

Figure 4-1: Description of study design was updated to reflect the stop of the recruitment in the the buparlisib/buparlisib-placebo treatment arm.

Section 4.1: Deletion of the central review of surgical specimen as supportive measure of primary endpoint assessment. Clarification of C1D15 biopsy time-point. Clarification on

[redacted]

treatment phase section (update randomization number). Clarification on study treatment continuation for patients randomized to buparlisib/buparlisib-placebo treatment arms.

Section 4.2: Timing of interim and design adaptations section has been added.

Section 5.2: Inclusion criterion #13 has been updated to reflect the changes in baseline FPG, Hb1Ac, amylase, lipase and potassium.

Section 5.2: Inclusion criterion #14: Clarification of study starting point.

Section 5.3: Exclusion criteria #3: update of compounds to be received by the patient.

Section 5.3: Exclusion criterion #5: Clarification of discontinuation of systemic therapy, radiotherapy, or hormone-replacement therapy.

Section 5.3: Exclusion criterion #6 on diabetes mellitus has been updated for more clarity.

Section 5.3: Exclusion criterion #10 has been updated for more clarity.

Section 5.3: Exclusion criterion #11, 12, 13, 14, 15 and 28 have been retired.

Section 5.3: Exclusion criterion #29 has been added for more clarity.

Section 5.3: Exclusion criterion # 30, related to uncontrolled hypertension, has been added for more clarity.

Section 6.1: Study treatment phase has been updated to reflect the discontinuation of the buparlisib/buparlisib-placebo treatment arm.

Section 6.1.4: Definition of treatment cycle is clarified for frequency.

Section 6.3.1.1 – Table 6.4: Criteria for interruption and re-initiation of BYL719/placebo or buparlisib/placebo table has been updated for the following adverse event reactions: AST/ALT, hyperglycemia, and pancreatitis. Rash, rash maculopapular, rash generalized, and pruritushave been grouped under Skin Toxicities in order to provide consistent and uniform management recommedations.

Section 6.3.2.1: The follow-up guidance on potential drug-induced liver injury (DILI) cases section has been added.

Section 6.3.2.2: The follow-up guidance on amylase or lipase elevation (≥ CTCAE Grade 3) has been added.

Section 6.3.2.3.2: The follow-up guidance on BYL719-induced hyperglycemia has been added.

Section 6.3.2.3.4: Guidelines for the treatment of study drug induced skin toxicity has been updated for more clarity.

Section 6.4: Clarification has been made with regards to the collection of the information with regards to the breast cancer diagnostic biopsy under the “Prior antineoplastic therapy eCRF”.

[redacted]

Section 6.4.1.5: Changes in the wording for more detailed explanation of coagulation.

Section 6.4.1.6: Removal of Contraceptives section as it is not applicable for the study population (postmenopausal women).

Section 6.4.2.3: Drugs with a known risk of QT prolongation or of causing Torsades de Pointes section has been updated.

Section 6.5.2: The treatment assignment or randomization section has been updated on discontinuation buparlisib/placebo arm and randomization number.

Section 6.5.3: The treatment blinding section has been updated.

Section 7.1: Table 7.1 -Update the category from "D" to "S" for the PIK3CA mutation and Ki67 status results entered in IRT item. Fasting amylase analysis was added, as well as collection of antineoplastic therapy data after discontinuation of study treatment for more clarity. The tumor biopsy at screening, at C1D15, and post-treatment follow up phase has been added to the Visit Evaluation Schedule table for more clarity. Clarification of the acknowledge of receipt of adequate tumor tissue has been added.

Fasting plasma amylase has been added on day of every cycle.

Section 7.1.1: Clarification on the material used for assessment of mutation status (tumor tissue).

Section 7.1.2, Section 7.1.2.1 and Section 7.1.3: Removal of buparlisib/placebo from screening section.

Section 7.1.2.2: Information to be collected on screen failures has been updated for clarity.

Section 7.1.2.3: Patients demographics and other baseline characteristics section has been updated for clarity and viral hepatitis serology (with the change of Exclusion criteria #28) and patient self-rating mood questionnaires have been removed.

Section 7.1.6: The follow up safety evaluation has been updated for clarity to mention that any antineoplastic therapy given until the surgery will be recorded in the eCRF.

Section 7.1.8: Deletion of the central review of surgical specimen.Section 7.2.1: Addition of ORR from secondary to primary efficacy endpoint and subsequent update in the pCR assessment.

Section 7.2.2.2: The wording for vital signs was refined for consistency with CRF page name.

Section 7.2.2.5: The hepatotoxixity testing was reworded for more clarity.

Section 7.2.2.5: Table 7-4: Biochemistry section was reviewed for consistency with table 7.1.

Section 7.2.2.5.6: The viral hepatitis serology test was reviewed for more clarity.

[redacted]

Section 7.2.2.6: Patient self-reported mood questionnaires and footnotes of table 7-6 have been updated for clarity for patients still under buparlisib/placebo treatment.

Section 7.2.3: Pharmacokinetics section has been updated with the removal of buparlisib/placebo wording per protocol changes.

Section 7.2.4.1: Table 7-9: Biomarker collection plan has been clarified (tumor DNA).

Section 7.2.4.3.1: Change in the timelines for sending the tumor tissue collected to laboratory based on actual study logistic experience.

Section 7.2.4.3.2: Blood collection plan was clarified.

Section 7.2.4.3.3: Central review of pCR was deleted and additional wording on surgical specimen has been added for more clarity.

Section 7.2.4.4: Reworded for more clarity.

Section 8.5: Data monitoring committee section added per protocol changes.

Section 9.4: Data management and quality control section updated with fasting lipase and amylase, ALP and Creatinine to align with the eCRF.

Section 10.1.2: Update of the safety set definition without considering at least one post-baseline safety assessment and of the treatment received as per new protocol template.

Section 10.1.3: Addition of RECIST evaluation in the PPS definition for consistency with the new added primary endpoint ORR and clarification as per new protocol template.

Section 10.1.4: The pharmacokinetic analysis set was clarified.

Section 10.1.4.2: Revision due to current course of the study in the BYL719 Full Sampling Pharmacokinetic Analysis Set (BYL719 FPAS).

Section 10.1.4.4: Revision due to current course of the study in the Buparlisib Full Sampling Pharmacokinetic Analysis Set (BKM120 FPAS).

Section 10.1.4.6: Revision due to current course of the study in the Letrozole Full Sampling Pharmacokinetic Analysis Set (LZ FPAS).

Section 10.1.5: Other analysis sets section added as per protocol template.

Section 10.2.2: Clarifications added regarding analysis sets used to describe demographics, analysis pooled on cohorts and description of relevant medical histories and current medical condition at baseline.

Section 10.3: Clarifications added regarding analysis set and methods used for descriptions of treatments, and that the duration of exposure to study treatment, the number of dose adjustements and reasons will also be described.

Section 10.4: Addition of the primary objective related to ORR and removal of buparlisib from the primary objectives as it is now an exploratory objective.

Section 10.4.1: Addition of ORR as a primary efficacy endpoint and of its definition.

[redacted]

Section 10.4.2: Addition of the statistical hypothesis, model, and method of analysis for ORR and of the Proof-of-Concept based on pCR and ORR. Deletion of the possibility to analyze one cohort if it completes the study earlier. Updates due to the assessment of the anti-tumor activity of buparlisib which is now an exploratory objective.

Section 10.4.3: Description of the rules applying for handling of missing values / censoring / discontinuations for ORR and reminder on the rules for pCR mentioned in section 10.4.1.

Section 10.4.4: Update of the supportive analyses section with additional supportive analyses to be performed if appropriate with specifications given in the RAP.

Section 10.5.2: Deletion of analysis related to ORR from the secondary objective section (since upgraded to primary efficacy endpoint) and addition of secondary analysis by PIK3CA status based on ctDNA.

Section 10.5.3.1: Deletion of safety analysis by cohort and addition of safety analysis separately for the continuous schedule and for the 5 days-on / 2 days-off schedule of buparlisib. Addition that selected safety outputs will be produced for the DMC.

Section 10.5.3.2: Adverse events section has been updated for clarification: summary tables for non-serious adverse events and AESI, all deaths both on-treatment and post-treatment, deletion of some details on SEC.

Section 10.5.3.3 Deletion of the use of clinical meaningful limits for laboratory abnormalitiesand addition of summary tables regardless of baseline value.

Section 10.5.3.4: ECG table type is changed to correct a mistake (“shift table of ECG” to “notable ECG parameter changes”) and analysis for cardiac imaging is specified.

Section 10.5.3.5: Tolerability section has been updated for clarity.

Section 10.5.4: Update of a technic reference in the pharmacokinetics section. Addition that T1/2 will be applicable to BYL719 only and that effective half-life will be provided instead for buparlisib, as T1/2 cannot be properly estimated for buparlisib due to its long half-life.

Section 10.5.5: Resource utilization section has been renumbered.

Section 10.5.6: Patient-reported outcomes section has been renumbered.

Section 10.6: Exploratory objectives section has been moved in order to have the Biomarker section in the exploratory objectives section for consistency with the objectives section.

Section 10.6.1.3.2: Addition that the concordance/discordance on PIK3CA mutation status between ctDNA and tumor tissue at study entry may be performed. Clarification added on exploratory analyses.

Section 10.6.2: Addition of the assessment of the anti-tumor efficacy for buparlisib as an exploratory analysis. Addition of a missing analysis related to the exploratory efficacy objective regardless of PIK3CA mutational status and deletion of analysis using other pCR definitions.

Section 10.8: Update of the sample size section taking into account the inclusion of ORR as a primary efficacy endpoint.

Section 13: Update of references.

[redacted]

Section 14.3-Appendix 3: Deletion of the "BCSS score" in the preoperative endocrine prognostic index (PEPI) score Table 14-12 as it will not be used for the PEPI analysis.

IRB/IEC/HA

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

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

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment. A separate ICF "BYL719 only" will be signed by the newly screened patients, and an updated ICF will be signed by patients enrolled prior to the current Protocol Amendment implementation.

Amendment 4

As of July 20th, 2015, 146 patients have been randomized in the study CBYL719A2201.

Amendment rationale

The main purpose of this protocol amendment is to provide additional guidance to investigators around management of liver toxicities.

Alterations in liver function tests (LFTs) have been commonly observed in clinical trials with buparlisib as an investigational agent. These include mostly transient increases in transaminase enzymes (ALT and/or AST), which often occur during the first 6 to 8 weeks of buparlisib treatment, and rarely are associated with signs/symptoms of impaired liver function. Current buparlisib protocols have conservative inclusion criteria for baseline LFTs with close monitoring guidelines to be followed during the treatment and stringent dose modification/interruption criteria.

In March 2015, a search for potential drug-induced liver injury (DILI) cases in buparlisib Novartis-sponsored trials using conservative biochemical criteria (e.g. AST/ALT >3.0x ULN and TBL>2.0xULN at any time during the treatment period, regardless of causality) identified 21 potential DILI candidates in the blinded pivotal breast cancer trials CBKM120F2302 and CBKM120F2303 conducted in combination with fulvestrant (HR-positive HER2-negative disease). No cases were identified in the unblinded CBKM120F2202 study in combination with paclitaxel (HER2-negative disease). Upon medical review, most of these occurred in the context of disease progression in terminally-ill advanced cancer patients and/or were confounded by other causes. However, for some of the DILI candidates causal relationship with study treatment is possible. The liver abnormalities generally have been transient and reversible; so far, no fatal case has been reported across any of the buparlisib studies as a result of study drug(s) related liver toxicity.

Six of the DILI candidates were further consistent with Hy's law criteria and probable causal relationship to blinded study medication (all enrolled in CBKM120F2302 study); two of these six patients had liver metastasis at baseline, one patient took concurrent herbal medications,

[redacted]

and one patient had >50% unconjugated peak bilirubin suggesting a component of Gilbert's syndrome or hemolysis as possible contributing or confounding factors (the latter was considered equivocal Hy's law based on external expert review). All Hy's Law candidates have recovered upon treatment discontinuation except one patient for whom outcome is not available because the patient refused to return for safety follow-up.

In May 2015 one additional DILI candidate was identified in the study CBYL719A2201, in a patient randomized to the buparlisib/placebo treatment arm. Briefly, a 55-year-old woman diagnosed with early-stage, non-metastatic breast cancer, and without any prior significant medical history or pre-existing risk factors for liver disease, presented on cycle 2 day 1 with elevated ALT (grade 3) and elevated AST (grade 2).The study treatment was stopped five days after the transaminases increase occurred. ALT and AST continued to increase (grade 4), and this was accompanied by grade 4 bilirubin elevation. Alkaline phosphatase was also elevated (grade 1). The patient remained asymptomatic during the entire period. Viral hepatitis serology and liver imaging did not reveal any findings. All previously elevated laboratory values returned to normal after six weeks.

Updated liver safety including the identified DILI/Hy's law candidates in studies CBKM120F2302 and CBKM120F2303 were presented to the Data Monitoring Committee (DMC) for these trials on 9-April-2015; the DMC noted no change or additional liver safety concerns and recommended continuing the respective studies as planned.

An Aggregated Safety Finding Report was submitted to Health Authorities and all investigators participating in buparlisib studies informing them about the liver findings. In addition, Novartis decided to update the current liver-related safety measures in ongoing protocols to enhance patient safety. Therefore, the main purpose of this protocol amendment is to provide additional guidance to investigators around management of liver toxicities as outlined below.

Changes in the background section:

- Update of the clinical background section on liver toxicity to align with the protocol amendment rationale.
- **Changes in the exclusion criteria:**
- Exclusion of patients with an acute viral hepatitis or with a history of chronic or active HBV or HCV infection (testing not mandatory).
- **Changes in the section on management and follow-up for selected toxicities:**
- Addition of hepatotoxicity management guidelines.
- **Changes to the visit schedule and assessments:**
- Clarification of laboratory parameters collection plan and viral hepatitis testing.
- In addition, clarifications have been made with regards to the definition of postmenopausal status at study entry and hormone-replacement therapy. The rationale for these clarifications is based on the fact that bilateral oophorectomy can effectively render patients postmenopausal, and has a therapeutic effect in hormone-sensitive breast cancer. Therefore, it can be considered an endocrine treatment in its own right. In those patients where bilateral oophorectomy was performed, this procedure must have been performed at least 6 months prior to study entry and prior to the diagnosis of breast cancer, in order to

[redacted]

ensure that women are truly menopausal at study entry, and to avoid any potential influence of bilateral oophorectomy in the study treatment effect (Neven et al, 2015). Similarly, hormone-replacement therapy in postmenopausal women can also influence the biology of hormone receptor positive breast cancer and its response to endocrine treatment. Therefore, a minimum wash out period of 28 days is mandated for those women who were taking hormone replacement therapy.

- Changes in the inclusion criteria #3: Patient must be postmenopausal at the time of breast cancer diagnosis. For those women that have had a prior bilateral oophorectomy, this procedure must have been performed at least 6 months before the diagnosis of breast cancer in order to be considered post-menopausal.
- Changes in the exclusion criteria #5: Patients receiving hormone-replacement therapy must have discontinued such therapy 28 days before study entry.
- In accordance to the Summary of Product Characteristics of letrozole clarifications have also been made with regards to the patient population of the study (i.e. patients for whom immediate chemotherapy or immediate surgery is indicated are not eligible).
- Changes in the patient population: clarification that patients for whom immediate chemotherapy or immediate surgery is indicated are not eligible.
- **Changes to the protocol**
- The following sections have been changed in the amended protocol:
- Section 1.2.1.2 Clinical experience: addition of the outcome from a recent medical review for the liver toxicity.
- Section 5.3 Exclusion criteria:
- Addition of exclusion criterion #28 to exclude patients with an acute viral hepatitis or a history of chronic or active HBV or HCV infection.
- Section 6.3.1.1 - Table 6-4 (Criteria for interruption and re-initiation of BYL719/placebo or buparlisib/placebo): Clarification of the management of AST or ALT side effects.
- Section 6.3.2.1.5 Additional management and follow-up for selected toxicities: New section added “Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BYL719/placebo or buparlisib/placebo” including detailed liver event follow-up assessments and close monitoring measures.
- Section 7.1 Study flow and visit schedule - Table 7-1 (Visit evaluation schedule): addition of hepatotoxicity follow-up testing/procedures.
- Section 7.1.2.3 Patient demographics and other baseline characteristics: addition of viral hepatitis serology.
- Section 7.2.2.5 Laboratory evaluations and Table 7-4 (Clinical laboratory parameters collection plan): addition of hepatotoxicity follow-up testing and procedures (Note: testing not mandatory). Updated full and partial biochemistry collections and parameters. Clarification on tests to be done fasting.
- Section 7.2.2.5.6: New section added “Viral hepatitis serology and other tests for hepatotoxicity follow-up”.
- Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

[redacted]

- Additional ChangesSection 5.1: Patient population has been clarified in alignment the therapeutic indications of letrozole laid out in the Summary of Product Characteristics.
- Section 5.2: Inclusion criteria: clarification in inclusion criterion #3 in those patients must be postmenopausal at the time of breast cancer diagnosis. For those women that have had a prior bilateral oophorectomy, this procedure must have been performed at least 6 months before the diagnosis of breast cancer in order to be considered post-menopausal.
  Clarification in inclusion criterion #4.
  Clarification in inclusion criterion #6.
- Section 5.3: Addition in the exclusion criterion #5 that patients receiving hormone-replacement therapy must have discontinued such therapy 28 days before study entry.
- Section 6.1.4: Clarification on treatment duration, including timing of surgery after finishing study treatment that includes letrozole.
- Section 6.3.1.1, Table 6-4: Dose adjustment and management recommendations for hyperglycemia have been described in more detail.
- Section 6.4.1.7 (Buparlisib paragraph): Reference was corrected.
- Section 6.4.2.3 Clarification that paragraph is also applicable for buparlisib and that either BYL719 or buparlisib need to be discontinued if study treatment is interrupted for > 28 days.
- Section 7.1 Table 7.1: Timing of assessment HbA1c, fasting lipase, fasting lipid profile, grouped under the time window of day -7 to day-1 to minimize patient visits and facilitate receipt of batched results from the central lab to the investigator at once.
- Section 7.1.1: Precision is brought for postmenauposal definition.
- Clarification on PIK3CA mutation status and Ki67 status procedure.
- Radiographic tumor assessments clarification in case of former source document.
- Section 7.1.2.3 and Table 7-1: Corrected section reference numbers for Laboratory evaluation, ECG and Cardiac imaging.
- Section 7.1.8: Breast Cancer Surgery: clarification that letrozole will be maintained until surgery when either BYL719/placebo or buparlisib/placebo has been prematurely discontinued.
- Section 7.2.1: Radiographic tumor assessments clarification in case of former source document Clarification on MRI/US procedure.
- Addtion of the FDA definition for pathological complete response.
- Section 7.2.2: ECG/MUGA clarification in case of former source document.
- Section 7.2.4: Biomarkers: Clarifications and renaming of tissue requirements and biopsies have been made to facilitate understanding and protocol compliance with regards to tumor tissue requirements and shipping. “Specimen 3” is now named “Cycle 1 Day 15 biopsy”. Figure 7-1 has been updated accordingly.
- Section 7.2.2.5, Table 7-4: Fasting and full biochemistry were defined.
- Section 7.2.2.5.2 Clarification on Biochemistry.
- Section 7.2.2.5.4: Clarification on INR.

[redacted]

- Section 7.2.4.1, Table 7-9 and section Section 7.2.4.3.2 and Section 7.2.4.4, Figure 7-1: Tumor tissue identification was changed for more clarity.
- Section 7.2.4.3.1: Clarification on tumor identification and on biomarker assessment procedure.
- Section 7.2.4.3.3: Rewording for more clarity.
- Section 7.2.4.4, Table 7-10: Rewording for more clarity.
- Section 13: Updated References.
- Section 14: Appendix 1 has been updated due to recent re-classification of the risk of certain QT prolonging drugs from possible / conditional risk to known risk. All other tables were also updated based on their sources.

IRB/IEC/HA

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

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

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

Amendment 3

Amendment rationale

The main purpose of this protocol amendment is to correct a typo identified in Inclusion criteria #4 and #13.

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

- Section 5.2: correct Inclusion criteria #4 from “T1c-Tc” to “T1c-T3”.
- Formatting issues identified in Inclusion criteria #13, INR and AST were re-aligned to be separate sub bullets as per the original protocol.

Amendment 2

Amendment rationale

As of January 23, 2015, 76 patients have been randomized in the study CBYL719A2201.

The main purpose of this protocol amendment is:

- To revise the dosing schedule of buparlisib, from 100 mg QD to 100 mg QD 5 days on/2 days off.
- To modify the guidelines for pneumonitis management that has been revised based on the Urgent Safety Measure released on Dec 19, 2014 following accumulation of pneumonitis ases up to nine (including three with fatal outcome) within the BYL719 development

[redacted]

program. The most recent fatal case was reported from the CLJM716X2103 trial (BYL719 in combination with the anti-HER-3 monoclonal antibody LJM716)."

- To modify and clarify some of the inclusion/exclusion criteria.
- To update clinical efficacy and safety data of both buparlisib and BYL719 as a result of new available data and in alignment with the latest Buparlisib and BYL719 Investigators' Brochure updates.
- To make administrative changes for clarification and typographical errors have been corrected.

Rationale for the change in the dosing schedule of buparlisib

The dosing schedule will change from 100 mg QD daily to 100 mg QD 5 days on/2 days off.

And recommended dose reductions for

- dose level -1: from 80 mg QD daily to 80 mg QD 5 days on/2 days off
- dose level -2: from 60 mg QD daily to 60 mg QD 5 days on/2 days off

The first blinded safety review of the CBYL719A2201 study (planned by protocol) was conducted on the first 27 patients enrolled (data cut off Oct 1st 2014). In the buparlisib/buparlisib placebo arms, among the 15 patients enrolled, 7 discontinued the study treatment: 5 for subject decision, and 2 for an adverse event (in both cases due to grade 4 transaminases increase). The overall aim of these changes is to improve tolerability and decrease severe side effects in buparlisib/buparlisibplacebo arms.

The intermittent dosing schedule of buparlisib (i.e. 5 days on/2 days off) has been investigated in two phase Ib studies conducted in HR-positive HER2-negative metastatic breast cancer (BC), showing less incidence of severe adverse events of the intermittent schedule when compared to continuous dosing. (Please refer to Section 1.2.2. and Section 1.2.4. for further details).

In addition, simulation by means of a Population PK model for buparlisib has also shown that the intermittent regimen has the benefit of decreasing Cmax while maintaining an efficacious level of exposure (Section 1.2.2.2.3).

Therefore, based on the abovementioned data and the preliminary safety findings in the current study in buparlisib/buparlisibplacebo arms, the present amendment buparlisib alters the current dosing schedule to intermittent administration 5 days on/2 days off.

Intermittent schedule is to be implemented for new patients after the amendment approval.

Rationale for the modifications in pneumonitis management

On 12, December 2014, Novartis issued an Investigator Notification regarding a patient on study CLJM716X2103 (combination of BYL719 and LJM716) with a serious, unexpected, possibly related adverse event of fatal pneumonitis. Subsequently, an Urgent Safety Measure (USM) was put in place for the overall BYL719 program assessment. A letter was sent to all sites and investigators participating in BYL719 studies on 19th December 2014, requiring them to implement the USM immediately to adequately protect the patients. Therefore, safety management guidelines have been updated (Section 6.3).

[redacted]

Rationale for the changes in the inclusion/exclusion criteria

- Inclusion criterion #4 (tumor stage) has been clarified: patients with the diagnosis of either multifocal or multicentric BC are allowed to participate. Similarly, patients with synchronous bilateral BC can also take part on the study provided only one unilateral tumor lesion is considered for study purposes (i.e. assessment of pathological complete response [pCR]). In addition, patients with cM0 (i+) staging are required to provide radiological evidence of no gross metastatic disease in order to qualify for study entry.
- The rationale for these clarifications reflects current clinical practice and international clinical guidelines for the use of neoadjuvant hormonal treatment in BC ([NCCN 2013 Guidelines].
- Inclusion criterion #13 has been modified to: ANC $\geq 1.5 \times 10^9$ /L
  - The rationale for this change is to ensure adequate bone marrow function and to align with NCI CTCAE v4.03.
  - Potassium, calcium (corrected for serum albumin) and magnesium have to be within normal limits or ≤ grade 1 severity according to NCI CTCAE version 4.03 if judged clinically not significant by the investigator, as these values are considered acceptable for the purpose of the study.
    The rationale for this change is to facilitate patient enrolment and is based on the exercise of clinical judgement in minimal electrolyte alterations (≤ grade 1 as per NCI CTCAE version 4.03) that otherwise would not pose any safety risk to the patient.
- The upper limit of normal (ULN) for AST/ALT will be increased to allow 1.5 x ULN for study inclusion.
  - The rationale for this change is that mild and asymptomatic transaminase elevations at baseline are a common finding in this patient population (e.g. related to concomitant medications, fatty liver, etc.), and are currently one of the most common reasons for screening failure in this study.
    Patient's safety will continue to be ensured given the weekly monitoring of transaminases during the two first 2 cycles. Based on recently reported and published data, a lower incidence and severity of transaminases increase is expected with the change from continuous to intermittent dosing schedule of buparlisib/buparlisibplacebo (Section 1.2.2).
- Exclusion criterion #6 (diabetic patients) has been clarified in such a way that only patients with diabetes mellitus type 1 and steroid-induced diabetes mellitus are excluded.
  - The rationale for this change is to gain alignment and consistency with current inclusion criterion #13, where HbA1c ≤8% is required for study entry. Since Hb1Ac values above 6.5% are considered in its own right a diagnostic criterion for diabetes mellitus (American Diabetes Association Position Statement 2010), patients with type 2 diabetes mellitus and values of HbA1c ≤8% will now be allowed to participate. This change also follows the the formal recommendation of the study Steering Committee.
- Exclusion criteria #11, #12, and #13 (criteria related to the PHQ-9 and GAD-7 questionnaires) will only apply to buparlisib/buparlisib placebo treatment arms. Patients meeting one of these criteria will be randomized to BYL719/BYL719 placebo arm.

[redacted]

- The rationale for this change is based on the fact that BYL719 does not cross the blood-brain barrier and no clinically relevant and/or severe (i.e. grade ≥3) treatment-related psychiatric side effects have been reported to date [BYL719 Investigators' Brochure].
- Exclusion criteria #23 (corticosteroid use) has been updated to reflect the recent finding of minor impact of corticosteroids on buparlisib metabolism (see Buparlisib Investigator's Brochure). However, patients on chronic corticosteroids or other immunosuppressive agents continue to be excluded from the study entry.
- Exclusion criterion #24 (warfarin use) has been retired based on changes with regards to the Conmed Section (see below).

Changes in the background section

Clinical background sections have been updated to align with the latest Invetigators' Brochure of each compound (buparlisib and BYL719), and to reflect the newly reported clinical data of buparlisib and BYL719, particularly in combination with endocrine therapy (e.g. letrozole, fulvestrant) in HR-positive BC.

Changes in the skin toxicity management section

More detailed guidance for management of skin toxicity has been added given that it is one of the most common side effects observed with buparlisib and BYL719. Such guidance is aimed at optimizing the treatment of this side effect. In particular, additional guidance is provided for different types of skin toxicity including specific recommendations for therapeutic approaches.

Changes in the concomitant medications section

Section 6.4 "Concomitant medications" and Appendix 14.1 "Concomitant medications" have been changed to simplify understanding of concomitant medications permitted and prohibited for both treatments arms.

In addition, some of the criteria were reworded based on the current knowledge on the pharmacology of BYL719, buparlisib and letrozole as follows:

- As it has been shown by the human ADME that the metabolism and clearance of BYL719 *in vivo* is not dependent on CYP3A4 (Section 1.2.1.1.2) and the label of letrozole does not require the exclusion of any CYP3A4 inhibitors or inducers (Femara Prescribing Information), strong inhibitors or inducers of CYP3A4/5 are now permitted to use with caution for the BYL719/placebo + letrozole arm. They are still prohibited for the buparlisib/placebo + letrozole arm due to the dependence of the metabolism of buparlisib on CYP3A4/5.
- Sensitive substrates of CYP3A4/5 and/or substrates of CYP3A4 that have a narrow therapeutic window are now permitted to be used with caution for both treatment arms in line with other BYL719 or buparlisib studies, where those have not been restricted. While BYL719 is a time-dependent inhibitor of CYP3A4 *in vitro* (KI,u=5.2 μM, kinact 0.011 min-1), recent data has shown that it is also an inducer of CYP3A4 (Section 1.2.1.1.2). Based on available clinical data and PBPK modelling both opposing effects seem to

[redacted]

balance each other out. As buparlisib is only a weak, reversible inhibitor of CYP3A4 (Ki,u = 13.4 μM) restriction of these substrates is not necessary.

- Warfarin and coumarin derivatives are now permitted with caution in both arms but should be avoided whenever possible (6.4.1.5). While both BYL719 and buparlisib have shown some inhibitory potential towards CYP2C9, the major metabolizing enzyme of S-warfarin, as well as other 2C-family enzyme, inhibition was weak (Section 1.2.1.1.2 and 1.2.2.1.2). The median Cmax values observed at steady state in the first in man trials at the respective MTDs were around 8.1 μM (0.9 μM unbound) for BYL719 and 4.3 μM (0.7 μM unbound) for buparlisib. A risk assessment based on the mechanistic static model (or a "net effect model") by Fahmi et al, 2008 assuming fraction metabolized (fm) by CYP2C9 to be 1 for warfarin and no gut metabolism (FG = 1), predicted an AUCR to be <1.1. Hence it is unlikely that inhibition of CYP2C9 or other CYP2C-family enzymes, which showed an even less inhibitory potential, translates into a clinical interaction with warfarin (R-warfarin is metabolized by multiple CYP enzymes). A clinical interaction study between letrozole and warfarin showed no clinically significant effect of letrozole on warfarin pharmacokinetics.

Changes in the discontinuation of study treatment section

Clarifications regarding the discontinuation of clinical trial protocol elements have been added throughout the protocol. Updated language in this protocol amendment is aimed at differentiating between patients who:

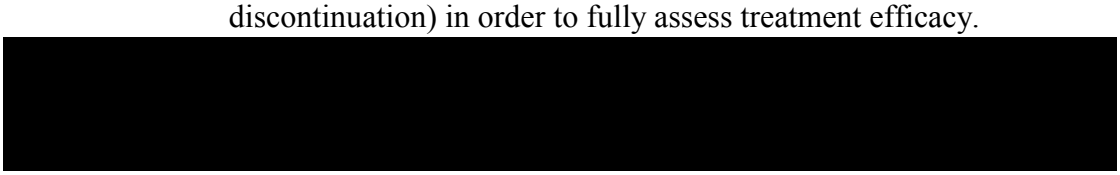
- discontinue certain clinical trial protocol (CTP) elements (discontinue study treatment, or some or all visits etc.);
- patients who withdraw consent;
- and patients who are lost to follow-up.

Changes in the treatment assignment and randomization section

- PIK3CA mutation status and Ki67 results will not be communicated to the site at the time of randomization to avoid any potential bias.
- As exclusion criteria #11 and/or #12, and/or #13, will now be applicable only to buparlisib/buparlisib placebo treatment arms, patients meeting any of these exclusion criteria will be randomized to BYL719/BYL719 placebo plus letrozole arm through the interaction response technology (IRT) system.

Changes in visit schedule and assessments

- The receipt of PIK3CA mutation status and Ki67 results by the site before randomization has been changed to indicate that these results will not be communicated to the site.Ophtalmologic evaluations will no longer be necessary at screening, based on the latest clinical safety information provided in the updated edition of the [BYL719 Investigators' Brochure].
- Instructions for sites have been added to capture pCR information of those patients who discontinued earlier than planned (i.e. before 24 weeks) study treatment (without withdrawal of consent) and opt for immediate surgery (i.e. within 30 days post-discontinuation) in order to fully assess treatment efficacy.



Changes in the biomarker section

Additional circulating DNA collections were added to assess feasibility of circulating DNA for monitoring for disease progression and correlation with tumor molecular profiling.

Changes to the protocol

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

- Section 1.2.1.1.2: added new information regarding induction of CYP3A4 by BYL719 *in vitro*.
- Section 1.2.1.2 (based on current BYL719 Investigators' Brochure version):
  - Updated list of ongoing BYL719 studies, and the new data collected since the last version of the protocol.
  - Updated clinical safety and efficacy of BYL719 to include new data acquired after the study has begun.
  - Section 1.2.1.3: updated Cmax and Racc information.
  - Section 1.2.1.4: added new supportive information regarding interaction of BYL719 with Letrozole.
- Section 1.2.2.2: updated section to include new clinical data (based on current Buparlisib Investigators' Brochure version).
  - Updated clinical safety and efficacy of Buparlisib to include new data acquired after the study has begun.
- Section 1.2.2.2.1: Updated with current program information based on current Buparlisib Investigators' Brochure:
  - Hyperglycemia language.
  - Psychiatric mood disorders and clarified who should do psychiatric consultation.
  - Liver Toxicity language with more current information.
  - Skin rash and hypersensitivity with more current information.
  - Lung Toxicity language with more current information.
- Section 1.2.2.2.2. Added preliminary results of an ongoing phase Ib study; updated references are provided.
- Section 1.2.4:
  - Added sub-headings to clarify if data provided is preclinical or clinical.
  - Updated Buparlisib + Letrozole information based on the preliminary results recently reported.
  - Updated BYL719+Letrozole information based on the preliminary results recently reported.
- Section 2.3:
  - Updated CBYL719X2101 study data.
  - Updated CBYL719ZUS03T study data.
  - Updated buparlisib dosing schedule and provided rationale for the change.

[redacted]

- Section 2.5: provided updated references.
- Section 3.1 Table 3-1:
  - Primary Objective: added "(QD continuous or QD 5 days on/2 days off)" to clarify that patients on a continuous regimen and intermittent regimen will be analyzed for the primary objective.
  - Updated Buparlisib administration schedule as "QD continuous or QD 5 days on/2 days off".
  - Replaced "Investigator" with "local".
- Section 4.1:
  - Updated the tumor requirements at screening for clarification.
  - Added "for any other reason than documented disease" in 5th paragraph for clarification.
  - Modified to clarify the tissue requirements for molecular prescreening/screening.
  - Explained logistical changes of receiving the PIK3CA mutation status and Ki67 results at screening.
  - Treatment Phase: change the buparlisib frequency from "QD" to "5 days on/2 days off".
- Section 4.2: deleted 'approximately" before 30 days for clarity.
- Section 4.3: Deleted "prematurely" and added "discontinued or" before" withdrawn patient".
- Section 5.2 (Inclusion Criteria):
  - Provided clarifying language to #3 for the definition of post-menopausal status.
  - Provided clarifying language to #4 of the types of breast cancer allowed into the study.
  - Updated requirements for potassium, calcium, magnesium, AST and ALT in #13.
- Section 5.3 (Exclusion Criteria):
  - Updated #6 to allow for diabetes mellitus type 2 patients to be now allowed into the study.
  - Updated language to #11, #12, and #13; to indicate that these criteria are applicable to the buparlasib/buparlisib placebo arm only.
  - Updated the use of corticosteroid use to #23.
  - Retired criterium #24.
- Section 6.1.1: Updated Table 6-1 with updated buparlisib dosing schedule.
- Section 6.1.2.1: Clarified dosing frequency of BYL719 and buparlisib and added that patients are allowed to drink water after administration of BYL719/placebo or buparlisib/placebo.
- Section 6.1.4: Updated language and provided new study drug dosing frequency.
- Section 6.3.1: clarified that patients must be permanently discontinued from BYL719/buparlisib if withheld for more than 28 days.
- Section 6.3.1.1:

[redacted]

  - Provided new buparlisib dosing frequency and timing of re-introduction in the event of a buparlisib interruption.
  - Updated Table 6-3 with buparlisib dosing frequency.
  - Clarified that if patients discontinue from BYL719/placebo or buparlisib/placebo that patients can continue on letrozole until study completion.
  - Updated Table 6-4 with clarifying language throughout, and adjusted dose modification for rash maculopapular (Grades 1-3).
- Section 6.3.2.1.1: Added new management of pneumonitis language per Dec. 19, 2014 Urgent Safety Measure and updated Table 6-5.
- Section 6.4: Updated entire section to include more specific instructions on the use of permitted (section 6.4.1) and the exclusion of prohibited (section 6.4.2) concomitant medications.
- Section 6.5.2: added that PIK3CA mutation and Ki67 status results will be not be communicated to study sites and that patients meeting exclusion criteria #11 and/or #12, and/or #13, and/or #15 will be randomized to BYL719+letrozole or placebo+letrozole and will be assigned to BYL719 or BYL719 matching placebo.
- Section 6.6.1: Updated Table 6-6 with new buparlisib dosing frequency.
- Section 7.1 added "Visit windows of +/- 3 days are allowed (except at cycle 1 Day 1 and where specified in Table 7-1)."
- Section 7.1 Table 7-1 removed "Receipt of" from "Receipt of PIK3CA mutation and Ki67 status results" from list of evaluations and added "entered into IRT" after "Ki67 status results"; updated frequency of vital signs evaluation by removing C1D8 and C1D22; deleted Ophthalmologic Evaluations; updating buparlisib administration schedule from "Daily Continuous Dosing" to "5 days on/2 days off".
- Section 7.1.1 removed all references to receipt of PIK3CA mutation and Ki67 status results by sites; specified that no previous treatment has been received for "current diagnosis"; updated the logistics of patient randomization.
- Section 7.1.2 specified that re-screening can be done only one time.
- Section 7.1.2.2 removed all references to receipt of PIK3CA mutation and Ki67 status results by sites.
- Section 7.1.2.3 added Ki67 results and deleted reference to Ophthalmologic examination.
- Section 7.1.4 added that patients who discontinue but do not withdraw study informed consent and go for surgery will have pCR results communicated to Novartis.
- Sections 7.1.4, 7.1.5, and 7.1.7 replaced Sections 7.1.3.1 and 7.1.3.2 to differentiate between patients who: discontinue study treatment, or some or all visits etc., withdraw consent, or are lost to follow-up.
- Sections 7.1.6 updated section title to clarify type of follow up visit.
- Section 7.2.1 indicated that pCR must be performed following pCR guidelines distributed by Novartis and timelines for pCR submission via eCRF and material to be sent to Genoptix after surgery and local pCR assessment is complete within recommended timeframes.

[redacted]

- Section 7.2.2.5 was removed as ophthalmologic exam is no longer required for this study as per latest BYL719 Investigators' Brochure update.
- Section 7.2.2.6 was replaced with 7.2.2.5 and updated to remove visit window language, which was moved to section 7.1.
- Sections 7.2.2.5 Table 7-4 removed calcium from Biochemistry collection panel and added "Prothrobin Time (PT)" and aPTT to Coagulation.
- Section 7.2.2.5.4 added "prothrombin time (PT)" and "or aPTT".
- Section 7.2.2.7 Table 7-6 removed word mandated from Visit/Cycle column; indicated that patients meeting exclusion criteria 11-13 or 15 will be excluded from the buparlisib arm.
- Section 7.2.2.8 updated PHQ-9 and GAD-7 language.
- Section 7.2.4 was adapted to add new collections of circulating DNA collections and tumor tissue requirements at surgery.
- Section 7.2.4.1 Table 7-9 was updated to capture the changes in the circulating DNA collection schedule.
- Section 7.2.4.2.1 updated the number of slides required for the diagnostic biopsy.
- Section 7.2.4.3.1 updated language for the collection of Specimen 2 and circulating DNA.
- Section 7.2.4.3.2 added language specific for blood collection.
- Section 7.2.4.3.3 added instructions for tumor tissue collection: "4 samples from the surgical specimen (2 of these samples should be formalin fixed and shipped in ethanol the other 2 should be snap frozen and shipped on dry ice)".
- Section 7.2.4.4 Figure 7.1 was updated to capture the changes in the circulating DNA collection schedule.
- Section 7.2.4.4 Figure 7.1 under Surgery updated language from "24 weeks (± 2 weeks)" to read "24 weeks (up to 26 weeks)".
- Section 7.2.4.4 Table 7-10 removed all references to additional biopsy informed consent as there is no additional biopsy ICF for this study; this biopsy is mandatory and hence part of the main ICF.
- Section 7.2.4.4 added "Optional additional biomarker studies" statement to indicate length of biomarker sample storage and potential usage of samples.
- Section 9.3: added "recommended to be" before "performed" and "within 5 days of the visit" after "performed".
- Section 10.1.4.4: replaced "for the last consecutive 7 days" with "on 10 days out of 14 days".
- Section 10.4: updated Buparlisib administration schedule as "QD continuous or QD 5 days on/2 days off", added 'QD" after "letrozole".
- Section 10.4.2: added "mean" after "estimated" to second bullet point for clarity.
- Section 10.4.4: added a supportive analysis using the subpopulation of patients who receive the intermittent schedule if the proof of concept is established with buparlisib plus letrozole in at least one cohort.

[redacted]

- Section 10.5.4 Table 10-1: Deleted CL and Vss and their definitions and updated units as appropriate throughout the table.
- Section 10.5.4.1.1: corrected LLOQ of 1.00 ng/ml to 5.0 ng/ml.
- Section 13: Added 5 new references.
- Section 14.1: Clarified the list of concomitant medications; replaced Tables 14-1, 14-2, 14-3 and 14-4 and added Tables 14-5 and 14-6.

Amendment 1

Amendment rationale

The recruitment of first patient will occur after implementation of the following amendment.

The purpose of this protocol amendment is:

- To revise the starting dose of BYL719 from 350 mg QD to 300 mg QD and corresponding dose reduction guidelines.
- To change study inclusion/exclusion criteria, concomitant medications, dose adjustments and follow up of toxicities.
- To include additional analyses for safety. Administrative changes are made for clarification and typographical errors have been corrected.

Change in starting dose of BYL719/placebo and corresponding dose reduction guidelines:

CBYL719ZUS03T is a phase I trial conducted to establish the recommended dose for the combination of BYL719 and letrozole in ER+ HER2- advanced/metastatic breast cancer. Updated results from this study have shown that the administration of BYL719 given at the dose of 350mg together with letrozole at the standard dose of 2.5mg was limited by the occurrence of adverse events and mainly rash: although only 1 patient experienced a DLT at this dose, 4 out of 6 patients required dose reduction. The 300mg dose was administered to a total of 5 patients so far: none of these patients presented DLT during cycle 1 nor needed a dose reduction due to adverse events, and 2 confirmed partial responses were observed. Based on these findings, 300 mg QD can be considered an acceptable starting dose for the combination of BYL719 and letrozole 2.5 mg (Communication from CBYL719ZUS03T principal investigator, Ingrid Mayer, October 2013).

As a consequence of the change in the starting dose of BYL719, dose reduction levels for BYL719/placebo are modified as follows: first dose reduction will consist of BYL719/placebo given at the dose of 250 mg QD daily and the second dose reduction will consist of BYL719/placebo given at the dose of 200 mg QD daily.

Changes in inclusion/exclusion criteria and concomitant medications:

To take into consideration the curative intent of neoadjuvant treatment - in the absence of any new safety signal within BYL719 and BKM120 programs - and to integrate new emerging findings, the following Inclusion/Exclusion criteria have been modified, as well as chapter 6.4 “concomitant medications”:

[redacted]

- Inclusion criteria # 4:

Patients with T1c breast cancer tumors are allowed to enroll in the trial per investigator's discretion.

The inclusion criterion is modified as these patients may benefit from neoadjuvant endocrine therapy. In a clinical trial where letrozole was given as neoadjuvant treatment (duration 3-12 months), clinical responses and benefit were seen in patients with T2 or T3 tumors, as well as in patients with T1 tumors (Dixon 2009).

- Exclusion criteria # 10 and addition of a new exclusion criteria (# 20):

Patients with a history of 'acute pancreatitis' and 'patients with a history of pneumonitis or interstitial lung disease' are excluded from the study per modified exclusion criteria # 10. 'Patients with congenital long QT syndrome or family history of unexpected sudden cardiac death' are excluded as per added exclusion criteria # 20.

The following are known adverse events for both BYL719 and buparlisib:

- Amylase/lipase increases have been observed in patients receiving either BYL719 or buparlisib, although the majority of these events were of mild to moderate severity.
- Cases of lung toxicity and pneumonitis have been observed with the administration of buparlisib and to a lesser extent, BYL719.

In addition, pre-clinical, clinical data and PK-QT modeling from study first in man single agent dose escalation trial CBKM120X2101 showed no effect of buparlisib on QT. From preclinical cardiac BYL719 safety studies, no relevant electrophysiological effect was seen and the only effect considered significant was an increase in systolic and diastolic blood pressure, observed in a dog telemetry study. In addition, as of May 2013, two patients in the single agent treatment (1.4%) experienced drug-related QTc prolongation/cardiac dysrhythmias/cardiac ischemia events; neither of these drug-related events was assessed as Grade 3 or 4, and BYL719 did not cause any clinically evident arrhythmia. PKQT modeling will be done in BYL719 first in man dose-escalation study CBYL719X2101 and results provided as they become available.

Monitoring of these potential adverse events and specific dose adjustments are already included in the protocol and no new safety findings have been seen within BYL719 and buparlisib programs.

Hence exclusion criteria #10 and #20 are modified/added to remain conservative in the curative setting of neoadjuvant treatment.

- Exclusion criteria # 25 is changed as well as Concomitant medication chapter (6.4):

The use of moderate CYP3A4 inhibitors and inducers is now allowed for patients entering the study: recent results from a buparlisib drug-drug interaction study conducted with a strong CYP3A4 inhibitor (ritonavir) [CBKM120C2111] have shown a lower than anticipated involvement of the CYP3A4 in the metabolism of buparlisib. This is also in line with the results of a drug-drug interaction study with dexamethasone (a weak CYP3A4 inducer) [CBKM120C2106] which showed no significant change in buparlisib pharmacokinetics. Thus, moderate CYP3A4 inhibitors and inducers can be used with caution with buparlisib on the basis of these trials.

[redacted]

As CYP3A4 inhibitors and inducers are per se not prohibited by the Femara label nor for BYL719, moderate CYP3A4 inhibitors and inducers will also be allowed for the BYL719 combination arm. Based on the potential risk of an interaction between letrozole and BYL719 due to time-dependent CYP3A4 inhibition by BYL719 and letrozole pharmacology, strong CYP3A4 inhibitors and inducers are still excluded. Hence the exclusion criteria # 25 has been modified to exclude only patients receiving strong inhibitors or inducers of isoenzyme CYP3A and not those receiving moderate inhibitors or inducers. The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the start of treatment. Switching to a different medication prior to randomization is allowed.

Changes in dose adjustment guidelines:

In the absence of any new safety signal within BYL719 and BKM120 programs, to ensure the most appropriate safety management in the current study, the following changes are made to implement more conservative dose modification adjustments:

- Patients who interrupt treatment due to febrile neutropenia or grade 4 neutropenia and who decide to continue on study should restart study drug at a lower dose level.
- Patients with symptomatic decline in ejection fraction or with an ejection fraction 20-39% or a >20% drop from baseline should permanently discontinue study drug.
- Patients with a grade 3 elevation of bilirubin or of AST/ALT who subsequently recover to grade ≤ 1 and who decide to continue on study should restart study drug at a lower dose level, and
- Patients with a grade 4 elevation of AST/ALT should permanently discontinue study drug.
- Management of grade 3 hyperglycemia adverse events is changed to be more stringent as permanent discontinuation of the study drug is now recommended when there is no recovery of the event to a grade 1 within 14 days (instead of 28 days originally), despite study drug omission.
- Management of skin toxicities has been updated and specific paragraphs for corresponding type of skin toxicities have been added to allow for a better management of this side effect.

Change in the follow up for toxicities:

In addition, as pneumonitis and skin rash are events that could be associated to PI3K inhibitors class, and not only specific for buparlisib only, the management and follow-up of them is applied to both buparlisib/placebo and BYL719/placebo. More detailed information on co-medications that can be used for the management of skin toxicities is added.

Changes in the statistical section:

Periodic review of safety data aggregated by blinded treatment group (BYL719/placebo or buparlisib/placebo) will be performed and results will be shared with Study Steering Committee.

[redacted]

Change in End of treatment phase completion and End of post-treatment follow-up

Pregnancy is not a criterion for End of treatment phase completion and End of post-treatment follow-up; as it is post-menopausal patient population.

Changes to the protocol

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

- Updated information related to the phase Ib clinical study of BYL719+letrozole (CBYL719ZUS03T) throughout the document: Sections 1.2.1.2, 1.2.4 and 2.3.
- Starting dose reduced from 350 mg to 300 mg throughout the protocol.
- Section 1.2.1.4: added rationale for decreased likelihood of letrozole plasma exposure when combined with BYL719 at 300 mg dosing.
- Section 1.2.2.1.2: replaced "(estimated fraction metabolized >0.9)" with "*in vitro*" to indicate how metabolism of buparlisib was obtained.
- Section 1.2.2.2.3: added rationale for allowing the use of moderate CYP3A4 inhibitors and inducers.
- Section 2.3: added "for 24 weeks" to read "BYL719 300 mg QD will be given in combination with letrozole 2.5 mg QD for 24 weeks."
- Section 2.3: added rationale for 24 week treatment.
- Section 5.1 and Section 5.2 (Inclusion Criteria #4): "T2-T3" is replaced by "T1c-T3"
- Section 5.3 (Exclusion Criteria):
  - Exclusion Criteria #10: Added "acute or" and "pneumonitis or interstitial lung disease".
  - Added Exclusion Criteria #20.
  - Exclusion Criteria # 25: Deleted "moderate" inhibitors of isozyme CYP3A.
- Section 6.1.1 Table 6.1 Dose and Treatment Schedule footnote #2 changed "300" to "250" and "2 X 50 mg" to "1 X 50 mg" to reflect changes in dose reductions.
- Section 6.3.1.1: updated the lowest dose which subjects can be administered before study treatment discontinuation to 200 mg and updated Table 6.2 (Dose reduction sequential steps for BYL719/placebo) with updated dosing schedule.
- Section 6.3.1.1: Updated Table 6.4 (Criteria for interruption and re-initiation of BYL719/placebo or buparlisib/placebo) to indicate study drug to be dose adjusted throughout the table and provide more conservative language to the Dose adjustment and Management Recommendations for hematology, cardiac, hepatic, hyperglycemia and rash maculopapular. Added dose adjustment and management recommendations for Pruritus and Rash (Acneiform).
- Section 6.3.2.1.1 broadened language to include treatment of patients for pneumonitis on either buparlisib or BYL719.

[redacted]

- Section 6.3.2.1.1 Table 6.5 Management of pneumonitis in patients receiving buparlisib/placebo added "is recommended and" to Grade 3 Required Investigations as no guidance was previously given in the protocol.
- Section 6.3.2.1.4 added "sunscreen" as an additional means to protect against study drug induced skin toxicities, recommendation to take photographs and biopsies of rashes, and added description of types of skin toxicities and suggested treatments.
- Section 6.4.1: removed "and moderate" throughout section to indicate only strong CYP3A4 inhibitors and inducers are prohibited.
- Section 6.4.2: added "or moderate" throughout section to indicate use of moderate CYP3A inhibitors and inducers are permitted.
- Section 7.2.2.5 added "or a qualified health care specialist." to make it easier for the sites to meet the requirement.
- Section 7.2.4.4 Figure 7.1 under Surgery updated language from "24 weeks (± 2 weeks)" to read "24 weeks (up to 26 weeks)".
- Section 7.2.4.4 Table 7-10 removed all references to additional biopsy informed consent as there is no additional biopsy ICF for this study; this biopsy is mandatory and hence part of the main ICF.
- Section 7.2.4.4 added "Optional additional biomarker studies" statement to indicate length of biomarker sample storage and potential usage of samples.
- Section 10.5.3.1 added periodic safety analysis in which results will be shared with the study steering committee.
- Section 13 added references supporting 24 week treatment duration.
- Section 14.1.1, Table 14.1 List of prohibited medications during BYL719+letrozole combined treatment, and Table 14.2 List of prohibited medications during buparlisib+letrozole combined treatment the following medications are deleted.

Moderate CYP3A Inhibitors	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera[2], tofisopam, verapamil
Moderate CYP3A Inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir

- Section 14.1.1, Table 14.3 List of medications to be used with caution during BYL719+letrozole combined treatment, and Table 14.4 List of medications to be used with caution during buparlisib+letrozole combined treatment: the following medications are added.

Moderate CYP3A Inhibitors	Amprenavir, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera2, tofisopam, verapamil
Moderate CYP3A Inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir

- Section 14.2.16 removed bullet "Central Blinded Review overall lesion response." or any reference to a central review.
- Section 14.2.29, removed Pregnancy as a criterion for End of treatment phase completion.
- Section 14.2.30, removed Pregnancy as a criterion for End of post-treatment follow-up.

[redacted]

IRB/IEC/HA

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Protocol summary:

Protocol number	CBYL719A2201
Title	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
Brief title	Study of safety and efficacy of neoadjuvant treatment with BYL719 or buparlisib plus letrozole in postmenopausal women with hormone receptor-positive HER2-negative breast cancer patients
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	● The purpose of the study is to determine whether treatment with a PI3K inhibitor (either alpha specific: BYL719 or pan PI3K inhibitor: buparlisib) plus letrozole leads to an increase in pathologic response and Objective Response Rate compared to treatment with placebo plus letrozole in patients with hormone receptor-positive HER2-negative breast cancer for the following populations: i) in patients with tumors harboring a mutation in the PIK3CA gene ii) in patients with tumors harboring a wild type PIK3CA gene. ● The addition of a PI3K-AKT-mTOR inhibitor to letrozole has already been shown to lead to improved clinical outcomes when compared to letrozole alone in a randomized phase II trial in neoadjuvant treatment of postmenopausal women (Baselga 2009). Promising pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy (Sanchez 2011). Furthermore, clinical activity has been observed with single agent BYL719 and buparlisib and combination of buparlisib and letrozole when given to pretreated metastatic breast cancer patients. ● Hence the use of BYL719 or buparlisib in combination with letrozole may improve letrozole single agent outcomes by increasing the rate of of pathologic complete response or Objective Response Rate and might prove to be an effective treatment in neoadjuvant treatment for postmenopausal HR+ HER2- BC patients.
Primary Objectives	● To assess the anti-tumor activity of BYL719 QD plus letrozole QD versus letrozole alone in increasing the pathologic complete response (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 type tumors based on tumor tissue. and ● To assess the anti-tumor activity of BYL719 QD plus letrozole QD 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 type tumors based on tumor tissue.
Secondary Objectives	● To assess the anti-tumor activity of BYL719 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.- To evaluate the safety and tolerability of the drug combinations, and separately for buparlisib continuous and intermittent schedules ● 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 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 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 of BYL719/buparlisib and letrozole when given in combination

[redacted]

Study design	● This is a multi-center randomized, double-blind, placebo controlled phase II study comparing, oral tablets of BYL719 300 mg daily in combination with daily letrozole 2.5 mg and oral capsules of buparlisib 100 mg 5 days on/2 days off in combination with daily letrozole 2.5 mg to placebo in combination with letrozole 2.5 mg as neoadjuvant treatment in postmenopausal patients with HR-positive HER2-negative breast cancer. ● Recruitment in the buparlisib/buparlisib placebo arm was stopped on December 22, 2015. The buparlisib/buparlisib placebo patients ongoing at the time of the end of patient recruitment in this buparlisib arm may continue to be treated under their assigned treatment if they benefit from the treatment according to investigator's clinical judgment. ● Patients will undergo screening phase including molecular pre-screening to establish the PIK3CA mutation status, and assess the Ki67 status for stratification and randomization. ● A total of approximately 320 patients will be grouped into two cohorts (i.e. PIK3CA mutated and PIK3CA wild-type). Within each cohort, patients will be randomized in one of the treatment arms, after stratification according to Ki67% (<14% vs. ≥14%, as measured by Novartis designated central lab) and lymph node status (positive or negative).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 BYL719 and placebo arms. However a lower number of patients will be randomized to buparlisib. ● Patients will be treated for 24 weeks until surgery, progression, unacceptable toxicity or discontinuation from the study treatment for any other reason. Definitive breast surgery will be performed as early as possible after treatment, no later than 14 days after the last dose of BYL719/placebo or buparlisib/placebo. Surgical breast and axillary node resection specimens will be evaluated for pathologic tumor response. ● Tumor evaluations will be performed at baseline, at cycle 4 day 1 (with a window of +/- 7 days) and at maximum 7 days before surgery. At least 15 patients in each treatment arm will have PK sampling performed in order to characterize the PK of buparlisib and BYL719 when given in combination with letrozole as well as the PK of letrozole. ● Safety follow-up assessments should be completed 30 days after the last dose of the study treatment.
Population	The patient population consists of postmenopausal women with HR-positive, HER2negative, T1c-T3 breast cancer, whose disease has never been treated with local nor systemic treatment, and are eligible for endocrine neoadjuvant treatment.
Key Inclusion criteria	● Patient has T1c-T3, any N, M0, operable breast cancer ● Patients must have measurable disease ● Patient has diagnostic biopsy available for the analysis of PIK3CA mutation and Ki67 level. ● Patient has estrogen receptor (ER) and/or progesterone receptor (PgR)-positive breast cancer as per local laboratory testing ● Patient has HER2-negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0 or 1+ as per local laboratory testing ● Patient has known PIK3CA mutation status (mutated or wild-type), based on tumor tissue analysis, as defined by a Novartis designated laboratory. (Patients with unknown PIK3CA mutation status will not be enrolled) ● Patient has Ki67 level status determined centrally ● Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 which the investigator believes is stable at the time of screening
Key Exclusion criteria	● Patient has locally recurrent or metastatic disease ● Patient has received any systemic therapy (e.g. chemotherapy, targeted therapy, immunotherapy) or radiotherapy for current breast cancer disease before study entry. ● Patient with type 1 diabetes mellitus, and/or not adequately controlled diabetes mellitus type 2
Investigational and reference therapy	● BYL719+letrozole ● Buparlisib+letrozole ● Letrozole
Efficacy assessments	● pCR ● Tumor response (ORR according to RECIST v1.1)

[redacted]

Safety assessments	● Adverse events (AEs) ● Laboratory Evaluations (biochemistry, hematology, coagulation, insulin, fasting plasma glucose, urinalysis, C-Peptide, and HbA1c) ● ECOG Performance status ● ECG, vital signs, weight, physical exam and cardiac Imaging ● Patient's self-reported mood questionnaires
Other assessments	● Plasma concentration time profiles of BYL719/buparlisib and 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) ● Ki67 and markers of cell death [redacted] ● Molecular analysis of the diagnostic biopsy and surgical specimen
Data analysis	● The primary analysis will be performed after all patients in each cohort have completed 24 weeks of treatment and pCR evaluation is completed or after ALL patients have discontinued due to any reason. ● The pCR rates and ORR in each of the treatment arms will be summarized by cohort using descriptive measures including 90% confidence intervals using Clopper and Pearson (1934) exact method. The pCR rates and ORR will also be summarized by each stratum. Patients receiving letrozole plus BYL719 placebo and letrozole plus buparlisib placebo in the control arm will be combined together for all analyses. Efficacy of treatment with either of the combination arms will be declared if Proof of Concept (PoC) criteria on pCR or ORR are met in the respective cohorts.
Keywords	Postmenopausal women, HR-positive, HER2-negative, treatment naive, T1c-T3 breast cancer, endocrine treatment, AI, neoadjuvant treatment, PIK3CA mutation status

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Hormone receptor-positive breast cancer

Breast cancer (BC) is the most common form of malignant tumor in women worldwide, and incidence rates are as high as 99.4 per 100,000 women (World Health Organization 2013). Subtypes of BC are distinguished by expression of estrogen receptors (ER), progesterone receptors (PgR) and human epidermal growth factor receptor-2 (HER2), as well as by distinct gene expression profiles (Perou 2000; Sotiriou 2009). Within these subtypes 60-70% of breast tumors are HR+ (ER and/or PgR-positive) HER2-.

Therapies that interfere with ER functions such as tamoxifen or aromatase inhibitors (AI) have significantly contributed to mortality reduction in advanced breast cancer. Among the AIs, letrozole, anastrozole (non-steroidal AIs) and exemestane (steroidal AI) are also indicated for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer.

In locally advanced breast cancer, treatment options include surgery, radiation therapy, and systemic treatment such as chemotherapy and endocrine therapy, given in adjuvant and/or neoadjuvant setting. Neoadjuvant treatment was historically reserved for large inoperable locally advanced breast cancers and used with the intent to make these breast cancers operable. This approach has also demonstrated its potential in allowing breast conservation and avoiding mastectomies (Makris 1999), in assessing the response to treatment and adjusting it as needed (not possible in adjuvant setting) as well as providing prognostic information. It is also an excellent setting to perform biomarker analysis of the tumor, as tumor may be sampled at diagnosis, after few weeks of treatment and at final surgery (Makris 1999, Petit 2004). Its increasing role in breast cancer therapy has been recognized recently in a publication by FDA of a guidance for industry on "the use of neoadjuvant treatment of high-risk early stage breast cancer as an endpoint to support accelerated approval" (FDA 2012) for HER2-positive and triple negative breast cancers.

Use of endocrine neoadjuvant therapy was initially restricted to elderly ER+ BC patients based on the fact that hormone receptor positive tumors were responding less to chemotherapy as compared to other breast cancer types (Gianni 2005, Berry 2006, EBCTCG 2005). More recent trials have shown the lack of interaction between neoadjuvant endocrine therapy outcome and age (Olson 2009), and comparable outcome between chemotherapy and endocrine neoadjuvant therapy in ER+ BC patients (Semiglazov 2007). Neoadjuvant endocrine treatment can thus now be proposed to postmenopausal women as neoadjuvant treatment regardless of their age (NCCN guidelines 2013).

In neoadjuvant trials, a variety of endpoints have been used like, pathological response rate, clinical response rate, breast conserving surgery rate, preoperative endocrine prognostic index (PEPI) score and Ki67 variation (.clinicaltrials.gov ongoing endocrine neoadjuvant clinical trials).

[redacted]

Pathological response rate is generally expected to be low with endocrine therapy alone and not predictive of clinical benefit (FDA 2012, Bottini 2005). However, it has been identified as an acceptable end-point for combination trials, in particular with PI3K inhibitors (Miller 2011a), and presents the advantage that it can be validated and is a reproducible endpoint.

Ki67 is a marker of proliferation and its high level of expression in breast tumors after two weeks of endocrine therapy has been shown to be predictive of lower recurrence free survival (Dowsett 2007).

PEPI score is related to relapse risk and is a prognostic model that incorporates standard pathological staging variables and "on-treatment" biomarker values. This model was developed using data from the P024 neoadjuvant endocrine therapy trial that compared 4 months of letrozole and tamoxifen before surgery, with follow-up data (median >60 months) to address the relationships between post-neoadjuvant endocrine therapy tumor characteristics and risk of early relapse. The model was validated using data from the IMPACT trial, an independent neoadjuvant endocrine therapy study that compared anastrozole, tamoxifen, or the combination for 3 months before surgery. 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 (see Appendix 3 for more details). The total risk point score for each patient is the sum of all the risk points accumulated from the four factors in the model (Ellis 2008).

1.1.2 PI3K Pathway

The phosphatidylinositol-3-kinase (PI3K) signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso 2001).

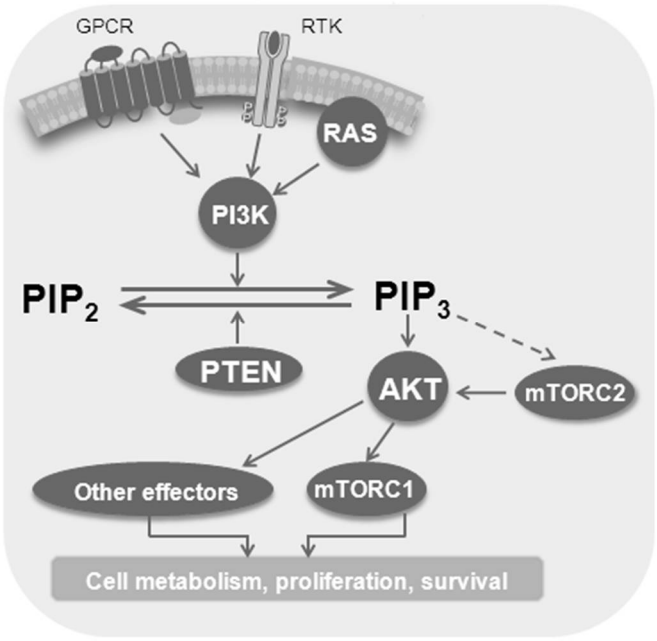
Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors and in many tumor types (Liu 2009). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006). Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers.

The dysregulation of the PI3K signaling pathway is implicated in many human cancers (Samuels 2004, Hennessy 2005, Markman 2010, Wong 2010, Yuan 2008) and includes the inactivation of the PTEN tumor suppressor gene (Sansal and Sellers 2004), amplification/overexpression or activating mutations of some receptor tyrosine kinases (e.g.: erbB3, erbB2, EGFR), and amplification of genomic regions containing AKT or PIK3CA genes (Cheng 1992, Cheng 1996, Shayesteh 1999, Markman 2010).

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

[redacted]

Figure 1-1 Schematic representation of the PI3K pathway



1.1.3 PI3K pathway activation in HR+ Breast Cancer

Over the past few years, progress has been made in understanding the molecular biology and genetics of BC which are central to the development of novel therapies.

PI3K is frequently altered in breast cancer. Gain-of-function mutations in oncogenes such as PIK3CA (encoding the catalytic subunit p110α) have been observed in about 10% to 40% of BC patients and are commonly observed in HR+ tumors. Inactivation of the tumor suppressor gene PTEN via loss-of-function mutations, gene deletion or transcriptional down-regulation also leads to PI3K pathway activation and has been reported in up to 13% of HR+breast cancer patients, see Table 1-1.

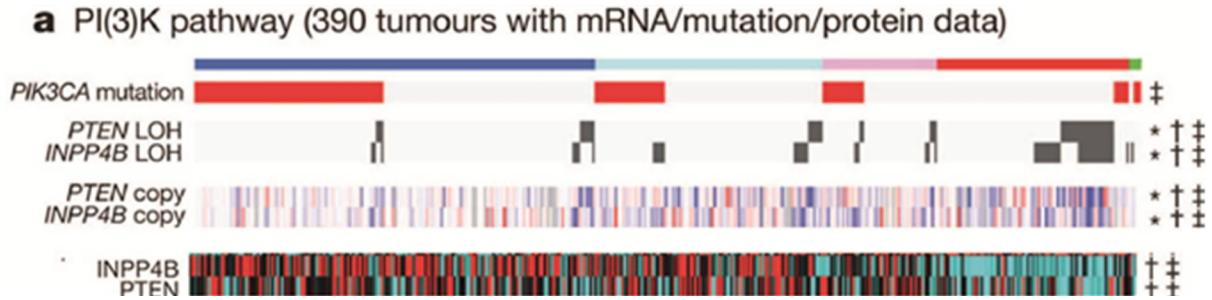
Table 1-1 PI3K signaling pathway mutations and alterations in breast cancer

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

It is anticipated that, on average, 36% of patients with HR+ breast cancer will be PIK3CA mutated. The overlap between PIK3CA and either PTEN or INPP4B alteration appears however relatively rare (Cancer Genome Atlas Network 2012 and Figure 1-2)

[redacted]

Figure 1-2 Frequency of PIK3CA, PTEN and INPP4B alterations in breast cancer



Extracted from TCGA publication in Nature 2012. Left portion of the graph (dark blue and pale blue bars) represent luminal A and B patients (Cancer Genome Atlas Network 2012).

Furthermore, pre-clinical data have shown that the ER pathway interacts with the PI3K pathway. Extensive crosstalk has been shown between ER and growth factor pathway (Miller et al 2011a; Osborne and Schiff 2011). For example estrogen deprivation leads to hyperactivation of the PI3K/mTOR pathway, which induces in turn an increase in cell proliferation and survival (Bjornsti 2004; Crespo 2002; Huang 2004; Mita 2003; Wullschleger 2006). This mechanism is linked to de novo or acquired resistance to endocrine therapy (Campbell 2001), including AI resistance (Shoman 2005; Crowder et al 2009; Miller 2011a). Treatment with PI3K inhibitors in absence of estrogen can inhibit proliferation of long term estrogen deprived cell lines supporting the concept of using combination of a PI3K inhibitor with an endocrine therapy in breast cancer.

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

Hence, the combination of endocrine treatment and PI3K-inhibitors, which have shown to lead to increased cell death *in vitro*, could also lead to an increased pathologic response in clinics by eliciting tumor apoptosis.

Together these observations suggest that PI3K pathway could constitute an important therapeutic target for the treatment of patients with HR+ breast cancer in a neoadjuvant setting. The combination offers potential for tumor cell death and delayed resistance to AI prolonging response to treatment.

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

1.2.1 Overview of BYL719

BYL719 is an oral class I α-specific PI3K inhibitor belonging to the 2-aminothiazole class of compounds. Targeting the alpha isoform of PI3K is expected to reduce the potential for inducing treatment related toxicity and improve the therapeutic window over inhibitors with less isoform specificity. BYL719 strongly inhibits the PI3Kα isoform (both p110α wild-type and p110α mutated) and much less strongly the β, δ and γ isoforms. It is inactive against the majority of other kinases.

[redacted]

BYL719 has demonstrated anti-tumor activity in preclinical *in vitro* and *in vivo* tumor models. *In vitro*, BYL719 has been shown to inhibit the proliferation of cell lines harboring PIK3CA mutations. The combination of BYL719 and letrozole was studied in an *in vitro* model of MCF7 breast cancer cells engineered to express aromatase (MCF7-Aro). The extent of growth inhibition of the MCF7-Aro cell line was assessed in dose matrices across escalating doses of BYL719, letrozole and both drugs in combination. From this data, significant synergy was observed.

In vivo, BYL719 has demonstrated dose-dependent tumor growth inhibition in various subcutaneous tumor transplant models. Both *in vitro* and *in vivo* cross indication models (other than breast cancer) provided evidence that PTEN driven model might display a lesser sensitivity to BYL719, in particular if the pTEN alteration is concomitant with PIK3CA mutation. This feature however might not be relevant in HR+ breast cancer patients (see Section 1.2.4). BYL719 is currently being investigated in Phase I dose escalation trials and in Phase Ib combination trials. Doses up to 450 mg once daily (QD) have been administered to cancer patients. The MTD of single-agent oral BYL719 has been declared at 400 mg QD.

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

1.2.1.1 Non-clinical experience

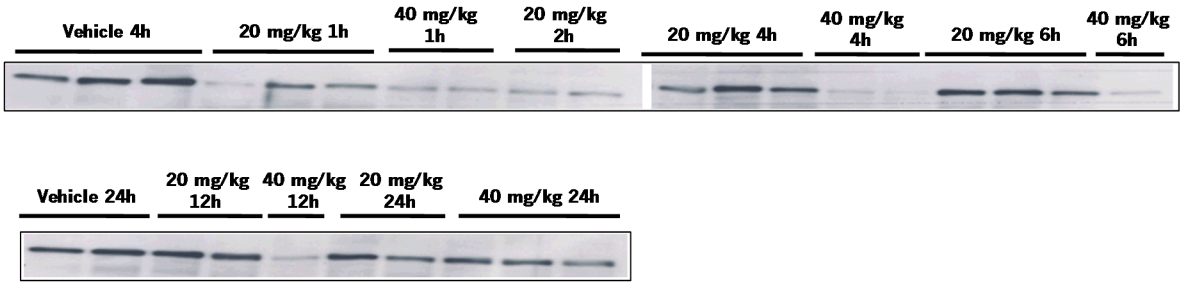
1.2.1.1.1 Pharmacodynamics of BYL719

In biochemical assays, BYL719 inhibits specifically p110α (IC_{50} = 5nM,) much more potently than the p110δ and γ isoforms. BYL719 is equipotent against the most common somatic mutations of p110α (H1047R, E545K) compared to wild type p110α. The BYL719 biological activity correlates with inhibition of various PI3K/AKT downstream signaling pathway components commonly used as indicators of pharmacodynamics. Please refer to the [BYL719 Investigators Brochure] for further details.

In vivo, BYL719 shows dose and time-dependent inhibition of the PI3K/AKT pathway in relevant tumor xenograft models (p110α-mechanistic model and p110α-mutant xenograft models) in nude mice and rats. *In vivo* analyses of tumor tissues, upon acute dose or after multiple treatments, show a good correlation between compound exposure and PI3K pathway blockade. Furthermore in lung cancer models, tumor samples from the animals treated at 20 or 40 mg/kg show that NVP-BYL719 inhibits partially S473P-AKT levels up to 2 h post 20 mg/kg treatment, but fully inhibits S473P-AKT levels up to 12 h post 40 mg/kg treatment (Figure 1-3).

[redacted]

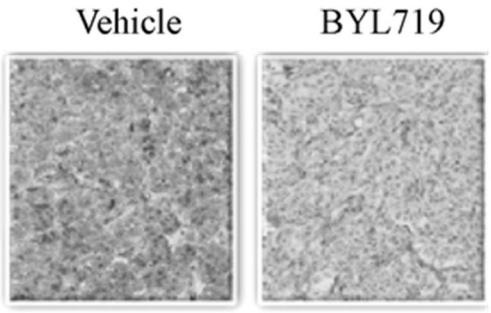
Figure 1-3 Pharmacodynamic profile of NVP-BYL719 after multiple treatments in NCI-H596 tumor bearing nude rats



*Female athymic rat bearing subcutaneous xenotransplants of NCI-H596 tumors were treated with 20 mg/kg or 40 mg/kg of NVP-BYL719, p.o. At the indicated time points post last treatment, the groups of rats (n=3) were sacrificed, blood and tissues removed. Each tumor tissue was flash-frozen then pulverized and analyzed by Western blot to determine S473P-AKT levels. (Novartis internal data)

Finally, in breast cancer xenografts models, treatment with BYL719 led to significant decrease in AKT phosphorylation (brown represent positivity for the antigen of interest, blue is hematoxylin used to label all nuclei). Please see Figure 1-4.

Figure 1-4 Supporting evidence for pathway inhibition in preclinical model of breast carcinoma (T47D) by NVP-BYL719 at 50 mg/kg



(Novartis internal data)

1.2.1.1.2 Nonclinical PK and metabolism of BYL719

BYL719 demonstrates low plasma clearance, a moderate volume of distribution at steady state and a good absolute oral bioavailability in all preclinical species tested. The compound is moderately bound to plasma proteins with no major species difference and this binding is independent of the concentration (free fraction in human plasma ~ 10.8%). BYL719 showed a rapid distribution to almost all rat tissues, except the brain (rat ADME study).

BYL719 is a substrate of Breast Cancer Resistance protein (BCRP) and has low affinity for P-glycoprotein (P-gp/MDR1). BYL719 does not inhibit BCRP or Multi-drug resistance protein-2 (MRP2), but showed very weak inhibition of P-gp (IC_{50} = 97 µM). As the maximal inhibition of P-gp was only about 32% with respect to positive control, the overall interaction potential is expected to be low. Uptake of BYL719 in human hepatocytes was not influenced by inhibitors of the transporter families organic cation transporter (OCT), organic anion transporter (OAT), organic anion-transporting polypeptide (OATP) and sodium taurocholate co-transporting polypeptide (NTCP).

[redacted]

BYL719 was found to be a time dependent inhibitor of CYP3A4 (Ki 5.6 μM, Kinact 0.011 min-1). Reversible inhibition of CYP2C8 (Ki 32 μM), CYP2C9 (Ki 22 μM) and CYP2C19 (IC50 75 μM) was also observed. BYL719 may inhibit metabolic clearance of co-medications metabolized by CYP3A4, CYP2C8, CYP2C9 and CYP2C19, if sufficiently high concentrations are achieved *in vivo* but given observed clinical peak plasma concentrations are unlikely to translate to a clinical effect.While clinically significant pregnane X receptor-(PXR)-mediated induction of CYP3A4 or aromatic hydrocarbon receptor-mediated induction of CYP1A2 by BYL719 has not been expected based on *in vitro* nuclear activation assays, there has been recent growing evidence from a hepatocyte induction assay that BYL719 can induce CYP3A4 (EC50 = 1.7 μM, Emax = 0.83 relative to RIF control), likely via activation and crosstalk with the constitutive androstane receptor (CAR) receptor. Based on preliminary clinical data from a combination with everolimus, which showed no increase of everolimus exposure after concomitant administration with BYL719 at steady state, as well as PBPK modelling using SimCyp, time-dependent inhibition and induction of CYP3A4 by BYL719 seem to balance each other out at clinical relevant doses.

Results from 4-week GLP toxicology studies in dogs showed a roughly dose-proportional increase in exposure, while in rats the exposure increased up to a dose of 30 mg/kg beyond which no further increase was noted following single dose administration. The toxicology studies provided no clear evidence of increase in exposure following multiple dosing. No gender differences in exposure were observed in rats or dogs.

The overall biotransformation of BYL719 in hepatocytes and microsomes across all tested species was low. The main biotransformation pathway that was observed was hydrolysis. CYP450 dependent oxidative metabolism is expected to be minor. No covalent drug protein adduct formation was noted in human microsomes or hepatocytes.

Disposition of BYL719

In vitro elimination of BYL719 - at the current stage of knowledge - appears to be a three-parted pathway consisting of CYP450-mediated oxidative metabolism, hydrolysis (enzymatic or chemical, currently unknown) and biliary elimination, but the extent of each of them remain uncertain and may be species-dependent.

Metabolism studies in both human and animal liver preparations (microsomes, hepatocytes) showed a low metabolism of BYL719 by phase I and phase II metabolic enzymes. Phenotyping studies in human liver microsomes and with recombinant CYPs confirmed that biotransformation mainly takes place via CYP3A4 (minor involvement of CYP2J2), with no major participation of UGTs. An *in vivo* rat ADME study with [14C]-BYL719 displayed, however, two monohydroxylation products (M2 and M3) in both plasma (≤ 5% total AUC) and feces (~5-15% of dose each), indicating some contribution of oxidative metabolism, at least in the rat. This is also be supported by the presence of two further metabolites yet to be identified (accounting for ≤ 7% total AUC in plasma).

Another metabolite, the carboxylic acid M4 (BZG791) formed by hydrolysis (a pharmacologically inactive amide hydrolysis product), was found to a comparable degree in plasma (≤ 5% total AUC) and feces (~15% of dose) in this study showing also a non-oxidative metabolism pathway.

[redacted]

A separate rat excretion study in bile-duct annulated rat demonstrated that 25% of the dose of [14C]-BYL719 was excreted in feces with 40% of the dose being found unchanged in bile. As BYL719 is a substrate for human BCRP *in vitro* there is strong evidence for a hepatobiliary excretion and potential for hepatic recirculation (active transport into the bile and intestinal reabsorption), at least in the rat, that is also supported by rat sandwich-cultured hepatocyte experiments.

In general, excretion in feces (via bile and direct secretion into the intestine) was the major route of excretion in rats with 77% of the dose rapidly eliminated as metabolites within 7 days. Contribution of renal excretion based on the results can be considered minor.

In humans, metabolite identification has been performed so far based on patient plasma of study [CBYL719X2101] that seems to confirm the implication of oxidative metabolism in human, though its extent is still unknown. An ongoing human ADME trial will provide more insight on the human situation which currently cannot be fully assessed based on the available *in vitro* data.

1.2.1.1.3 Safety pharmacology and toxicology of BYL719

Routine safety pharmacology and toxicology studies were conducted in rats and dogs. In addition, for exploratory studies, such as insulin/glucose tolerance tests, mice were also used.

BYL719 was relatively well tolerated in the repeated-dose toxicity studies (daily dosing of up to 4 weeks of duration) at dosages at which tumor growth control was achieved in mouse or rat tumor models. BYL719 affected rapidly dividing tissues which only resulted in pharmacologically relevant observations in the animals exposed to a BYL719 dose close to or at MTD. The most frequently affected organs were the bone marrow and lymphoid tissue (spleen, thymus), the epithelia of the alimentary tract, while other tissues like the vagina and uterus in rats, or prostate in dogs were also affected at higher doses. Bone/cartilage and tooth-forming structures were only affected in rats. In dogs, epithelial effects were seen in the cornea; however, the dose-dependency of this cornea observation was not evident. No other ophthalmologic abnormalities, associated with BYL719 treatment, were observed in rats or in dogs.

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

Cardiac safety studies, conducted *in vitro* and *in vivo*, did not indicate an electrophysiological risk. Furthermore, BYL719 in the rat safety pharmacology studies showed no effect on neuronal or pulmonary function, and no evidence of a phototoxic potential was found in a 3T3 neutral red uptake test *in vitro*.

In conclusion, the majority of the observed toxicological effects of BYL719 were related to the pharmacological activity of BYL719 as a p110α specific inhibitor of PI3K pathway, such as an influence on insulin (and potentially glucose) homeostasis and the risk of increased blood pressure. The pharmacologically relevant toxicity was mainly observed at dosages close

to or at MTD with the bone marrow and lymphoid tissue, pancreas, and some reproductive organs of both genders being the main target organs of the toxic effects (refer to the [BYL719 Investigators Brochure] for further details).

Genotoxicity status of BYL719

BYL719 is not genotoxic *in vitro*, based on the results of an Ames test and a chromosome aberration test.

1.2.1.2 Clinical experience

There are six ongoing studies assessing the safety and tolerability of BYL719 in solid tumors: [CBYL719X2101], [CBYL719X1101], [CBYL719X2104], [CBYL719X2105J], [CMEK162X2109] and [CSTI571X2103]. These trials are briefly described below with a focus on safety and efficacy data for the first-in-human dose escalation study [CBYL719X2101].

[CBYL719X2101]: is a first-in-human phase 1 study of oral BYL719 in adult patients with advanced solid malignancies whose tumors have an alteration of the PIK3CA gene. This study also includes the investigation of BYL719 in combination with fulvestrant in patients with HR-positive advanced or metastatic BC.

Clinical safety of BYL719

As of 20th May 2014, 134 patients had been enrolled into the single dose arm of the study [CBYL719X2101]. Nine patients were still on treatment, and 124 had discontinued; of those, 99 patients (73.9%) discontinued due to disease progression, 19 patients (14.2%) due to AEs, 3 patients (2.2%) due to withdrawn consent, and 3 patients (2.2%) due to death. The median age of patients was 58.5 years (range 21 to 82), with the majority of patients (70.9%) below 65 years of age. The majority (92.5%) of patients were Caucasian. The male/ female ratio was 36/98, and baseline ECOG performance status was 0 or 1 in all patients (33.3% and 66.7%, respectively). Nine dose levels have been tested using a QD dosing regimen: 30 mg (N=1),60 mg (N=3), 90 mg (N=6), 180 mg (N=6), 270 mg (N=4),300 mg (N=8), 350 mg (N=6), 400 mg (N=65), and 450 mg (N=9).Three dose levels have been tested using a BID dosing regimen: 120 mg (N=5), 150 mg (N=15), and 200 mg (N=6). In the single agent arm of this study, the maximum tolerated dose (MTD) of BYL719 was determined to be 400mg QD. The median duration of exposure across all dose levels was 11.9 weeks (range 0.4 to 105.6).

A total of 127 patients (94.8%) experienced AEs suspected of being drug related, the most frequent of which were hyperglycemia (65 patients, 48.5%), nausea (64 patients, 47.8%), diarrhea (53 patients, 39.6%), decreased appetite (50 patients, 37.3%), vomiting (39 patients, 29.1%) and fatigue (37 patients, 27.6%). Grade 3 or 4 AEs were experienced by 100 patients (74.6%), of which 57 patients (42.5%) experienced Grade 3 or 4 AEs suspected of being drug related. The most common treatment-related Grade 3 or 4 event was hyperglycemia (32 patients, 23.9%); all other Grade 3 to 4 AEs occurred in ≤ three patients. For further details, refer to current [BYL719 Investigators Brochure].

In the combination part of the study with fulvestrant, 74 patients had been enrolled as of 20th May 2014; thirty patients (40.5%) were still on treatment and forty four (59.5%) had discontinued: thirty patients (40.5%) due to disease progression, seven patients (9.5%) due to

[redacted]

AEs, five patients (6.8%) due to withdrawn consent, and one patient (1.4%) each for lost to follow up and administrative reasons.

Three dose levels have been tested in the combination part of the study using the QD regimen: 300 mg (N=9), 350 mg (N=7) and 400 mg (N=58). The MTD was declared at 400mg QD BYL719 in combination with fulvestrant intramuscular (IM) at 500mg/q28 days. Sixty seven patients (90.5%) experienced at least one suspected treatment-related AE. The most frequent AEs suspected of being drug-related were hyperglycemia (33 patients, 44.6%), diarrhea (32 patients, 43.2%), nausea (24 patients, 32.4%), decreased appetite (18 patients, 24.3%), vomiting (18 patients, 24.3) and fatigue (17 patients, 23.0%).

For further details, refer to the current [BYL719 Investigators Brochure].

In addition, the following Novartis-sponsored clinical studies are conducted with BYL719 either as single agent or combination study:

[CBYL719X1101] is a phase I study of BYL719 in adult Japanese patients with advanced solid malignancies. The study was initiated in September 2011. As of the cutoff date of 20th May 2014, 27 patients had been enrolled, of which 2 were still on treatment and 25 had discontinued (5 due to AEs, 17 due to lack of efficacy, 2 due to patient/guardian decision, and 1 due to death). The median age of patients was 55.0 years (range 24.0 to 76.0). Five dose levels have been tested in the dose escalation part, all using QD regimen: 90 mg (N=3), 180 mg (N=4), 270 mg (N=5), 350 mg (N=6), and 400 mg (N=7). An expansion part is ongoing at the dose of 350 mg (N=2). Two patients in the 400 mg QD cohort experienced dose-limiting toxicities: (DLT) one patient Grade 3 maculopapular rash and one patient Grade 3 maculo-papular rash with Grade 2 conjunctivitis. The recommended phase 2 dose (RP2D) was declared at 350 mg BYL719 QD. The median duration of exposure across all dose levels was 56.0 weeks (range 17.0 to 440.0).

[CBYL719X2104]: BYL719 is being tested in combination with cetuximab in patients with head and neck squamous cell cancer (HNSCC) in a phase Ib dose escalation trial.

For Arm A, the RP2D was declared to be 300 mg QD BYL719 in combination with cetuximab. For Arm B, the RP2D which was declared after the cut-off date, was also 300 mg QD BYL719 in combination with cetuximab. The median duration of exposure to study treatment was 12 weeks for Arm A and 6 weeks for Arm B, respectively. For both Arm A and Arm B, the RP2D for BYL719 in combination with cetuximab has been declared at 300 mg QD. For further details, refer to current [BYL719 Investigators Brochure].

[CBYL719X2105J]: a Phase Ib/II open-label study of the combination of BYL719 plus AMG 479 (ganitumab) in adult patients with selected advanced solid tumors.

[redacted]

[redacted]

[CMEK162X2109]: a Phase Ib, open-label, multi-center, dose escalation and expansion study of an orally administered combination of BYL719 plus MEK162 (binimetinib) in adult patients with selected advanced solid tumors. [redacted]

[CSTI571X2103]: a Phase Ib multicenter study of imatinib in combination with BYL719 in patients with gastrointestinal stromal tumor (GIST) who failed prior therapy with imatinib and sunitinib. As of 20th May 2014, 38 patients have been enrolled to study treatment. For more information, refer to [Imatinib (Glivec) Investigators' Brochure].

[CBYL719XUS03T] is an ongoing phase Ib study the evaluates the combination of BYL719 and letrozole in metastatic HR-positive BC. The RP2D of BYL719 in combination with letrozole was declared at 300 mg. Rash was the DLT at 350 mg. The most common AEs were consistent with those observed with BYL719 single agent, i.e. rash, hyperglycemia, nausea, fatigue, and diarrhea.

Clinical efficacy in ER+ metastatic breast cancer (MBC) [CBYL719X2101]

In [CBYL719X2101], 133 patients were evaluable for efficacy as of 20 May 2014. Seven patients (5.3%) experienced a confirmed partial tumor response (PR); an additional eight patients (6.0%) achieved an unconfirmed PR; and 70 patients (52.6%) had SD; 21 patients (15.8%) could not be assessed for tumor response per RECIST. All tumor responses were observed following treatment with total daily dose of 270 mg BYL719 orhigher. The disease control rate (CR/PR/SD, including unconfirmed PR) was 57.9% (Juric 2014).

Eighty-four patients had been enrolled (50 with PIK3CA mut tumors, 31 wild-type, 3 unknown). The MTD for BYL719 was declared at 400 mg, with DLTs in 4 patients (diarrhea, vomiting, decreased appetite, abdominal distension and fatigue). Preliminary efficacy results have been reported (Janku F, SABCS 2014). Best overall response achieved was confirmed PR for 12 (24%) patients and SD for 28 (56%) patients with PIK3CA mutated tumors vs SD in 14 (45%) patients with PIK3CA wild-type tumors. Disease control rate was 80% (95% CI: 66.3–90.0) and 45% (95% CI: 27.3–64.0) in the PIK3CA mutated and PIK3CA wild-type groups, respectively. Estimated median PFS was longer in the PIK3CA mutated group vs PIK3CA wild-type group (8.3 months vs 4.7 months).

Preliminary efficacy data have also been reported for the phase Ib study [CBYL719XUS03T] that evaluates BYL719 in combination with letrozole in post-menopausal women with HR-positive HER2-negative BC (n=26). Three patients (11%) achieved a PR and 14 (54%) had SD as their best response (clinical benefit rate [PR + SD ≥6 months] of 27% (Mayer 2014)

1.2.1.3 Clinical pharmacokinetics of BYL719

Preliminary pharmacokinetic data of study [CBYL719X2101] showed that BYL719 is well absorbed after oral administration. Median time to reach the peak plasma concentration (Tmax) at the MTD dose (400 mg once daily) was 2 hours. Tmax did not correlate with dose and the median values at different doses spanned a wide range (range 1 to 7 hours), both after single and repeated dose. Plasma concentrations of BYL719 generally declined in a mono-exponential manner, suggesting rapid distribution towards the tissue (relative to absorption).

[redacted]

Median terminal elimination half-life (T1/2) after a 400 mg oral dose was 7 to 8 hours and generally appeared to be independent of dose and time. Steady-state BYL719 plasma levels can be expected to be reached at 2 to 3 days following onset of therapy in most patients.

At the MTD (400 mg QD), Cmax and drug exposure within a dosing interval (AUC0-24h) after one month of daily dosing (steady-state) were 3560 ng/mL (range 501; 7930), and ~39600 hr*ng/mL (range 5210; 81700), respectively (Table 5-2). At clinical relevant doses (270-400 mg) between-subject variability in Cmax and AUCinf (CV%) was moderate to high with 40-60% at C1D8.

The median accumulation ratio (Racc) of BYL719 across all dose levels and regimens ranged between 1.0 and 2.0, which is in agreement with the short T1/2 of BYL719. At 400 mg QD the median Racc was 1.2 after 1 week. An apparent higher drug accumulation than expected based on the drug half-life was observed in some patients, with no clear relationship with dose. Also, an approximate dose proportional increase in both Cmax and AUC was found, indicating no relevant deviation from linear pharmacokinetics.

1.2.1.4 Potential drug-drug-interactions between BYL719 and letrozole

As BYL719 is a time dependent inhibitor of CYP3A4, and CYP3A4 is the main metabolism pathway for letrozole, there is likelihood for an increase of letrozole plasma exposure when combined with BYL719 at 350 mg QD. Based on the median Cmax observed for BYL719 in [CBYL719X2101] an increase in letrozole exposure of between 1.6 and 4-fold is predicted at steady-state when not accounting for induction of CYP3A4 (see below). Because the normal half-life of letrozole is long (about 2 days), reduction in clearance due to a drug-drug-interaction with BYL719 could prolong the time to reach elevated steady state levels depending on the magnitude of the potential change in half-life. Dynamic DDI predictions by SimCYP based on PK models of BYL719 (400 mg QD dose) and letrozole, simulated over a time of 24 days, showed that the steady state was not yet reached at day 24 and predicted a median increase of > 1.8 fold. As a recent phase II trial (Dixon 2001) showed no safety concerns with an administration of 10 mg letrozole daily in the neoadjuvant setting over a period of three months, a safety margin of at least 4-fold can be expected if PK is linear to this dose. Thus, even if an interaction can be confirmed it is postulated that this margin will be sufficient to alleviate the safety risk. At 300mg QD BYL719 a lower increase in letrozole exposure is predicted in comparison to the dose at 350 mg, further reducing the safety risk for the combination of BYL719 and letrozole.

In addition, based on new *in vitro* findings that BYL719 is also a potential inducer of CYP3A4 and growing evidence that time-dependent inhibition and induction are balancing each other out (see Section 1.2.1.1.2), an interaction is considered to unlikely. This has also been supported by preliminary clinical PK data from study [LEE011X2107] showing that in combination of letrozole with BYL719 (doublet assessment, Arm 2) letrozole exposure was comparable or rather slightly lower relative to historical single agent data for letrozole on both Day 1 and Day 21 of the first cycle.

An interaction is not anticipated to have an impact on BYL719 exposure. Letrozole itself is a reversible but strong inhibitor of CYP2A6 and moderate inhibitor of CYP2C19

[redacted]

(see Section 1.2.3). Since BYL719 is not metabolized by either of these cytochrome P450 isoenzymes (see Section 1.2.1.1.2), a drug-drug-interaction based on metabolism is unlikely.

1.2.2 Overview of buparlisib (BKM120)

Buparlisib (BKM120) is a potent and highly specific oral pan-class I (PI3K) inhibitor that is a 2, 6-dimorpholino pyrimidine derivative. This compound has been studied extensively in non-clinical models and is currently being evaluated in clinical trials. Further information concerning the non-clinical and clinical properties of buparlisib may be found in the [Buparlisib Investigator's Brochure].

1.2.2.1 Non-clinical experience of buparlisib

1.2.2.1.1 Pharmacodynamics of buparlisib

Buparlisib inhibits wild-type PI3Kα (IC_{50}: 35 nM), with greater than 50-fold selectivity compared to activity against other protein kinases outside the PI3K family. The compound is equipotent against somatic PI3Kα mutants (H1047R-, E542K- and E545K-p110α) and is active against the other three PI3K paralogs (PI3Kβ, -γ, -δ; IC_{50} 108 to 348 nM range). buparlisib does not significantly inhibit the related kinases mTOR or Vps34, nor does it inhibit (IC_{50} >10 μM) other receptors and ion channels profiled.

1.2.2.1.2 Non clinical pharmacokinetics and metabolism of buparlisib

Buparlisib showed favorable pharmacokinetic properties in all animal species tested. The absorption of [14C]-buparlisib- related radioactivity was > 84% in the rat. Oral bioavailability was moderate to high in rats, dogs and monkeys (42-100%). The estimated steady state plasma volume of distribution (Vss) was moderate in all species (3.0–3.5 L/kg). Buparlisib penetrated the blood brain barrier in rats with a tissue-to-plasma ratio about 2. Buparlisib was moderately bound to plasma protein across all species examined (free fraction ~15% and independent of concentration in humans).

Oxidative metabolism of buparlisib is predominantly mediated by cytochrome P450 (CYP) isoenzyme 3A4 *in vitro*. Recombinant human CYP1A1 also has the capacity to metabolize buparlisib; however, its endogenous expression in the human liver is negligible, and therefore it is not expected to have any impact on hepatic buparlisib metabolism. Direct Phase II metabolism (glucuronidation) via UGT1A4 is also observed in human liver microsomes supplemented with uridine diphosphate glucuronic acid (UDPGA). All Phase I metabolites identified in human hepatocytes and microsomes are not unique to humans and were also detected in animals. Buparlisib and identified metabolites have a low potential for covalent binding to protein.

At the concentrations observed in the clinic, buparlisib is a weak reversible inhibitor of CYP3A4 (IC50=8μM, Ki = 13.6 μM,). The [I]/Ki ratio was estimated around 0.3. It also weakly inhibits the CYP2C family (2C8, 2C9 and 2C19) with IC50 values ranging from 35–65 μM. Buparlisib did not show time-dependent inhibition of CYP450 enzymes. With respect to transporter-based drug-drug interactions, buparlisib is not an inhibitor or substrate of Pglycoprotein (P-gp), multidrug resistance associated protein (MRP)-2, breast cancer resistance protein (BCRP), or OCT-2. Buparlisib can inhibit hMATE1 and hMATE2K *in vitro*

[redacted]

at concentrations above 10 μM. Based on the observed free concentrations of buparlisib in plasma, the impact *in vivo* of such inhibition is expected to be very limited. It is possible that buparlisib activates the pregnane X receptor (PXR) *in vivo* and induces CYP3A4 at concentrations ≥50 μM; however, the absence of any time-dependent changes in the pharmacokinetics of buparlisib in the relevant therapeutic dose range in humans suggests that this might not be relevant *in vivo*. Finally, experiments showed a potential for buparlisib to induce UGT1A1 at concentrations between 0.5 and 100 μM. The mean maximum free concentration calculated at steady state to date in the study [CBKM120X2101] was 0.671 μM (Cmax, tot=4.20 μM). Therefore a potential induction of UGT1A1 cannot be formally excluded, although the clinical relevance of observed activation of UGT1A1 activity is unclear.

1.2.2.1.3 Safety pharmacology and toxicology of buparlisib

Safety pharmacology and toxicology

Safety pharmacology studies in rats revealed no effects on neuronal (behavior) or respiratory functions. Cardiac safety studies, conducted *in vitro* and *in vivo* did not indicate a prominent electrophysiological risk. No relevant electrophysiological effect was seen in dogs. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure that was observed in two dog telemetry studies. In rats and dogs, clinical pathology and histopathology findings showed quantitative reductions of lymphoid and erythroid counts and lymphoid tissue hypoplasia.

The pancreas was seen to be affected by treatment with buparlisib, particularly in dogs, where acinar cell toxicity was seen in the exocrine part of this organ. In the 4-week study in rats, no pancreatic toxicity was observed. However, at higher doses in the 2-week dose-range-finding study in rats, there were histopathological findings in both the endocrine as well as the exocrine pancreas.

Male sexual organs and associated tissues were found to be targets of toxicity in both rats and dogs. Changes included minimal to slight germ cell depletion, formation of spermatic giant cells and abnormal spermatids, and cellular debris in epididymal tubules. Testicular toxicity did not fully reverse after the 4-week treatment-free period in rats (highest dose), although a clear trend towards recovery was seen. In individual female rats, minimal to slight cyst formation occurred in the Graafian follicles. In dogs, there was no effect on female sexual organs.

Glucose homeostasis was affected in various species (mice, rats, dogs), as expected from the mode of action of buparlisib. However, these effects were minimal in both rats and dogs at the doses used in the 4-week studies.

Other safety considerations include:

- No evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests *in vitro* with buparlisib. However, evidence of a genotoxic potential with buparlisib has been seen *in vitro* and *in vivo* and is likely due to an aneugenic effect.
- No phototoxic potential or any effect on wound healing has been identified with buparlisib in pre-clinical studies.

[redacted]

In conclusion, the majority of the observed effects were related to the pharmacological activity of buparlisib as an inhibitor of PI3K, such as a potential influence on glucose homeostasis and the risk of increased blood pressure.

Genotoxicity status of buparlisib

In preclinical *in vitro* and *in vivo* studies, buparlisib elicited a genotoxic potential. Although no evidence for a direct DNA interaction was found in an Ames test and in two chromosome aberration tests *in vitro*, an aneugenic potential was observed in the latter. Because clinical studies with buparlisib enroll patients with advanced malignancies that often have no remaining standard treatment options, it is deemed justified to include adults (men and women of childbearing potential) with the clear recommendation to all patients that they must use appropriate contraception.

1.2.2.2 Clinical experience of buparlisib

As of September 8th, 2014, approximately 3000 patients and healthy volunteers have been enrolled into 35 Novartis sponsored clinical studies of buparlisib, including 5 blinded phase II or III studies (for further details please refer to the [Buparlisib Investigators' Brochure]):

1. Phase I single agent studies [CBKM120X2101], [CBKM120X1101], [CBKM120Z2102], [CBKM120C2110], [CBKM120C2104], [CBKM120C2106], [CBKM120C2111], [CBKM120C2102], [CBKM120C2108], [CBKM120C2113] and [CBKM120C2114].
2. Phase I combination studies [CBKM120B2101], [CBKM120X2107], [CBKM120E2101], [CBKM120E2102], [CBEZ235A2118], [CLDE225X2114], [CSTI571X2101], [CMEK162X2101], [CINC424A2104], [CBEZ235D2101], [CBKM120D2204] [CBKM120D2205], [CLEE011A2112C] and [CLEE011X2108].
3. Phase II single agent studies [CBKM120C2201], [CBKM120Z2402] and [CBKM120D2201].
4. Phase II combination studies, [CBKM120F2203], [CBKM120H2201], [CBYL719A2201] [CBKM120F2202] and [CINC280X2204].
5. Phase III double-blind randomized combination studies [CBKM120F2302] and [CBKM120F2303]

1.2.2.2.1 Human safety, tolerability data, single agent buparlisib

Generally, single agent buparlisib is well tolerated with the majority of the reported adverse events (regardless of study drug relationship) being mild or moderate (Grade 1 or 2) and transient in nature.From current clinical experience, special attention needs to be paid to the following side effects: hyperglycemia, psychiatric disorders, liver toxicity, skin rash / hypersensitivity, lung toxicity and pneumonitis. Details on these AEs of special interest are briefly summarized below.Please refer to [Buparlisib Investigator's Brochure] for more detailed information on specifics of clinical safety and tolerability of buparlisib.

Hyperglycemia

The PI3K/AKT pathway is important in regulating glucose metabolism, particularly by regulating glucose transport into adipocytes and muscle tissue. Therefore, hyperglycemia is considered to be an "on target" effect of buparlisib, and it has been commonly observed in

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patients treated with buparlisib with an incidence of all-grade hyperglycemia ranging between 17.6% in [CBKM120B2101] and 63.6% in [CBKM120D2205] study, and Grade 3 or 4 between 7.3 in [CBKM120X2101] and 36.4% in [CBKM120D2205]. The highest rate of hyperglycemia has been observed in trials conducted in patients with controlled diabetes mellitus such as [CBKM120C2201] and in [CBKM120D2205] study requiring corticosteroid as premedication for docetaxel (current version of Buparlisib IB).

In order to mitigate the potential risk of developing uncontrolled hyperglycemia, conservative inclusion/exclusion criteria are implemented in the protocol as well as detailed guidelines to monitor patients.

Psychiatric and mood disorders

There is evidence indicating that the modulation of AKT/GSK3 signaling pathway may play an important role in the behavior regulation (Beaulieu et al 2009). Psychiatric side effects events have been reported in patients treated with buparlisib and are currently under investigation. The current data does not allow the identification of any sign or symptom that could predict patient susceptibility to buparlisib induced psychiatric disorders. At least one AE (regardless of study drug relationship) belonging to system organ class (SOC) "psychiatric disorders", which include a broad range of AEs e.g. depression, anxiety, mood altered, confusional state, affective disorders, insomnia, hallucination, panic disorders, suicidality, have been reported. The overall frequency ranges between 23.5% [CBKM120B2101] to 66.7% [CBKM120X1101] of patients treated with buparlisib monotherapy and combination. Overall the incidence of grade 3 and 4 psychiatric events ranged from 0 to 13.2%. The frequency of mood disorders, regardless of study drug relationship, ranged from 0% in [CBKM120B2101] and [CBKM120Z2402] studies to 44.4 % in [CBKM120X2101] study, the majority of events being of grade 1 or 2 severity.

Conservative inclusion/exclusion criteria are implemented in the protocol as well as detailed guidelines to monitor patients, including the use of PHQ-9 and GAD-7 questionnaires, and psychiatric consultation. Psychiatric consultation should be performed by a qualified person able/entitled to make correct diagnosis and prescribe appropriate treatment, preferably by a psychiatrist.

Liver toxicity

Although transaminase increases are relatively common, only a few of the patients with liver function tests (LFTs) alterations had other simultaneous observations related to impair liver function (e.g. bilirubin increase or clinical symptoms). Based on these findings, conservative inclusion criteria and guidelines to monitor and to follow patients with LFT alterations (including dose and schedule modifications) are currently implemented in study protocols investigating buparlisib.

The rates of liver toxicity observed with buparlisib in combination with conventional chemotherapy and/ or with targeted therapies are similar to those reported in single agent trials. Liver function test (LFT) alterations observed during ongoing and completed studies have been mostly transaminase enzyme increases (ALT and/or AST). The frequency of liver toxicity thus defined, regardless of study drug relationship, ranged from 4.2% from [CBKM120Z2402] to 44.4 % in [CBKM120X1101] study, the majority of events being of

[redacted]

grade 1 or 2. The highest rate of grade 3 and 4 LFT alterations have been observed in [CBKM120Z2102] study conducted as single agent in Chinese patients (64.7%) including a cohort of 17 patients treated at 100mg/d.

Between 25 to 45% of patients treated with single agent buparlisib reported liver toxicity (all grades, regardless of study drug relationship, 100 mg/d dose) based on a search of multiple MedDRA event terms (e.g. SMQ preferred terms). The incidence of grade 3 and 4 events was approximately 10 to 30%. Liver function test (LFT) alterations observed during ongoing and completed studies have been mostly transaminase enzyme increases (ALT and/or AST). Data suggest a slightly higher rate of grade 3 and 4 liver enzyme elevations in Japanese patients (44%) in the [CBKM120X1101] study, however, the number of patients treated at 100 mg in this study was limited (n=9). Transaminase elevations typically occur during the first 6 to 8 weeks of treatment start.

Although transaminase increases are relatively common, only a few of the patients had other simultaneous observations related to impaired liver function (e.g. bilirubin increase or clinical symptoms).

Based on these findings, conservative inclusion criteria and guidelines to monitor and follow patients with LFT alterations (including dose and schedule modifications) have been implemented. Please refer to the respective inclusion/exclusion criteria and Section 5 in this protocol for more detailed guidelines.

A recent liver safety review across Novartis-sponsored trials with buparlisib identified several potentially drug-induced liver toxicity (DILI) cases (e.g. AST/ALT >3.0 x ULN and TBL >2.0 x ULN at any time during the treatment, regardless of causality. Upon medical review, most of these cases occurred in the context of disease progression in terminally ill, advanced cancer patients and/or were confounded by other causes. However, six of these DILI candidates were consistent with Hy's law criteria (e.g. AST/ALT >3.0x ULN and TBL >2.0xULN in the absence of cholestasis and other explanatory causes) with probable causal relationship to study treatment. Five of these cases were enrolled in the study [CBKM120F2302], a double-blind phase III randomized study that evaluates buparlisib or buparlisib/placebo in combination with fulvestrant in metastatic HR-positive breast cancer; and one study evaluating buparlisib in combination with the investigational drug LDE225 (sonidegib). All patients have recovered upon treatment discontinuation except one patient for whom no data is available since the patient refused to return for safety follow-up.

Skin rash and hypersensitivity

Skin rash is commonly observed in patients treated with buparlisib. The rate of skin rash and other related event terms MedDRA Version 16.0 and Novartis Medical Queries (NMQs) is ranged from 23.5% in [CBKM120Z2102] study conducted in Chinese patients to 85.3 % in [CBKM120B2101] study conducted in combination with MEK inhibitors in patients with advanced solid tumors

The frequency of skin rash reported in studies of buparlisib in combination with other agents might be slightly higher when buparlisib is combined with trastuzumab (45.3%) in [CBKM120X2107] study or with MEK inhibitor (85.3%) in [CBKM120B2101] study (Table 5-26).The skin rashes seen have no typical location or distribution pattern, are mainly

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papulo-macular (only a minority acneiform) and are frequently associated with pruritus. Events have been reversible after treatment interruption and/ or dose reduction. Effective medications have included antihistamines, topical corticosteroids and/or low-dose systemic corticosteroids (the latter should be used with caution due to the increased risk of hyperglycemia). There have been few cases reported of allergic reactions and DRESS (drug rash with eosinophilia and system symptoms), but these have not been of acute onset or of a severe nature.

Complementary information collected suggests that sun exposure may exacerbate the condition and should be avoided; however, genuine photosensitivity reaction has not been confirmed and no phototoxic potential was seen pre-clinically. Patients are advised (e.g. in the written patient information) to avoid sun exposure, or take measures to protect themselves from intense sunlight, during study treatment.

Lung Toxicity/Pneumonitis

Lung changes compatible with pneumonitis have not been observed in the preclinical setting. The safety database, as of 08-Sep-2014 contains in total 30 cases reporting 31 events including 23 events of pneumonitis occurring in buparlisib trials, and 8 events of interstitial lung disease (ILD). Twenty seven of these 30 cases were reported as suspected to treatment with buparlisib, and 5 of these had a fatal outcome. One fatal case was in a complex clinical context, combining progression of lung metastases and possible infection with pneumocystis carinii or cytomegalovirus. [redacted] The third case was a patient with lung cancer who was reported to have non-infective inflammatory ILD and died. The investigator considered that the underlying malignancy was an alternative causal explanation. The fourth case occurred in a patient with metastatic breast cancer enrolled in a combination trial of buparlisib and fulvestrant and was not suspected to buparlisib but to the progression of the underlying disease. The last case was reported in subject who received abiraterone acetate plus buparlisib for prostate cancer. The CT scan features were consistent with pneumonitis rather than with an infection. The investigator reported that the pneumonitis was suspected to buparlisib. Ten of the non-fatal suspected cases were reported as resolved or improving. Others were unchanged or improving at the latest report, or the outcome not reported. The currently available data support preliminary assessment of causal relationship of pneumonitis with buparlisib treatment. Clinical activity of buparlisib in Breast Cancer

The main clinical safety and efficacy experience of buparlisib given for the treatment of breast cancer patients is based on the completed Phase I first-in-human study of single agent oral buparlisib [CBKM120X2101] and the completed phase Ib study [CBKM120XUS13T], where buparlisib was combined with letrozole (2.5 mg/day) (Mayer 2014).

The CBKM120X2101 study was designed as a Bayesian dose-escalation trial with an MTD dose-expansion arm enrolling patients with advanced solid tumors. Out of the total 83 patients treated in the study, twenty one had metastatic breast cancer (Rodon 2011). At the cut-off date of 4th July 2011 and for the MBC patients, the most common adverse events (AEs) (25%) (all Grades) included nausea and fatigue/asthenia, each in 9 patients (43%), anxiety and diarrhea, each in 8 patients (38%), hyperglycemia and rash, each in 7 patients (33%) and decreased

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appetite, depression and pruritus in 6 patients each (29%). Fatigue/asthenia and transaminase increase were the most common Grade 3 AEs suspected to be related to the study drug, and were observed in 3 patients each. The only Grade 4 AE suspected to be related to buparlisib was hyperglycemia, which was observed in 1 patient at the 150 mg/day dose level. Overall, buparlisib was well tolerated with only a minority of patients experiencing grade 3 and 4 toxicities. The safety profile for MBC patients is similar to the safety profile for the full population enrolled in the [CBKM120X2101] study.

At the cut-off date of 4th July 2011, twenty breast cancer patients were evaluable for objective tumor response by RECIST 1.0. Two breast cancer patients exhibited partial responses, which were confirmed in a triple-negative MBC patient, and unconfirmed in an ER-positive HER2-negative MBC patient. For these 2 patients, the treatment duration was respectively 27 months (ongoing) and 5 months. An additional 8 breast cancer patients (40%) had stable disease (Rodon 2011).

An ongoing phase Ib study of buparlisib and fulvestrant in post-menopausal women with metastatic HR-positive HER2-negative BC (n=31) has been reported. A similar toxicity profile for buparlisib in combination with fulvestrant to that reported for buparlisib given as a single agent (Ma C et al 2013). The observed grade 3 and 4 events in continuos schedule (n=6) were grade 3 ALT increase in 2 cases, and grade 3 rash and hyperglycemia in one case each; in intermittent schedule (n=11), grade 3/4 ALT increase in 2 cases, grade 3 AST increase and hyperglycemia in one case each. The authors concluded that a slightly lower incidence of severe AEs were observed with the intermittent dosing schedule. In addition, in a recent update of this study a similar outcome in terms of tumor response and treatment duration has been reported with both the continuos and intermittent schedules (Ma et al 2014).

In the completed phase Ib study [CBKM120XUS13T], buparlisib was combined with letrozole (2.5mg/day) (Mayer 2014). Results are presented in Section 1.2.4.

1.2.2.2.2 Clinical Pharmacokinetics

Buparlisib has been administered from 25 mg to 150 mg daily, and the single agent RP2D is 100 mg. When orally administered, buparlisib is rapidly and well absorbed, and the extent of absorption is estimated to be between 57 and 85%, with a median Tmax between 0.5 and 3 hours after administration. Cmax and AUC appeared to be linear in the tested range, with an estimated slope close to 1, but the 90% CI for both AUC0-24, [0.75, 1.21], and Cmax, [0.72, 1.16], was fairly wide, most likely due to low sample size at extreme doses. In plasma, buparlisib concentrations follow a bi-exponential decay, with a long terminal half-life that could not be well estimated given the initial sampling schedule used after daily dosing. It was however well estimated from the terminal half-life cohort and was found to be 48 hours.

After repeated dosing the effective half-life (T1/2, acc), was obtained from the observed drug accumulation (Racc). The median T1/2, acc (T1/2 accumulation) calculated from exposure data on Day 28 ranged between 36 and 58 hours across all dose levels. After repeated single dose, steady state is reached in 8 days with an accumulation ratio around 3.

The intermittent schedule QD 5 days on / 2 days off employed in this study was assessed based on a population pharmacokinetic model (Novartis Internal Data). This alternative regimen has the benefit of maintaining a weekly exposure slightly higher than an 80 mg QD regimen. The mean

exposure (AUCtau) was predicted to be around 114000 ng x h/mL with an estimate for oral plasma clearance (CL/F) of 4.38 L/h, while the weekly exposure under daily dosing of buparlisib would be 154000 ng.h/mL for 100 mg QD and 126000 ng.h/mL for 80 mg QD, respectively. In the [CBKM120X2101] study, the maximum concentration (Cmax) reached at steady-state whith a 100 mg QD regimen was reported to be 1939 ng/mL while the Cmax achieved on the Day 5 of the alternative regimen was predicited to be only 1440 ng/mL. Therefore, this alternative regimen presents the benefit of decreasing Cmax, maintaining an efficacious level of exposure to ultimately propose a better safety profile for buparlisib.

Buparlisib is eliminated mainly through metabolism in a plethora of entities. After administration of a single dose of [^{14}C]-buparlisib, 51% of the radioactivity was recovered in urine even though buparlisib only contributed to less than 2%. The remainder of the radioactivity was recovered in feces, with buparlisib representing 15%, all other metabolites being below 5%. CYP3A4 was found *in vitro* to be a major contributor to buparlisib metabolism together with direct glucuronidation, which contributes to less than 10%.

A drug-drug interaction study has recently been conducted with a strong CYP3A4 inhibitor (ritonavir) [CBKM120C2111], showing only a 1.73 fold increase of the exposure and 1.19 fold of Cmax when buparlisib was co-administered with ritonavir. These findings support the involvement of the CYP3A4 in the metabolism of buparlisib but to a lower extend that anticipated from *in vitro* results. The increase of exposure was not considered as clinically relevant and moderate CYP3A4 inhibitors (and consequently inducers) can be used with caution on the basis of this trial. This is also in line with the results of a drug-drug interaction study with dexamethasone (a weak CYP3A4 inducer) [CBKM120C2106] which showed no significant change in buparlisib pharmacokinetics.

1.2.2.3 Potential drug-drug-interactions between buparlisib and letrozole

The chance of a clinically important drug-drug interaction between letrozole and buparlisib is low. Both drugs are metabolized primarily via CYP3A4. While *in vitro* tests have indicated burparlisib is a weak inhibitor of CYP3A4 (see Section 1.2.2.1.2), letrozole exposure could be increased.

In a phase Ib study [CBKM120XUS13T], buparlisib (100mg QD or 5 on/2 off days) was combined with letrozole (2.5mg QD) in ER+/HER2- postmenopausal breast cancer patients (see Section 1.2.4), and the combination was found to be both safe and well-tolerated.

1.2.3 Overview of letrozole

Letrozole is a non-steroidal competitive inhibitor of the aromatase enzyme system with demonstrated efficacy in the treatment of postmenopausal patients with HR+ breast cancer. Letrozole acts by inhibiting in a highly selective fashion the conversion of adrenal androgens estrogens, which is the primary source of estrogens in postmenopausal women. Letrozole is a highly selective inhibitor of aromatase that induces 75% to 95% decrease of estrogen levels after two weeks of treatment with daily doses of 0.1 to 5 mg, with no significant clinical and laboratory toxicities or changes in levels of other hormones of the endocrine system as shown in early phase I (Lipton 1995; Trunet 1996). It is indicated for the adjuvant treatment of women with HR+ early breast cancer as well as the extended adjuvant treatment of patients who have received 5 years of tamoxifen therapy. It is also indicated for the treatment of

[redacted]

advanced HR+ breast cancer, both in the first-line setting as well as in patients who have disease progression following anti-estrogen therapy. Letrozole was compared with tamoxifen in a Phase III trial in the first line setting in ER+/HER2+ breast cancer. Letrozole was superior to tamoxifen for time to progression (median, 9.4 v. 6.0 months) and median OS trended superior for letrozole (median, 34 v. 30 months) but this difference was not statistically significant (Mouridsen et al 2001).

Letrozole is administered orally at a dose of 2.5 mg and is rapidly and completely absorbed from the gastrointestinal tract. Concomitant intake of food has no effect on the extent of letrozole absorption and only a minor effect on the rate of absorption, which is considered to be of no clinical relevance. The terminal elimination half-life of letrozole is 2 days and steady-state plasma concentration with daily dosing at the standard dose is reached in 2-3 weeks. Letrozole is metabolized primarily via CYP3A4 to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. In addition, CYP2A6 forms the carbinol metabolite as well as its ketone analog. *In vitro* metabolism studies performed to examine the inhibition of cytochrome P450 enzymes showed that letrozole is a reversible inhibitor of CYP2A6 (Ki = 0.12 µM, strong) and CYP2C19 (Ki = 9 µM, moderate). Based on its labeling, no further information is available on the induction and inhibition potential of letrozole on other metabolizing enzymes or transporters (Femara Prescribing Information).

The most frequently reported adverse events that were significantly different from placebo for letrozole in the adjuvant and extended adjuvant setting include hot flashes, arthralgia/arthritis and myalgia. In the first line setting, the most frequently reported adverse events include musculoskeletal pain (bone/back pain and arthralgia), hot flashes, nausea and dyspnea and incidences of adverse events were similar for tamoxifen in this setting. In general, the observed adverse reactions are mild to moderate in nature. (Femara SmPC)

Refer to the package insert of the local supply of letrozole for more details.

1.2.4 Overview of BYL719/buparlisib plus letrozole

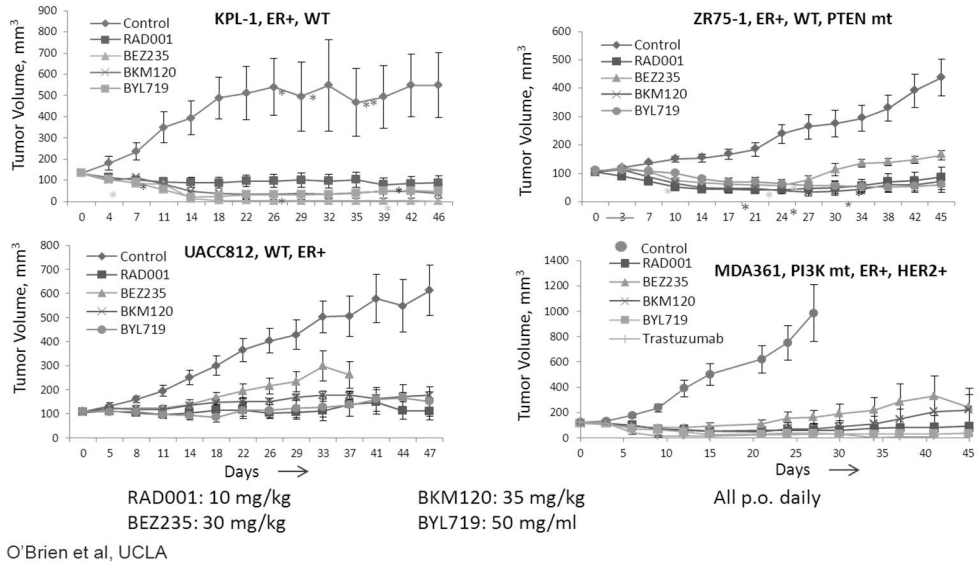
The relevant role of the PI3K pathway activation in breast carcinoma has been described in Section 1.1.3. BYL719 and buparlisib are potent and highly specific oral class I phosphatidylinositol-3-kinase (PI3K) inhibitors. Buparlisib is a pan-PI3K inhibitor while BYL719 is an alpha-specific PI3K inhibitor.

Preclinical data

Experiments in a panel of 18 luminal BC cell lines show that 7 out of 10 ER-positive and HER2-negative cell lines have displayed cell-death (average 44%) when treated with buparlisib (Novartis internal data). While cell line data suggest that PIK3CA mutation is correlated with BYL719 and buparlisib (although to a lesser extent) sensitivity in a broad panel of cancer cell lines, data specific to ER+ breast cancer models have shown comparable responses to BYL719 and buparlisib in PIK3CA mutated, PIK3CA wild-type and PTEN mutated xenografts models (O'Brien et al, 2014). Indeed, in each of these xenografts models, buparlisib and BYL719 have shown similar ability to regress tumor burden over several weeks of treatment (Figure 1-5).

[redacted]

Figure 1-5 Single agent activity of BYL719 in ER+ breast cancer models



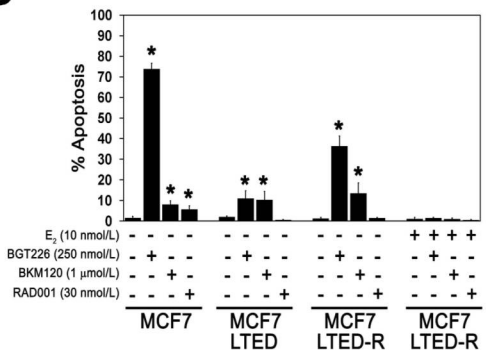
O'Brien et al, UCLA

In vitro combination of letrozole with BYL719 in a PIK3CA mutated cell line of ER+ breast cancer (MCF7) displays synergy (Novartis internal data) in line with the concept of synthetic lethality seen previously when PI3K was inhibited in an estrogen deprived cell line (Crowder 2009, Figure 1-6 – Sanchez 2011).

Similarly buparlisib was shown to induce cell death in a series of breast cancer cell lines in the context of ER deprivation using fulvestrant (Figure 1-7 - Miller 2011b; Sanchez 2011).

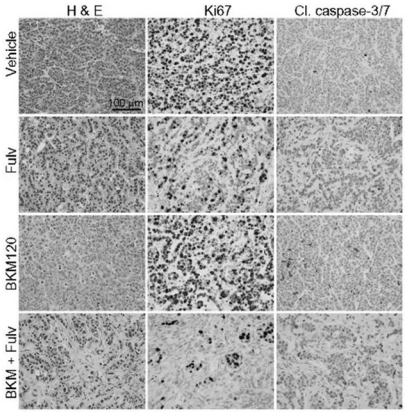
Figure 1-6 Apoptosis rate with BKM120 in MCF7, MCF7-long term oestrogen deprived (LTED) and MCF7-estrogen retreated LTED cell lines

D



[redacted]

Figure 1-7 Activity of BKM120 as single agent in ER+ breast cancer model; HE staining and IHC for Ki67 and cleaved caspase-3/7 (analysis of tumor tissue from animals treated with either fulvestrant (2nd row), BKM120 (3rd row) or a combination of both (bottom panel))



Together these data support the hypothesis that combination of letrozole with a PI3k inhibitor might induce tumor cell death in breast cancer.

Orally administered, letrozole is rapidly and almost completely absorbed. Its absorption was not substantially modified by food. Its apparent volume of distribution is moderate to high (130 L) and it exhibits a low systemic clearance. Letrozole has a long apparent terminal half-life estimated at 82 hours in breast cancer patients. Steady-state was achieved in 2 to 6 weeks. The metabolism of letrozole is > 90% mediated by CYP3A4 through formation of the the major metabolite (4,4'-methanol-bisbenzonitrile). This metabolite is then glucuronidated and ninety percent of the dose is recovered as this glucuronide in the urine. The high dependence of letrozole for its systemic clearance on CYP3A4 together with the potential of BYL719 to inhibit CYP3A4 in a time-dependent manner suggests the potential for a drug-drug-interaction with letrozole as the victim and BYL719 as perpetrator. The predicted increase in letrozole exposure at steady state when combined with 400 mg QD of BYL719 is around 4 fold. Additionally, because the clearance of letrozole may be very low when combined with BYL719, the effective half-life may be very long, so steady state for letrozole in combination could take several months to reach.

Clinical data

Buparlisib + Letrozole

In the completed phase Ib study [CBKM120XUS13T], buparlisib was combined with letrozole (2.5mg QD) in post-menopausal women with HR-positive HER2-negative metastatic BC (Mayer 2014). Fifty-one ER+/HER2- postmenopausal BC patients were accrued in two different arms: buparlisib (100 mg/day) was given continuously (Arm A, n=20) or intermittently (5 days on/2 days off; Arm B, n=31). Forty-nine out of these 51 patients had previously been treated with an AI for advanced or metastatic disease. Patients characteristics were different amongst the two arms, with a longer median time since diagnosis in arm A (76 months versus 29 months), and more chemotherapy in the metastatic setting for patients in the arm B (42% versus 15%).

[redacted]

Buparlisib's maximum-tolerated dose (MTD) was 100 mg/d. Common drug-related adverse events included ≤ grade 2 hyperglycemia, nausea, fatigue, transaminitis, and mood disorders. The DLTs observed in Arm A and B were elevated transaminases and depression respectively; both at 100 mg. Overall all grade AEs were less frequent with the intermittent schedule as compared to the continuous schedule; main AE rates amongst the two arms were respectively 45% versus 75% for transaminases increase, 48% and 70% for hyperglycemia, 42% and 70% for fatigue, 35% and 50% for diarrhea, 32% and 55% for depression, 26% and 65% for nausea 42% and 45% for anxiety, 30% and 40% for rash maculopapular. The clinical benefit rate was similar for both treatment arms (30%). Eleven patients (55%) in the continuous arm had SD; of those, six patients (30%) had SD≥6 months. None of the patients in the intermittent arm had a response, but 14 (45%) of them had SD; of those, 10 (32%) had SD ≥6 months.

BYL719 + Letrozole

[CBYL719ZUS03T] is a phase Ib dose-escalation study of BYL719 and letrozole in women with HR-positive HER2-negative metastatic BC (n=26). Preliminary safety and efficacy results have been reported (Mayer IA, ASCO 2014).

The RP2D was declared at 300 mg. The safety profile was consistent with that described for BYL719 as a single-agent, being the most common toxicities observed at 300 mg (n=20) as follows: diarrhea (81%), nausea (68%), hyperglycemia (50%), fatigue (37%), and rash (30%). There were 3 PRs (15%) documented at 300 mg. Seven patients stayed on treatment for more than 6 months, five of whom had a PIK3CA mutation.

2 Rationale

2.1 Study rationale and purpose

Letrozole is indicated for adjuvant and first line therapy for HR+ BC patients and is considered a valid therapeutic option for neoadjuvant treatment of postmenopausal HR+ BC patients (Charehbili A et al 2014). While the introduction of adjuvant treatment of ER+ postmenopausal breast cancer patients with hormonal therapy has led to improved long term outcomes, there remain a non-negligible percentage of patients relapsing after standard adjuvant treatment with 5 years of letrozole (16%) (Kennecke H et al 2007), justifying the need for more efficient treatments. Because efficacy of adjuvant treatment is based on long term outcomes, neoadjuvant testing offers a quick way to identify which combination may lead to a better outcome over a single agent endocrine treatment. Pathological complete response is one of the indicators of response to neoadjuvant treatment and it has been shown to be linked to long term outcomes for neoadjuvant chemotherapy treatment in certain breast cancer diseases (VonMinckwitz 2012). However, pCR rate remains low with endocrine single agent (Dixon 2001).

As a general concept, the inhibition of the PI3K-AKT-mTOR pathway has already been shown to lead to improved clinical outcomes when everolimus was added to letrozole in a randomized phase II trial in neoadjuvant treatment of postmenopausal women (Baselga 2009) or in a phase III trial in a metastatic setting in combination with exemestane

[redacted]

(Baselga 2012). Promising pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy (Sanchez 2011). Furthermore, clinical activity has been observed with single agent BYL719 or buparlisib in heavily pre-treated ER+ BC patients (Juric 2012, Rodon 2011) and when buparlisib was given in combination with letrozole to metastatic breast cancer patients (Mayer 2014a; Mayer 2014b).

As shown in Section 1.1, the PI3K pathway might be activated via different routes. Within the given ER+/PR+ subtype, activation can be seen via PIK3CA mutations (activation of the alpha subunit) or PTEN alterations (activate the pathway primarily via beta subunits). Hence, the use of an alpha-specific PI3K inhibitor like BYL719 or a pan-PI3K inhibitor like buparlisib (equipotent against alpha and beta subunits) in combination with letrozole may improve letrozole single agent outcomes by increasing the rate of tumor cell apoptosis. It is hypothesized that inhibiting the PI3K pathway upfront in combination with estrogen deprivation might be sufficient to lead to an increase in pathologic response and might prove to be an effective treatment in neoadjuvant treatment for postmenopausal HR+ HER2- BC patients.

In addition, in theory, an alpha specific inhibitor would demonstrate superior efficacy in the PIK3CA-mutant cancer population, with a potentially improved safety profile as compared to pan class I PI3K inhibitors. On the other hand, a panPI3K inhibitor may offer benefit over an alpha- specific one by being possibly active in circumstances where PI3K is activated via other subunits (beta, delta or gamma) [redacted]

However, there is lack of sufficient preclinical data to predict respective impact of alpha versus pan-PI3K inhibition in ER positive breast cancer in the clinic and only a trial using both compounds in the same patient population could provide additional preliminary information to help differentiate the compounds in this context.

The purpose of the study is to determine whether treatment with a PI3K inhibitor (BYL719 or buparlisib) plus letrozole leads to an increase in pathologic response and in Objective Response Rate (ORR) compared to treatment with placebo plus letrozole in patients with hormone receptor-positive HER2-negative breast cancer for the following populations: i) in patients with tumors harboring a mutation in the PIK3CA gene ii) in patients with tumors harboring a wild type PIK3CA gene.

2.2 Rationale for the study design

This study is a multicenter, randomized, double-blind, placebo-controlled phase II trial in neoadjuvant patients with ER+/HER2- breast cancer. The trial is double-blinded with respect to buparlisib or matching placebo and BYL719 or matching placebo, but not with respect to the type of treatment (i.e. buparlisib or BYL719 arm).

The primary purpose of this part would be to assess the treatment effect of BYL719 plus letrozole and buparlisib plus letrozole versus letrozole alone on pathological complete response (pCR) and Objective Response Rate (ORR), in neoadjuvant treatment of HR+ HER2-negative locally advanced breast cancer in each of the two cohorts, namely, i) PIK3CA mutated and ii) PIK3CA wild type.

[redacted]

Breast conserving surgery rate, objective response rate, Ki67 changes as well as PEPI score will be assessed. The safety, tolerability and pharmacokinetics of the combination of BYL719 and letrozole and buparlisib plus letrozole will also be assessed.

2.2.1 Rationale for study design and inclusion of wild-type patients

Based on the mechanism of action understood to date, HR+ breast cancer patients with PI3K pathway activation seen through a mutation of the PIK3CA gene, may be particularly suited to treatment with the alpha specific PI3K inhibitor, BYL719; while HR+ BC patients with activation of the PI3K pathway via loss of the negative regulators [redacted] might gain more benefit from the pan PI3K inhibitor buparlisib. However, while initial preclinical experiments have shown some level of predictivity of PIK3CA mutation status on cell lines sensitivity to BYL719 treatment and to buparlisib treatment, this was not confirmed in xenograft models of ER+ breast cancer (Novartis internal data and Figure 1-4). HR+ breast cancer may display a dependency on the PI3K pathway independent of PIK3CA gene mutation status and hence confer sensitivity in a broader population.

Furthermore clinical data acquired to date with buparlisib has not yet revealed whether a PI3K pathway activated breast cancer patient would derive superior clinical benefit. However, differences in molecular features between primary tumor and metastasis, as well as recurrent tumor after previous chemotherapy have been described (Kuukasjärvi 1997, Jensen 2011, Gonzalez-Angulo AM 2011) and may explain the lack of predictivity of PIK3CA mutations on responses to buparlisib seen in early phase I trials in metastatic setting so far.

In addition, data from the TCGA demonstrate a lack of correlation between activation of the PI3K pathway via phosphorylation and the presence of mutation. Indeed tumors without PIK3CA mutations may still display PI3K pathway dependency due to other pathway interactions.

Thus, enrollment of patients with mutated as well as wild-type PIK3CA gene, based on tumor tissue assessment, is considered appropriate. In addition, to assess the treatment effect of each of the PI3K inhibitors specifically in patients with PIK3CA wild-type and PIK3CA mutated HR+ BC, patients will be separated into two different cohorts and within each of these cohorts, 60 patients will be randomized in each of the three arms (i.e. BYL719+ letrozole, buparlisib+letrozole, or placebo+letrozole). Within the placebo+letrozole arm, half the patients will receive matching BYL719 or buparlisib placebo, respectively (See Figure 4-1).

In addition, all patients will receive standard of care treatment with letrozole at the standard approved dose (either in monotherapy or in combination), regardless of mutational status of the tumor.

2.2.2 Rationale for the stratification factors

There are two stratification factors in this study: Ki67 level (≥14% or <14%) and lymph node status (positive versus negative). Within each cohort (PIK3CA mutated tumors and PIK3CA wild type tumors), patients will be randomized into one of the three treatment arms stratified by the above factors.

Luminal A and luminal B are the two different subtypes of ER+ breast cancer, presenting with different prognosis. From a histopathological point of view, apart from ER and/or PR

[redacted]

positivity, luminal A and B differ by the level of expression of Ki67 (Goldhirsch 2011), the Ki67 index cutpoint being below 14% for luminal A and above or equal to 14% for luminal B (Cheang 2009). Using that cutpoint, 35% of patients are expected to be classified as luminal B-like, and 65% as luminal A-like. To ensure homogeneity, Ki67 assessment will be made centrally for stratification purposes.

A number of prognostic factors predict for future recurrence or death from breast cancer. Among these, the number of axillary lymph nodes involved is one of the strongest prognostic factors (Cianfrocca 2004). Clinical lymph node status (positive or negative) will be used for stratification purpose. It is expected that about 30% of patients will have clinically positive lymph nodes at study entry (Ellis 2011).

2.3 Rationale for dose and regimen selection

The recommended dose for letrozole is 2.5 mg once daily (Femara Prescribing Information and Section 1.2.3).

BYL719 300 mg QD will be given in combination with letrozole 2.5 mg QD for 24 weeks. The rationale for the choice of BYL719 dose level (300 mg QD) together with letrozole 2.5 mg is based on the following elements:

1. Ongoing FIH study [CBYL719X2101] showed 400 mg QD to be the MTD for BYL719 given as single agent and 350 mg QD to be an acceptable starting dose for phase II trials. The recommended phase 2 dose (RP2D) for BYL719 given as a single-agent in the Japanese phase I dose escalation [CBYL719X1101] study was also established at 350 mg (see Section 1.2.1.2).
2. Study [CBYL719ZUS03T] has determined 300 mg as the RP2D of BYL719 in combination with letrozole (see Section 1.2.1.2).
3. In addition, overlapping toxicities for BYL719 and letrozole are very limited and consist mainly of asthenia: in the ongoing phase I trial (IIT; [CBYL719ZUS03T]) combining BYL719 and letrozole, no DLTs have been observed at 300 mg in five patients (with two confirmed partial responses out of three patients evaluable for efficacy). Six patients received BYL719 at 350 mg starting dose: dose reduction was required in four patients and after dose reduction two patients were able to resume and continue treatment ~~in 3~~. Other phase I dose escalation trials of BYL719 in combination with different compounds have also shown that the dose of BYL719 that can be used in combination lies between 270 mg and 400 mg (see Section 1.2.1.2). BYL719 will thus be given at the starting dose of 300 mg with standard dose of letrozole.
4. Letrozole doses of 0.1 to 5 mg QD have led to selective and almost complete decrease of the level of circulating estrogens with no significant clinical and laboratory toxicities nor impact on levels of other hormones. In a recent clinical study, doses of letrozole (10 mg per day) higher than the recommended one (2.5 mg per day) have been administered without safety concerns in a phase II trial (Dixon 2001) when the drug was given in the neoadjuvant setting over a period of three months. If the PK is linear in this dose range, this implies a wide margin of safety for letrozole of at least 4-fold. Thus, even if a drug-drug interaction between BYL719 and letrozole is confirmed, leading to higher concentrations of letrozole (Section 1.2.4), it is postulated that this will not cause

[redacted]

additional safety concerns compared to the standard dose of 2.5 mg QD (see Section 1.2.3).

Buparlisib will be administered at a dose of 100 mg QD 5 days on/2 days off in combination with letrozole 2.5 mg QD. For the rationale of this regimen please refer to Section 1.2.2.3.

Duration of treatment will be 24 weeks. While in initial trials of neoadjuvant endocrine therapies, treatment has been given for 16 weeks (Ellis 2001) more recent data have shown that a longer duration of treatment can yield greater benefits for patients (Dixon 2009, Dixon 2011, Allevi 2013) and 24 weeks can be considered as an acceptable duration for therapy.

2.4 Rationale for choice of combination drugs

Promising pre-clinical data showing potential for leading to cell death instead of decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy (see Section 1.1.3). In addition, mechanism of endocrine resistance thought to play a key role in ER+ breast cancer is that multiple receptor tyrosine kinases and intracellular signaling pathways are activated in the presence of endocrine therapy to compensate for the loss of estrogen signaling. Many of the receptor tyrosine kinases responsible for this mechanism signal via the PI3K/AKT/mTOR intracellular cascade. Hence, early treatment with PI3K inhibitors might delay resistance to endocrine therapy and prolong response to treatment.

The relevance of inhibiting the PI3K/AKT/mTOR pathway has been shown in the clinical setting already when everolimus (an allosteric inhibitor of TORC1 inducing cytostasis) was added to letrozole in neoadjuvant treatment of postmenopausal breast cancer patients and resulted in a significant increase in the clinical response rate (68.1% of the patients receiving the combination treatment vs 59.1% in the placebo arm; p=0.062) and significant decrease in Ki67 levels at day 15 (in 57% of the patients receiving the combination treatment versus 30% in the placebo arm; p<0.01) (Baselga 2009). Mechanistically, inhibiting the pathway at the p110 level is expected to induce cell death instead of cell stasis.

Therefore it is hypothesized that combining agents that target the PI3K and ER pathway simultaneously may be a way to improve letrozole single agent outcomes by increasing the rate of tumor cell apoptosis and thus the pCR rate.

2.5 Rationale for choice of comparators drugs

Letrozole is indicated for adjuvant and first line therapy for HR+ BC patients. Letrozole has been evaluated in several neoadjuvant trials (Eiermann 2001, Ellis 2001, Thomas 2007, Dixon 2009, Ellis 2011, Dixon 2011) including three randomized trials against other endocrine agents. In two of these trials, letrozole was compared to tamoxifen and found to have superior activity in terms of response rate and breast conserving surgery; when used in a phase II study comparing exemestane, letrozole and anastrozole (Ellis 2011), letrozole and anastrozole were selected for further clinical development based on clinical response rate.

Letrozole is thus considered as a valid therapeutic option for neoadjuvant treatment of postmenopausal HR+ BC patients (NCCN Guidelines 2013, Dixon 2009).

[redacted]

2.6 Risks and Benefits

Potential benefits for clinical trial participants

Treatment with alpelisib in combination with letrozole as a neoadjuvant endocrine therapy for women with early-stage hormone receptor-positive breast cancer may result in an improved clinical and pathological response compared to letrozole alone in this patient population. All patients enrolled in this trial receive standard of care endocrine therapy (i.e. single agent letrozole) for their disease. Based on preclinical and clinical data, treatment with alpelisib in combination with letrozole is expected to be well tolerated and it is hypothesized to increase clinical efficacy (Mayer IA et al 2016). For further details on clinical safety, please refer to the latest version of the [Alpelisib (BYL719) Investigator's Brochure].

Potential risks for clinical trial participants

Patients in this study will be closely monitored for key toxicities that have been observed with alpelisib, letrozole, or the combination of both. Some of the safety assessments include, but are not limited to, laboratory assessments of hematology, chemistry (including amylase and lipase), renal function, and ECGs. In addition, patients have a mandatory imaging efficacy evaluation at cycle 4 day 1 and before surgery (i.e. after cycle 6 day 28). Further efficacy evaluations can also be performed during the conduct of the study based on clinical judgement.

Risks will be further minimized by i) the adherence to the inclusion/exclusion selection criteria; ii) the avoidance of concomitant medication that may pose a drug-drug interaction risk; and iii) the observance to the detailed dose adjustment guidelines based on the toxicities that a patient may experience.

In summary, Novartis considers that the benefit-risk assessment of the clinical trial CBYL719A2201 remains favorable. The newly added safety information in the latest version of the [Alpelisib (BYL719) Investigator's Brochure] has been taken into consideration and CBYL719A2201 upcoming amendment and updated ICF will reflect such changes.

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To assess the anti-tumor activity of BYL719 QD plus letrozole versus letrozole alone in increasing the pathologic complete response (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 To assess the anti-tumor activity of BYL719 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.	Pathologic complete response (pCR) per investigator assessment following completion of 24 weeks defined as of treatment 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 neoadjuvant systemic therapy Objective response rate (complete + partial response) per investigator assessment according to RECIST 1.1	
Secondary		Refer to Section 10.5
To assess the anti-tumor activity of BYL719 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.	pCR and ORR (complete + partial response) according to RECIST 1.1 criteria, per investigator assessment	
To evaluate the safety and tolerability of the combinations	Frequency/severity of AEs, laboratory abnormalities	
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	Rate of breast conserving surgery is defined as the percentage of patients with no mastectomy following completion of 24 weeks of treatment	
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 type based on tumor tissue	Correlation between pCR and change in Ki67 from baseline to day 15 and baseline to surgery	
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	Response defined as central PEPI score of 0	
To characterize the pharmacokinetics of BYL719/buparlisib and letrozole when given in combination	● Plasma concentration time profiles of BYL719/buparlisib and appropriate individual PK parameters (e.g. AUCtau, Cmax, Tmax	

[redacted]

Objective	Endpoint	Analysis
	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)	
Exploratory		Refer to Section 10.6
To assess the anti-tumor activity of BYL719 QD plus letrozole and buparlisib (QD continuous or QD 5 days on/2 days off) plus letrozole versus letrozole alone in increasing the pathologic complete response (pCR) rate during neo-adjuvant treatment among postmenopausal patients with HR+, HER2-negative breast cancer regardless of PIK3CA mutational status (overall patient population).	Pathologic complete response (pCR) per investigator assessment following completion of 24 weeks of treatment defined as 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 neoadjuvant systemic therapy	
To assess the anti-tumor activity of a PI3K inhibitor (BYL719 QD plus letrozole and buparlisib QD continuous or QD 5 days on/2 days off plus letrozole arms pooled together) versus letrozole alone in increasing the pathologic complete response (pCR) rate during neo-adjuvant treatment among postmenopausal patients with HR+, HER2-negative breast cancer for the overall patient population (regardless of PIK3CA mutational status).	Pathologic complete response (pCR) per investigator assessment following completion of 24 weeks of treatment defined as 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 neoadjuvant systemic therapy	
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 pathologic complete response (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 (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 and ctDNA.	Pathologic complete response (pCR) per investigator assessment following completion of 24 weeks of treatment defined as 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 neoadjuvant systemic therapy Objective response rate (complete + partial response) per investigator assessment according to RECIST 1.1	
[redacted]	[redacted]	
To explore the change in cell proliferation and cell death in the context of letrozole treatment alone versus letrozole treatment in combination	Ki67 and markers of cell death [redacted]	

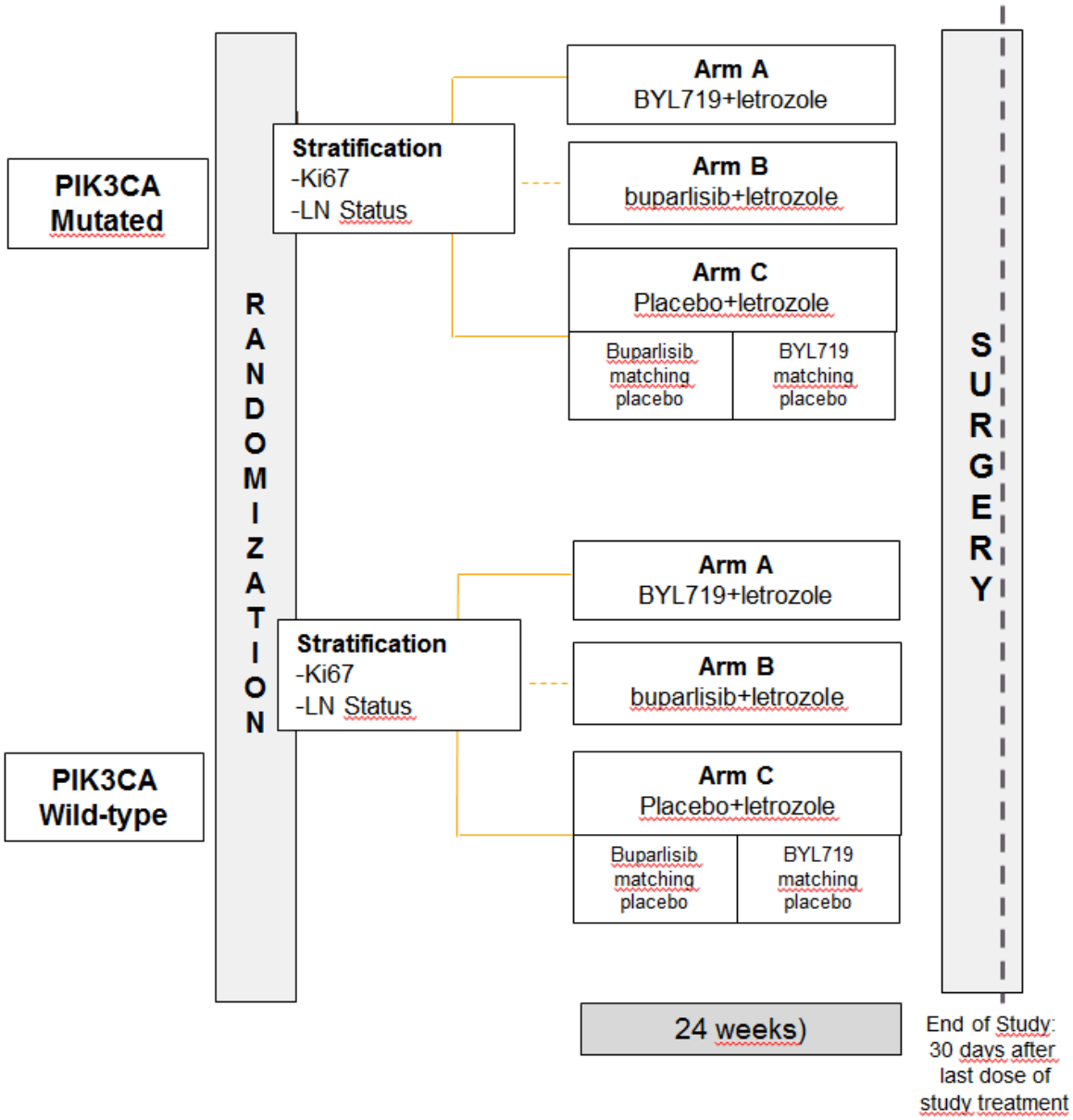
[redacted]

Objective	Endpoint	Analysis
with BYL719 or buparlisib		
[redacted]		

4 Study design

4.1 Description of study design

Figure 4-1 Description of study design



This is a multicenter phase II randomized, double-blind placebo controlled, study of letrozole 2.5 mg with or without BYL719 300 mg or buparlisib 100 mg, for the neoadjuvant treatment of postmenopausal women with hormone receptor-positive HER2-negative breast cancer.

[redacted]

A total of approximately 320 patients will be randomized. Patients will be assigned to one of 2 cohorts: PIK3CA mutated and PIK3CA wild-type. 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 BYL719 and placebo arms. However a lower number of patients will be randomized to buparlisib.

Within each of these 2 cohorts, randomization will be stratified according to Ki67% (<14% vs. ≥14%, as measured by Novartis designated central lab) and lymph node status (positive or negative) (see Figure 4-1 for study design). Lymph node status should be assessed radiologically and/or histologically.

A sample from the diagnostic biopsy (referred thereafter as specimen 1) (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+BYL719 vs. letrozole+placebo according to PIK3CA mutation status.

PK profiles will be collected in at least 15 patients in the BYL719 and Placebo arms from selected centers. Final PK evaluations will only be conducted at the end of the trial.

Patients who discontinue letrozole for any other reason than documented disease progression (e.g. because of toxicity attributed to letrozole or at the discretion of the investigator) will be allowed to continue BYL719/placebo or buparlisib/placebo until treatment is completed or surgery, progression or unacceptable toxicity, and vice versa. Patients will be followed up to 30 days post-treatment. The end of study is defined when the 30 day follow up is completed for all patients or all patients have discontinued treatment for any reason. No follow up other than safety follow up for 30 days after treatment discontinuation will be done.

After patients have completed 24 weeks of study treatment, surgery will be performed as early as possible but not more than 14 days after the last dose of BYL719/placebo or buparlisib/placebo. In the case that surgery is not immediately performed after the last dose of BYL719/placebo or buparlisib/placebo, letrozole will be continued until the day of surgery. Surgery isn't considered 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.

Primary endpoints are based on local assessment.

Screening period

Upon signing the Study Informed Consent Form, patients will be evaluated for study inclusion and exclusion criteria. Eligible patients will be enrolled in the study within 28 days of the commencement of the screening assessments and evaluations (Table 7-1 and Section 7.1.2). A molecular prescreening assessment will be conducted and may occur in advance of the other assessments of the screening phase (any time after the site is initiated) or in parallel with the other assessments. Once the patient provides molecular pre-screening informed consent, demography will be collected and the diagnostic biopsy (7-9 sections or a full core, referred to as specimen 1) will be sent to a Novartis designated laboratory. If the diagnostic biopsy is not available a newly obtained tumor biopsy may be sent in its place. If a full core is not submitted at screening a second specimen (specimen 2) will be required for enrollment at

[redacted]

screening. The first specimen submitted at molecular pre-screening, (specimen 1), the diagnostic biopsy (full core (block) preferred but 7 to 9 pre-cut slides or punch are acceptable), will be used primarily to establish the PIK3CA mutation status, and assess the Ki67 status. The laboratory will provide this information to the IRT for allocation of the patient to a given cohort (PIK3CA mutated or wild-type) and allow stratification (Ki67<14% or ≥14%) during the randomization process (see Section 7.1.1). Collection and shipment of Specimen 1 to a Novartis designated laboratory must occur as soon as possible and at least 14 days prior to the planned randomization date. The Novartis designated laboratory must provide acknowledgment of receipt of adequate tumor tissue quantity within 3 days of sample receipt. If a full core block of sufficient size and tumor content is submitted as specimen 1, no additional material needs to be submitted to cover specimen 2 analyses (Figure 7-1). If a full core was not initially submitted, a second tumor specimen should be collected from all patients. In institutions where research cores are taken at diagnosis, one of these cores can be sent to Novartis. Alternatively specimen 2 can be prospectively collected from the patients. This specimen will be primarily used to assess ER, PR, HER2 status centrally (PEPI score) as well as molecular characterization using deep sequencing approaches and baseline phosphoproteins status (see Section 7.2.4). The second specimen can be collected and sent at any time before the first dose of treatment. The overall study informed consent must be signed by the patient prior to performing any other screening phase assessments.

Treatment phase

Once eligibility criteria have been confirmed, patients will be grouped into one the two cohorts (i.e. PIK3CA mutated and PIK3CA wild-type). Within each cohort, patients will be randomized into one of the arms (i.e. BYL719+letrozole or placebo+letrozole).Within the placebo+letrozole arm, the patients will now receive matching BYL719 placebo. 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).

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

Newly randomized patients will receive BYL719 300 mg QD or matching placebo given once daily continuously starting from Cycle 1 Day 1. In addition, letrozole 2.5 mg QD will be administered continuously starting at Cycle 1 Day 1.

Ongoing patients with buparlisib/buparlisib-placebo who are still benefiting from the treatment may continue the treatment based on the investigator's clinical judgement. Buparlisib/placebo and BYL719/placebo dose modifications will be allowed (see Section 6.3). Safety will be monitored as outlined in Section 7.2.2.

In addition to the PK samples collected prior to the permanent stop of the enrollment in the buparlisib arm which will be kept for analysis, at least 15 patients in the treatment arms BYL719+letrozole, and placebo+letrozole, whether in the PIK3CA mutated or wild-type cohort) will have PK sampling. This is performed in order to characterize the PK of buparlisib and BYL719 when given in combination with letrozole as well as the PK of letrozole. All letrozole samples will be analyzed for letrozole. Samples from buparlisib or BYL719 treated patients will be analyzed for either buparlisib or BYL719 (see Section 10.1.4).

[redacted]

A core biopsy (14 to 16 gauge recommended) will be performed in all patients at the end of second week of treatment (C1D15 Biopsy) to assess Ki67 status and additional biomarkers as described in Section 7.2.4.

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 7 days before surgery. Disease progression should always be documented radiologically, if needed adding earlier than planned time point for tumor evaluation.

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

30-day safety follow-up assessments

The End of Treatment visit occurs within 14 days after the last administration of study treatment (see Section 7.1.4). Safety follow-up assessments should be completed 30 days after the last dose of the study treatment.

4.2 Timing of interim analyses and design adaptations

There is no planned efficacy interim analysis. Safety data will be periodically reviewed by the internal DMC (Section 8.6).

4.3 Definition of end of the study

The study will end when the treatment phase and follow-up for safety period have ended for all patients. The study does not formally include the surgical procedure needed for pathological assessment as a study assessment. Appropriate safety follow-up will last for approximately 30 days after the last dose of study treatment.

4.4 Early study termination

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

5 Population

5.1 Patient population

The patient population consists of postmenopausal women with hormone receptor-positive, HER2-negative, T1c-T3 operable breast cancer, whose disease has never been treated with

[redacted]

local nor systemic treatment, and are eligible for endocrine neoadjuvant treatment. Patients for whom immeadiate chemotherapy or immediate surgery is indicated are not eligible.

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

5.2 Inclusion criteria

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

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

1. Patient is an adult, female ≥ 18 years old at the time of informed consent.
2. Patient has a histologically and/or cytologically confirmed diagnosis of breast cancer.
3. Patient is postmenopausal at the time of breast cancer diagnosis. Postmenopausal status is defined either by:
   - Prior bilateral oophorectomy (in these cases, the oophorectomy must have been performed at least 6 months before the diagnosis of breast cancer in order to be considered post-menopausal for study entry)
   - Age ≥60
   - Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifen, or ovarian suppression) and FSH and estradiol in the postmenopausal range for the local laboratory (if local ranges not available: FSH should be >40mIU/mL and estradiol <20 pg/mL)
   - For women with therapy-induced amenorrhea, oophorectomy or serial measurements of FSH and/or estradiol are needed to ensure postmenopausal status.
   - Note: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression.
4. Patient has T1c-T3, any N, M0 operable breast cancer. Multifocal and/or multicentric disease is allowed. Synchronous bilateral breast cancer patients are allowed provided ONLY ONE of the tumors in one of the breasts is considered for study purposes. Patients with cM0 (i+) disease are allowed to participate only if a documented radiographic test showing no signs of metastatic disease exists.
5. Patients must have measurable disease. Measurable disease will be defined as any mass that can be reproducibly measured by MRI and/or ultrasound in at least one dimension
6. Patient has diagnostic biopsy available for the analysis of PIK3CA mutation and Ki67 level. One tumor block (preferred) or a minimum of 7to 9 unstained slides is recommended. For details on collection, handling and shipment please refer to the [CBYL719A2201 Laboratory Manual].
7. Patient has estrogen-receptor and/or progesterone positive breast cancer as per local laboratory testing
8. Patient has HER2 negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0 or 1+ as per local laboratory testing.

[redacted]

9. Patient has PIK3CA mutation status known (PIK3CA mutated or wild-type) as defined by a Novartis designated laboratory. (Patients with unknown PIK3CA mutation status will not be enrolled)
10. Patient has Ki67 level status determined centrally
11. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 which the investigator believes is stable at the time of screening
12. Patient is able to swallow and retain oral medication
13. Patient has adequate bone marrow and organ function as defined by the following laboratory values:
    a. Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
    b. Platelets (plt) ≥ 100 x 10^9/L
    c. Hemoglobin (Hgb) ≥ 9 g/dL
    d. Calcium (corrected for serum albumin) and magnesium within normal limits or ≤ grade 1 according to NCI-CTCAE version 4.03 if judged clinically not significant by the investigator.
    e. Potassium within normal limits, or corrected with supplements.
    f. INR ≤ 1.5
    g. Serum creatinine ≤ 1.5 x Upper Limit of Normal (ULN)
    h. Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) ≤ 1.5 ULN
    i. Total serum bilirubin below ULN; or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal range in patients with well documented Gilbert's Syndrome, which is defined as presence of several episodes of unconjugated hyperbilirubinemia with normal results from CBC count (including normal reticulocyte count and blood smear), normal liver function test results, and absence of other contributing disease processes at the time of diagnosis
    j. Fasting plasma glucose ≤ 140 mg/dL or 7.7 mmol/L HbA1c ≤ 6.5 %
       Serum amylase ≤ 2 × ULN
       Serum lipase within normal limits
14. Patient has signed informed consent before any screening procedures and according to local guidelines

5.3 Exclusion criteria

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

1. Patient has locally recurrent or metastatic disease
2. Patient has inflammatory breast cancer
3. Patient has a known hypersensitivity to any of the excipients of BYL719 or letrozole
4. Patient has a concurrent malignancy or malignancy within 3 years of study enrollment (with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer).
5. Patient has received any systemic therapy (e.g. chemotherapy, targeted therapy, and immunotherapy) or radiotherapy for current breast cancer disease before study entry.

[redacted]

Patients receiving hormone-replacement therapy must have discontinued such therapy 28 days before randomization.

6. Patient with type 1 diabetes mellitus or not adequately controlled type 2 diabetes mellitus (according to FPG and HbA1c values as outlined in inclusion criterion #13)
7. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
8. Patient classified into Child-Pugh class C
9. Patient has a known history of HIV infection (testing not mandatory)
10. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment contraindicate patient participation in the clinical study
11. Patient has a score ≥ 12 on the PHQ-9 questionnaire. This criterion will only apply to buparlisib/buparlisib placebo arms (patients meeting this exclusion criterion will be randomized to BYL719/BYL719 placebo). **This exclusion criterion is retired as of Amendment #5.**
12. Patient selects a response of "1, 2 or 3" to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9). This criterion will only apply to buparlisib/buparlisib placebo arms (patients meeting this exclusion criterion will be randomized to BYL719/BYL719 placebo). **This exclusion criterion is retired as of Amendment #5.**
13. Patient has a GAD-7 mood scale score≥ 15. This criterion will only apply to buparlisib/buparlisib placebo arms (patients meeting this exclusion criterion will be randomized to BYL719/BYL719 placebo)
14. Patient has a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (e.g. risk of doing harm to self or others), or with an active severe personality disorder (defined according to DSM- IV). Note: for patients with psychotropic treatments ongoing at baseline, the dose and the schedule should not be modified within the previous 6 weeks prior to start of study drug. **This exclusion criterion is retired as of Amendment #5.**
15. Patient has ≥ CTCAE grade 3 anxiety This exclusion criterion is retired as of Amendment #5.
16. Patient has active cardiac disease or a history of cardiac dysfunction including any of the following:
    a. Unstable angina pectoris within 6 months prior to study entry
    b. Symptomatic pericarditis
    c. Documented myocardial infarction within 6 months prior to study entry
    d. History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    e. Documented cardiomyopathy
17. Patient has a Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
18. Patient has any of the following cardiac conduction abnormalities

[redacted]

   a. Ventricular arrhythmias except for benign premature ventricular contractions
   b. Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
19. Conduction abnormality requiring a pacemaker
   a. Other cardiac arrhythmia not controlled with medication
20. Patient has a QTcF > 480 msec on the screening ECG (using the QTcF formula)
21. Patients with congenital long QT syndrome or family history of unexpected sudden cardiac death.
22. Patient is currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to randomization.
23. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects
24. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or has not fully recovered from side effects of such treatment. The following uses of corticosteroids are permitted: single dose, topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g. intra-articular)
25. Patient is currently receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed. **This exclusion criterion is retired as of Amendment #2**.
26. Patient is currently receiving treatment with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A. The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the start of treatment. Switching to a different medication prior to randomization is allowed.
27. Patient has a history of non-compliance to medical regimen or inability to grant consent.
28. Patient is concurrently using other approved or investigational antineoplastic agent.
29. Patient has acute viral hepatitis or a history of chronic or active HBV or HCV infection, (typically defined by elevated AST/ALT (persistent or intermittent), high HBV DNA level, HBsAg positive, or high HCV RNA level (testing not mandatory, refer to Section 7.2.2.5.6 Viral hepatitis serology and other tests for hepatotoxicity follow-up). **This exclusion criterion is retired as of Amendment #5.**
30. History of acute pancreatitis within 1 year of study entry or past medical history of chronic of pancreatitis
31. Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.

[redacted]

6 Treatment

6.1 Study treatment

For this study, the term "investigational or study drugs" refers to Novartis study drug BYL719 and Novartis study drug buparlisib, which will be supplied by Novartis. The other drug to be used in this study is letrozole, which will be procured locally. "Study treatment" in this study refers to the combination of drugs in each of the study arms and includes investigational drugs (BYL719 and buparlisib) as well as the approved drug letrozole.

A control will be a BYL719 or buparlisib matching placebo (placebo). As this is a multi-center randomized, double-blind study, the investigator and patient will be blinded (i.e. will not know if the patient is receiving active buparlisib/BYL719 or placebo of either drugs). In addition, all patients will receive open label letrozole as part of study treatment.

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

In December 22, 2015, the buparlisib/buparlisib-placebo arm was permanently stopped for enrolment. For those patients enrolled in the buparlisib/buparlisib placebo arms before December 22, 2015, treatment with buparlisib/buparlisib placebo and letrozole may continue based on the investigator's clinical judgement.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose[2]	Frequency and/or Regimen (28 day cycles)
BYL719	tablet for oral use	300 mg (e.g. 2 x 50 mg tablets+ 1 x 200 mg tablet[1])	Daily (continuous)
Letrozole	tablet for oral use	2.5 mg	Daily (continuous)
Buparlisib (BKM120)	capsule for oral use	100 mg (2 x 50 mg capsules[1])	5 days on/2 days off

[1] In case of patient supply difficulties, any combination of BYL719/buparlisib/placebo (according to patient assignment) may be taken to consume the total dose.
[2] Dose reduction levels for BYL719/buparlisib/placebo will be administered accordingly. For example, buparlisib/placebo 80 mg should preferentially be administered as 1x 50 mg size capsule, and 3x10 mg size capsule, and BYL719/placebo 250mg should preferentially be administered as 1 X 50 mg tablets + 1 x 200 mg tablet.

The study drugs will be administered orally, and dosed on a flat-fixed dose (see Table 6-1), and not by body weight or body surface area.

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

[redacted]

6.1.2 Instructions for administration

6.1.2.1 Study Drug Administration instructions for all patients

- Patients should be instructed to take the study treatment of one or more tablets of BYL719/placebo daily or one or more capsules of buparlisib/placebo days 1-5 out of 7 days, and letrozole daily together with a glass of water (~250 mL or ~8 fluid ounces) at approximately the same time each day (preferably in the morning after breakfast), except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic at any later point of time. Patients should be instructed to swallow the capsules and tablets whole and not to chew, crush or open them.
- Patients should record if the dose was taken or not in the patient diary.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increase stool frequency) during a treatment cycle must be noted in the adverse events section of the eCRF. In addition, on the days of full pharmacokinetic sampling, the exact onset time of any episodes of vomiting and diarrhea (or increase stool frequency) within the first 24 hours post-dosing on that day must be noted in a separate section of the eCRF.
- Patients must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, starfruits and cranberry juice from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A interaction. Regular orange (Citrus X sinensis) juice is allowed.

The following general guidelines should be followed for BYL719/placebo administration:

- Patients should be instructed to take the dose of BYL719/placebo once daily at approximately the same time each day after a meal (preferably in the morning after breakfast) except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic at any later point of time.
- BYL719/placebo must be taken within 1 hour after a meal or snack. If, for any reason, a breakfast (or other meal) was not consumed, then the patient should take study treatment with a glass of water within 1 hour after a snack at any later point in time. If this happens on days of PK sampling, it should be documented in the CRF.
- If the patient forgets to take study treatment during the daytime it should be taken in the evening (at approximately 6 pm) at the latest within 1 hour after a meal. If not taken by this time, the dose should be withheld that day. Missed doses should not be made up the next day.

6.1.3 Guidelines for continuation of treatment

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

Patients who permanently discontinue one of the study drugs for any reason other than disease progression may continue the other study drug as part of the trial therapy at the investigators discretion for 24 weeks of treatment until disease progression, surgery, unacceptable toxicity, death or discontinuation from study treatment due to any other reason and should follow the protocol safety and efficacy assessments as scheduled (see the criteria for patient withdrawal

[redacted]

in Section 7.1.4). After discontinuing study treatment, further treatment is left to the physician's discretion. No cross over to another treatment arm (from placebo to either buparlisib or BYL719 or from buparlisib to BYL719 and vice versa) will be allowed.

6.1.4 Treatment duration

Patients will be treated for 24 weeks. Patients may be discontinued from study treatment earlier than 24 weeks due to unacceptable toxicity, disease progression (radiologically documented according to RECIST 1.1), and/or if treatment is discontinued at the discretion of the investigator or the patient, or withdrawal of consent. For further details refer to Section 7.1.4.

After patients have completed 24 weeks of study treatment (BYL719/placebo or buparlisib/placebo, or letrozole), 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 BYL719/placebo or buparlisib/placebo, letrozole will be continued until the day of surgery. Surgery is not considered a study assessment.

Definition of treatment cycle

A complete treatment cycle is defined as 28 calendar days (± 3 days) during which BYL719/placebo with letrozole are given once a day, in a continuous daily regimen (BYL719/placebo treatment arms); and buparlisib/placebo is 5 days on/2 days off; and letrozole is given once a day, in a continuous daily regimen(letrozole arm).

6.2 Dose escalation guidelines

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Any changes in BYL719/placebo, buparlisib/placebo, or letrozole administration must be recorded on the eCRF.

BYL719/buparlisib/placebo dose modification guidelines are described in Section 6.3.1.1. Toxicities attributed to letrozole should be managed in a manner consistent with the investigator's usual clinical practice and the package insert for letrozole, and should be reported in the eCRF. Refer to the package insert of the local supply of letrozole for more details. Any planned variance from these guidelines in the view of the patient safety must be previously discussed with the Sponsor unless there is an urgent need for action.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycle.

[redacted]

If the administration of BYL719/placebo or buparlisib/placebo is interrupted for reasons other than toxicity, then treatment with the respective study drug may be resumed at the same dose. The same provision applies if the patient experienced an unacceptable toxicity not specifically described in Table 6-4 provided that this toxicity resolved to ≤ CTCAE grade 1, unless otherwise specified.

If one or both study drugs are being held due to toxicity, scheduled visits and all assessments should continue to be performed (with the exception of the dosing of the held study drug), as described in Table 7-1.

If administration of BYL719/buparlisib or matched placebo dosing is held for more than 28 days, then BYL719/buparlisib must be permanently discontinued. If letrozole is held for more than 28 days then letrozole mustbe permanently discontinued. Patients who permanently discontinue one of the study drugs for any reason other than disease progression may continue letrozole as part of the trial therapy at the investigators discretion, and vice versa.

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

6.3.1.1 Criteria for BYL719/placebo and buparlisib/placebo dose modification

A BYL719/placebo dose reduction will be administered as shown in Table 6-2 below. A maximum of 2 dose reductions will be allowed, after which the patient will be discontinued from treatment with BYL719/placebo. Dose reduction should be based on the worst preceding toxicity. Dose reduction below BYL719 200 mg QD is not allowed. If a dose reduction below 200 mg QD is required, the patient should be permanently discontinued from BYL719/placebo.

Table 6-2 Dose reduction sequential steps for BYL719/placebo

BYL719 / placebo dose level	Dose and schedule
Starting dose	300 mg/ day continuously
Dose level -1	250 mg/ day continuously
Dose level -2	200 mg/ day continuously

A buparlisib/placebo dose reduction will be administered as shown in the Table 6-3 below. A maximum of 2 dose reductions will be allowed, after which the patient will be discontinued from treatment with buparlisib/placebo. Dose reduction should be based on the worst preceding toxicity. Dose reduction below buparlisib 60 mg/day 5 days on/ 2 days off is not allowed. If a dose reduction below 60 mg/day 5 days on/ 2 days off is required, the patient must be permanently discontinued from buparlisib/placebo. In the event of a study treatment interruption in patients randomized to buparlisib/placebo, the reintroduction of buparlisib/placebo treatment should not start on either Day 6 or Day 7 of the intermittent dosing schedule.

Table 6-3 Dose reduction sequential steps for buparlisib/placebo

Buparlisib/placebo dose level	Dose and schedule
Starting dose	100 mg/ day 5 days on/2 days off

[redacted]

Buparlisib/placebo dose level	Dose and schedule
Dose level -1	80 mg/ day 5 days on/2 days off
Dose level -2	60 mg/ day 5 days on/2 days off

Guidelines for dose modification and dose interruption for toxicities suspected to be related to BYL719/placebo or buparlisib/placebo are described in Table 6-4.After treatment is resumed at a lower dose, if the same toxicity recurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration.

If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose of BYL719/placebo or buparlisib/placebo, then the patient must be discontinued from BYL719/placebo or buparlisib/placebo, but can continue on letrozole at the discretion of the investigator until study completion (i.e. 24 weeks), in which case all scheduled assessments will continue to be performed. Patients who discontinue from the study for a study-related AE or an abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Table 6-4 Criteria for interruption and re-initiation of BYL719/placebo or buparlisib/placebo

These changes must be recorded on the Dosage Administration Record eCRF. Letrozole may be continued while BYL719/placebo or buparlisib/placebo dose is being held, at the investigators discretion. Letrozole administration until surgery should be recorded on the Dosage Administration Record eCRF page.

Adverse drug reaction	Severity	Dose adjustment and management recommendations
Hematology	ANC <0.5 x 10^9/L without fever and/or platelets < 25 x 10^9/L	Omit buparlisib/placebo or BYL719/placebo until ANC is ≥ baseline value and the platelet count is ≥ 75 x 10^9/L.then reduce 1 dose level
	ANC <1.0 x 10^9/L with fever (≥38.5°C)	Omit buparlisib/placebo or BYL719/placebo until ANC is ≥ baseline value and no fever, then reduce 1 dose level
Cardiac – QTc prolongation	QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	- First Occurrence: Omit buparlisib/placebo or BYL719/placebo Perform a repeat ECG within one hour of the first QTcF of > 500 ms or >60ms from baseline: if QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input; address electrolytes, calcium and magnesium abnormalities; concomitant medication must be reviewed. Once QTcF prolongation has resolved, buparlisib/placebo or BYL719/placebo may be restarted at one lower dose level - Second Occurrence: Permanently discontinue patient from buparlisib/placebo or BYL719/placebo
Cardiac – Left Ventricular systolic dysfunction	Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level, and continue buparlisib/placebo or BYL719/placebo with caution Repeat LVEF within 4 weeks or as clinically appropriate
	Symptomatic, responsive to intervention, ejection	Permanently discontinue patient from buparlisib/placebo or BYL719/placebo

[redacted]

Adverse drug reaction	Severity	Dose adjustment and management recommendations
	fraction 20-39% or > 20% drop from baseline	
	Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue patient from buparlisib/placebo or BYL719/placebo
Cardiac Events (other than QTc prolongation or left ventricular systolic dysfunction)	Grade 1 or 2	Maintain dose level
	Grade 3	Omit dose until resolved to ≤ Grade 1, then reduce buparlisib/placebo or BYL719/placebo 1 dose level
	Grade 4	Permanently discontinue patient from buparlisib/placebo or BYL719/placebo
Diarrhea Please see Appendix 5 for guidelines for study drug-induced diarrhea management.	Grade 1	Maintain dose level
	Grade 2	Omit dose until resolved to ≤ Grade 1, then restart at same dose
	≥ Grade 3	Omit dose until resolved to ≤ Grade 1, then reduce buparlisib/placebo or BYL719/placebo 1 dose level
Eye disorders	≥ Grade 3 ocular/vision symptoms interfering with activities of daily life or requiring medical intervention	Discontinue patient from buparlisib/placebo or BYL719/placebo
Hepatic – Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	Grade 1 (> ULN – 1.5 x ULN)	Maintain dose level with liver function tests (LFTs)* monitored as per protocol
	Grade 2 (> 1.5 – 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If treatment delay is ≤ 7 days, restart at same dose If resolved in > 7 days, reduce buparlisib/placebo or BYL719/placebo 1 dose level
	Grade 3 (> 3.0 – 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: ● If resolved in < 7 days, reduce buparlisib/placebo or BYL719/placebo 1 dose level ● If resolved in > 7 days, then discontinue patient from buparlisib/placebo or BYL719/placebo
	Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from buparlisib/placebo or BYL719/placebo
Hepatic – AST or ALT	AST or ALT without bilirubin elevation > 2ULN Note: confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorder, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction	
	Same grade as baseline (i.e. Grade 0 or Grade 1	Maintain dose level AND monitor LFTs* weekly until AST/ALT is ≤ baseline
	Increase from baseline Grade 0 to > 1.5 ULN or from baseline Grade 1 to Grade 2	Can continue treatment with reduce buparlisib/placebo or BYL719/placebo 1 dose level
	Increase of two grades from baseline (from baseline Grade 0 to Grade 2 or from baseline Grade 1 to Grade 3)	Omit dose until resolved to Grade 1 or less, then ↓ 1 dose level** If no recovery in ≤ 28 days, discontinue permanently buparlisib/placebo or BYL719/placebo
	Grade 4 (> 20.0 x ULN)	Discontinue patient from buparlisib/placebo or BYL719/placebo

[redacted]

Adverse drug reaction	Severity	Dose adjustment and management recommendations
Hepatic – AST or ALT and concurrent Bilirubin	AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue buparlisib/placebo or BYL719/placebo***
	Hepatic toxicity monitoring (for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only). The monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT: ● **Cycle 1 and 2: every other week** (if visit schedule allows a more frequent monitoring this should be considered) or more frequently if clinically indicated especially for patients with borderline acceptable AST/ ALT/ bilirubin values ● **Cycle 3 and onward: monthly** or more frequently if clinically indicated In case of any occurrence of ALT/AST/ bilirubin increase ≥ **grade 2** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ grade 1** In case of any occurrence of ALT/ AST/ bilirubin increase ≥ **grade 3** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ grade 1**; hereafter the moknitoring should be continued **every other week** or more frequently if clinically indicated **until the end of treatment with study medication** Patients who discontinued study treatment should be monitored weekly, including LFTs* or more frequently if clinically indicated **until resolved to ≤ grade 1 or stabilization** (no CTCAE grade change over 4 weeks). *LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT ** In case of recurring Grade 3 or higher toxicity after re-challenge, patients should be permanently discontinued *** All patients with ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN in the absence of cholestasis must immediately be withdrawn from buparlisib/placebo or BYL719/placebo and every attempt should be made to carry out the liver event follow-up assessments as described below in Section 6.3.2.1.5 Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BYL719/placebo or buparlisib/placebo and viral hepatitis serology and other tests for hepatotoxicity follow-up).	
Hyperglycemia	**Hyperglycemia** (see also Section 6.3.2.3.2) Always consider consultation with a diabetologist and recommend/reinforce on lifestyle changes as per ADA, i.e. exercise and dietary advice (e.g. small frequent meals, low carb, high fiber, balancing carbs over the course of the day. Three small meals and 2 small snacks rather than one large meal). Note: this table provides dose management recommendations. The preferred option for treating alpelisib-induced hyperglycemia is metformin, given its wide availability and well characterized safety profile. However, in case of intolerance to or unavailability of metformin, investigator's judgment should be exercised and other insulin sensitizers such as thiazolidinediones or dipeptidyl peptidase-4 Inhibitors can be used.	
Hyperglycemia	Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For patients with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this apply only	**Maintain dose level**, and remind patient on lifestyle changes*. ● If FPG < 140 mg/dl, consider adding metformin as per guidance below or in cooperation with diabetologist ● If FPG 140-160 mg/dl, start/intensify metformin as per guidance below or in cooperation with diabetologist Metformin 500 mg once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase

[redacted]

Adverse drug reaction	Severity	Dose adjustment and management recommendations
	for values > 140 mg/dL (7.7 mmol/L)	to 500 mg bid, with breakfast and dinner. If tolerated, increase to 500 mg with breakfast, and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Monitor FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every two weeks until FPG is within baseline values.
	Grade 2 (>160 – 250 mg/dL) [> 8.9 – 13.9 mmol/L]	**Maintain dose level** and remind patient on lifestyle changes*, exclude confounding factors like e.g. urinary tract infection, consider consultation with a diabetologist and start oral-antidiabetic treatment, e.g. metformin 500 mg bid with breakfast and dinner. If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Titrate to the maximum tolerated dose over a period of 3 weeks. ● If FPG is still rising on maximum tolerated dose of metformin or persistently >160mg/dl (>8.9 mmol/L), add an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose). ● Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1. ● If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib/placebo by 1 dose level. ● Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl.
Hyperglycemia	Grade 3 (> 250 – 500 mg/dL) [> 13.9 – 27.8 mmol/L]	**Omit alpelisib/placebo** and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Exclude confounding factors like e.g. urinary tract infection and consider consultation with a diabetologist. Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate. Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of alpelisib-induced hyperglycemia given the short half-life of alpelisib. Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1. ● If FPG resolves to ≤ Grade1 within 3-5 days, while off study treatment and on metformin, re-start alpelisib/placebo and reduce 1 dose level, continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG>250mg/dl. ● If FPG does not resolve to Grade1 within 3-5 days while off study treatment and on metformin, consult a diabetologist for management of diabetes is strongly recommended. ● If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue patient from alpelisib/placebo treatment.
	Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L]	**Omit alpelisib/placebo**, confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.

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Adverse drug reaction	Severity	Dose adjustment and management recommendations
		Exclude confounding factors like e.g. urinary tract infection. Consider cooperation with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours. ● If grade improves then follow specific grade recommendations. ● If FPG is confirmed at Grade 4 and confounding factors could be excluded, permanently discontinue patient from alpelisib/placebo.
	A diabetologist consultation should always be considered. For all grades : instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study, e.g. .small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal *specific recommendations please see Section 6.3.2.3.2.	
Investigations (Metabolic)	**Asymptomatic amylase and/or lipase elevation (see also Section 6.3.2.2)**	
	Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
	Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
	Grade 3 (> 2.0 x ULN)	Omit dose until resolved to ≤ baseline, then ● If resolved in ≤ 14 days, maintain dose level ● If resolved in > 14 days, then reduce 1 dose level. Note: In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase) as specified in Section 6.3.2.2
	Grade ≥ 3 Discontinue buparlisib/placebo or BYL719/placebo treatmentNote: Omit both buparlisib/placebo or BYL719/placebo and letrozole for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Pancreatitis		
	Grade 2 (enzymatic elevation or radiologic findings only)	Omit dose until resolved to Grade ≤ 1, then resume treatment at decrease 1 dose level. If toxicity recurs, discontinue patient from study treatment
	Grade 3 ● for patients deriving clinical benefit upon investigator's judgement: ● for other patients:	● Omit dose until complete resolution of symptoms and lipase resolved to Grade ≤ 1, then resume treatment at decrease 1 dose level. Only 1 dose reduction is allowed. ● If recovery to ≤ Grade 1 is greater than 28 days, the patient must be discontinued from the study. ● If toxicity reoccurs, discontinue patient from study treatment ● Permanently discontinue patient from study treatment
	Grade 4	Permanently discontinue buparlisib/placebo or BYL719/placebo treatment
Pneumonitis	please see Section 6.3.2.3.1	
Skin and subcutaneous tissue disorders Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. (see also Section 6.3.2.3.5)		

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Adverse drug reaction	Severity	Dose adjustment and management recommendations
	Grade 1 (<10% body surface area (BSA) with active skin toxicity*)	Maintain dose level ● Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are Triamcinolone, Betamethasone as long as skin toxicity is active, during maximum 28 days ● For patients with symptoms like burning and/or pruritus add non-sedating anti-histamine, consider adding a sedating anti-histamine at night ● If active rash is not resolved within 28 days of appropriate treatment, consider adding low dose systemic corticosteroid (20-40 mg/d)
	Grade 2 (10-30% BSA with active skin toxicity*)	**Maintain dose level**. ● Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone as long as skin toxicity is active, during max. 28 days ● Consider adding systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued ● For patients with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine, consider adding a sedating anti-histamine at night
	Grade 3 (>30% BSA with active skin toxicity*)	**Omit alpelisib/placebo** dose until rash /skin toxicity is no longer active but fading (G1), consider exploratory skin biopsy for central assessment ● Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone for at least 28 days. ● Add systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued. For patients with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine during day time, consider adding a sedating anti-histamine at night Re-start alpelisib/placebo dose once rash /skin toxicity is no longer active but fading (G1): - at same dose in case of first occurrence, at reduced dose level in case of second occurrence. - If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with alpelisib/placebo; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued. For patients with symptoms like burning, stinging and/or pruritus antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib/placebo.
	Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Permanently discontinue patient from alpelisib/placebo and consider a dermatology consult. Treatment of rash should follow guidelines for Grade 3 above with the exception of rechallenge and with any additional measures needed. Consider exploratory skin biopsy for central assessment.
*"Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.		
Serum creatinine	Grade 1 (< 2 x ULN)	Maintain dose level

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Adverse drug reaction	Severity	Dose adjustment and management recommendations
	Grade 2 (2 – 3 x ULN)	Omit dose until resolved to ≤ grade 1, then: If treatment delay is ≤ 7 days, restart at same dose If resolved in > 7 days, then reduce buparlisib/placebo or BYL719/placebo 1 dose level
	Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue patient from buparlisib/placebo or BYL719/placebo
	Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from buparlisib/placebo or BYL719/placebo
Stomatitis/Oral mucositis	Grade 1 / Tolerable Grade 2	Maintain dose level. Non-alcoholic or salt water mouthwash (see also Section 6.3.2.3.4).
	Intolerable Grade 2 or Grade 3	First occurrence: omit until ≤ Grade 1 and reduce buparlisib/placebo or BYL719/placebo 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: omit until ≤ Grade 1 and reduce buparlisib/placebo or BYL719/placebo 1 dose level.
	Grade 4	Permanently discontinue patient from buparlisib/placebo or BYL719/placebo.
All other adverse events	Grade 1 or 2	Maintain dose level
	Grade 3	Omit dose until resolved to ≤ Grade 1, then reduce buparlisib/placebo or BYL719/placebo 1 dose level
	Grade 4	Permanently discontinue patient from buparlisib/placebo or BYL719/placebo **Note***:* Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic
Buparlisib specific dose modifications for mood alterations	Grade 1*	Maintain dose level Consider psychiatric consultation at the investigator's discretion and introduce optimal management
	Grade 2*	Omit dose until resolved to ≤ Grade 1 or baseline status Consider psychiatric consultation at the investigator's discretion and introduce optimal management First event: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then maintain the dose level Second and further events: if the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then reduce buparlisib/placebo 1 dose level
	Grade 3*	Omit dose until resolved to ≤ Grade 1 or baseline status Psychiatric consultation is required and introduce optimal management If the condition resolved to Grade ≤ 1 or to baseline status, continue to co-medicate and then reduce buparlisib/placebo 1 dose level
	Grade 4*	Permanently discontinue patient from buparlisib/placebo Psychiatric consultation is required and introduce optimal management
	* Note: For all grades, if question 9 on the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit study drug and refer patient for psychiatric consult regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued.	

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6.3.2 Follow-up for toxicities

All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment (BYL719/placebo, buparlisib/placebo, and/or letrozole). Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first which includes all study assessments appropriate to monitor the event.

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

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events. The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value.

Patients meeting any of the following criteria will require further follow-up as outlined below:

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

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

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

In the absence of cholestasis, these patients should be immediately discontinued from study treatment, and repeat liver function tests (LFT) as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, a detailed history and physical assessment, and consideration should be given for newly diagnosed liver metastasis or new liver lesions, hepato-biliary obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)and/or INR, and alkaline phosphatase.
2. A detailed history, including information such as review of ethanol consumption, concomitant medications, herbal remedies, supplements consumption, and history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute viral hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug. In this case, an unscheduled PK will be done.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with a specialist (e.g. an hepatologist).

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All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

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

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

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

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

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

6.3.2.3 Additional follow-up for selected toxicities

6.3.2.3.1 Management of pneumonitis

All patients will be routinely asked about and observed for the occurrence of adverse events including new or changed pulmonary symptoms (consistent with lung abnormalities). Patients who are suspected to have developed pneumonitis should suspend (BYL719/placebo or buparlisib/placebo) immediately (but may continue letrozole if clinically indicated) and undergo appropriate imaging (high resolution CT scan) and broncho-alveolar lavage and biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out. Investigators should follow institutional practice for management of pneumonitis which generally includes treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment. BYL719/placebo or buparlisib/placebo should be permanently discontinued in all patients with confirmed pneumonitis.

Table 6-5 Management of pneumonitis

Pneumonitis (any grade)	Immediately interrupt BYL719/placebo or buparlisib/placebo for any case of suspected pneumonitis. Letrozole may be continued if clinically indicated. Obtain appropriate imaging (high resolution CT scan) and consider broncho-alveolar lavage (BAL) and biopsy if appropriate based on clinical judgment. See Section 6.3.2.3.1 for details of management of pneumonitis. Treatment for pneumonitis should be initiated based on institution guidelines and generally includes high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. BYL719/placebo or buparlisib/placebo should be permanently discontinued in all patients with confirmed pneumonitis

6.3.2.3.2 Guidelines for the treatment of BYL719 induced hyperglycemia

BYL719, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy 2012). Alpelisib induced hyperglycemia is generally manageable with adequate antidiabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Patients with pre-diabetes (i.e. FPG 100 – 125 mg/dl; 5.6 - 6.9 mmol/L) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in FPG while on alpelisib/placebo treatment. However all patients, even those with FPG within normal limits at screening, may develop alpelisib induced hyperglycemia. Patients should always be instructed to follow dietary guidelines provided by the American Diabetes Association, e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal and exercise, as appropriate.

Detailed guidelines for management of alpelisib induced hyperglycemia is provided in Table 6-4_following discussion with an advisory board. This includes early administration of metformin. Metformin may be titrated to a daily dose of 1000 mg BID. Local protocols per standard clinical practice may be followed. Fasting plasma glucose may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance. Special attention should be paid to the risk of hypoglycemia in patients interrupting alpelisib treatment and concomitantly receiving insulin and/or sulfonylureas.

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

6.3.2.3.3 Guidelines for the treatment of study drug induced psychiatric disorders in patients receiving buparlisib/placebo

Psychiatric adverse events will be closely monitored and evaluated at each planned visit until recovery to Grade ≤ 1 or baseline status. The grading of psychiatric adverse events/mood alterations must be based on the clinical interpretation of severity according to the NCI-CTCAE (v 4.03) guidelines.

For patients who experience new or worsening of existing psychiatric Aes of Grade ≥1, psychiatric consultation should be considered as described in Table 6-4.

Patient self-reported mood questionnaires (GAD-7 and PHQ-9) will be used for screening and during the study treatment phase to aid the investigator in identifying new or worsening of

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events. For additional information regarding safety assessments based on patient self-reported mood questionnaires, please refer to Section 7.2.2.6.

If question 9 in the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit treatment with study drug and refer the patient for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient's PHQ-9 self-assessment. During the study, subjects will be monitored at regularly scheduled visits (i.e. Day 15 of Cycle 1, Day 1 and Day 15 of Cycles 2 and 3, Day 1 of each subsequent cycle, and at the End of Treatment visit) by the investigator/site staff through personal interaction and the two self-reported questionnaires. Additional assessments may be done according to the clinical judgment of the investigator.

6.3.2.3.4 Guidelines for the treatment of study drug induced stomatitis/oral mucositis

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

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

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

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

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with BYL719 and buparlisib metabolism (see Section 6.4).

6.3.2.3.5 Guidelines for the treatment of study drug induced skin toxicity

Skin toxicity is a class-effect adverse event observed with PI3Ki/mTORi agents. Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as AE. The most frequent skin AEs reported are: maculopapular rash (only a minority present acneiform rash) pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate comedication and treatment interruption if needed. Skin reactions may fade slowly over 10 days or more and may not require ongoing concomitant therapy. If there are no new lesions or new areas of involvement developing, and if the appearance is changing color from red to pale or light brown, it is likely the eruption has begun to fade, i.e. not considered active any longer. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-

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induced skin toxicity. Photographs of skin rashes events as well as skin biopsy, if possible, are recommended. According to the investigator discretion, a paired skin biopsy could be obtained (from both affected and an unaffected skin area for local histopathology assessment) to further assess rash if clinically appropriate.

In case of Grade 3/4 skin toxicity, Novartis requests that a skin biopsy is performed and sent to Novartis Central laboratory for further research purpose on the pathology and mechanism of PI3K inhibitor treatment induced skin toxicity. At the Investigator's discretion, non-sedating antihistamines (e.g. cetirizine (Zyrtec©) once daily) may be used as prophylactic treatment to reduce severity of rash, especially for patients with a history of hypersensitivity reactions like seasonal allergies, hay fever, allergic asthma or drug induced exanthema.

Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity.

Recommended therapies for skin toxicity events include:

- Topical steroids Triamcinolone or Betamethasone 3-4x daily for at least 28 days. Consider spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation
- In case of burning, stinging, pruritus: oral antihistamines (sedating, evening): diphenhydramine 25-50mg t.i.d.; hydroxizine 25mg t.i.d. or q.i.d
- Oral antihistamines (non-sedating, day time): fexofenadine 180mg q.d. or 60mg TID (monitor the use of this class of drugs since skin toxicity has also been reported)
- Low dose oral corticosteroids, e.g. 20-40mg q.d. prednisone or equivalent up to 10 days of treatment.
- If lesions are still not controlled with all of the above, consideration can be given to the use of:
    - Topical antibiotics: clindamycin 1 - 2%; erythromycin 1% -2% (gel or solution formulation can be used, ointments cannot be used); metronidazole 1%; silver sulphadiazine
    - Oral antibiotics: doxycycline 100mg b.i.d.; minocycline 100mg b.i.d.; oxytetracycline 500mg b.i.d
    - Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
    - GABA Agonists: Gabapentin 300mg every 8 hours, Pregabalin 50-75 mg every 8 hours (to adjust of renal impairment). Depending on patient's clinical condition be aware of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others adverse events.

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

Although preclinical experiments demonstrated that buparlisib and alpelisib have no potential phototoxic effect, it is recommended to caution patients to avoid sun exposure during treatment with buparlisib or alpelisib, especially when they already have experienced rash or

other skin toxicities as the increased blood flow of the skin may worsen skin symptoms. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts and long pants when outdoors.

6.3.2.3.6 Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving buparlisib/placebo and BYL719/placebo

Criteria for interruption and re-initiation of buparlisib/placebo or BYL719/placebo treatment in case of the occurrence of AST, ALT or bilirubin increase are detailed in Section 6.3.1, Dose Modification (Table 6-4).

Patients with clinically significant liver test abnormalities should perform liver-directed medical history, physical examination and other tests as medically indicated to assess potential relationship with study treatment and rule out other underlying causes (e.g. disease progression/obstruction, infection/hepatitis or other liver diseases, sepsis, metabolic diseases including diabetes, concomitant medications including herbals, alcohol, drug-drug interaction, cardiovascular disease/ischemia, other organ injuries, etc.). Any pre-existing liver conditions or risk factors should be reported in the respective medical history and concomitant medication CRF pages (if not done already).

All patients with ALT or AST >3.0 x ULN and total bilirubin > 2.0 x ULN in the absence of cholestasis (elevation of ALP in patients without bone metastasis or if bone metastasis are present elevation of 5'-nucleotidase and ALP liver fraction) must be immediately withdrawn from buparlisib/placebo or BYL719/placebo, and every attempt should be made to carry out locally the liver event follow-up assessments as described below:

- Inform the sponsor about the event immediately after its occurrence by reporting the event immediately in the clinical database if it meets the criteria for an AE or SAE.
- Evaluate if associated with the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, or other organ involvement.
- Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia.
- Perform liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease including metastasis or new lesions, obstruction/compression, etc.
- Perform viral hepatitis and other serology tests:
  - Hepatitis C (HCV) serology and viral DNA, Hepatitis B (HBV) serology and viral DNA, Hepatitis A (HAV) Immunoglobulin M (IgM) and HAV total
  - Hepatitis E (HEV) serology: IgM and IgG, viral DNA
  - Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), Epstein-Barr viral (EBV) serology

[redacted]

- Obtain PK sample, as close as possible to last dose of study drug . Record the date/time of the PK blood sample draw and the date/time of the last dose of buparlisib /placebo prior to blood sample draw on the eCRF
- Verify and record the use of concomitant medications, acetaminophen, herbal remedies, and other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Consultation with a specialist(s) or a hepatologist(s) is recommended.
- Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury
- LFTs should be followed-up weekly until resolve to ≤ grade 1, baseline or stabilization (no CTCAE grade change over 4 weeks) and outcome documented on the respective AE and lab chemistry pages.

6.4 Concomitant medications

All medications (other than the study drugs) taken within 4 weeks of study treatment initiation and all concomitant therapy and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study, with reasons for use, will be recorded in the "Concomitant medications/Significant non-drug therapies" section of the eCRF. Medications include not only physician prescribed medications, but also all over-the counter medications, and nutritional or vitamin supplements.

The diagnostic biopsy of the primary breast cancer will be recorded as prior antineoplastic surgery in the "Prior antineoplastic therapy" section of the eCRF.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after starting study drug.

Patients taking medication chronically should be maintained on the same dose and schedule throughout the study period, as medically feasible. The days of full PK blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of full PK sampling, if medically feasible.

6.4.1 Permitted concomitant therapy

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited in Section 6.4.2 and Table 14-3 and Table 14-4 in Appendix 1. Please refer to the BYL719 and buparlisib Ibs.

6.4.1.1 Antiemetics

Use of anti-emetics is allowed. Prophylactic anti-emetics should be started only once the patient experiences nausea or vomiting, at the discretion of the investigator. It is recommended that patients use drugs that do not cause QT prolongation. Please note that some anti-emetics have a known risk for TdP and are prohibited (refer to Section 6.4.2 and Table 14-4 in Appendix 1).

[redacted]

6.4.1.2 Bisphosphonates

The use of bisphosphonates is allowed provided patients have been on stable doses for at least 2 weeks prior to study entry. Stable dose should be maintained during the treatment period. Patients requiring initiation of bisphosphonates for the treatment of metastatic breast cancer during the course of the study should be discontinued due to progressive disease.

6.4.1.3 Oral anti-diabetics

Patients who develop diabetes mellitus during the study should be treated according to the ADA (American Diabetes Association) guidance. It is recommended to start treatment with metformin. Patients receiving oral antidiabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, should be monitored for hypoglycemia as BYL719 was found to be weak reversible inhibitor of these enzymes (refer to Table 14-1 in Appendix 1) *in vitro*.

6.4.1.4 Hematopoietic growth factors

Hematopoietic growth factors (e.g. erythropoietins, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered prophylactically. Use of these drugs should be reserved to patients with severe neutropenia and anemia as per the labeling of these agents or as dictated by local practice (see also the guidelines established by the American Society of Clinical Oncology (ASCO)).

6.4.1.5 Anticoagulation

All anticoagulants or anti-aggregation agents may be administered under the discretion of the investigator.

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants should be used with caution because of its known interaction with many commonly used medications and certain foods. As warfarin has a narrow therapeutic range and both buparlisib and BYL719 are possible inhibitors of CYP2C9, the major metabolizing enzyme of S-warfarin (R-warfarin is metabolized by multiple CYP enzymes), it should be carefully monitored whenever used.

Caution is also advised when BYL719 and buparlisib is co-administered with anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4, CYP2C9 and CYP2C19. While the weak reversible *in vitro* inhibition potential of BYL719 and buparlisib towards CYP2C-family enzymes is unlikely to translate into clinical significance as the steady-state plasma concentrations at the maximum therapeutic doses are significantly lower than the experimentally determined inhibition constants, patients using anti-platetet pro-drugs should still be carefully monitored.

Direct Thrombin inhibitors (DTIs) and Factor Xa inhibitors are allowed as anticoagulants. Individual medications from each of the classes should be checked if they are not prohibited due to other drug-drug-interactions with BYL719. Please see Section 6.4.2 for Prohibited concomitant therapy and Appendix 14.1 for a list of prohibited drugs.Alternatively, therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

[redacted]

6.4.1.6 CYP450 substrates

BYL719

In vitro studies demonstrate that BYL719 is both a time-dependent inhibitor (TDI) and inducer of CYP3A4. While BYL719 may increase exposure to drugs strongly metabolized by CYP3A4 (e.g. midazolam) by more than 6.5-fold or reduce exposure by ~10-fold when applying either only time-dependent inhibition (enzyme inactivation) or induction (de novo protein synthesis) effects in an BYL719 PBPK model (SimCYP) at a 400 mg dose at steady state, both opposing effects seem to balance each other out, leading to a net exposure increase of 1.2-fold when applying both effects simultaneously during a simulation. This result has been supported by preliminary clinical PK results from a combination trial with everolimus (a sensitive CYP3A4 substrate) which showed no change in Everolimus PK upon co-administration with BYL719.

Still, as time-dependent inhibition and induction of CYP3A4 may not be fully in balance after the first doses of BYL719, when equilibrium of CYP3A4 protein levels may have not yet been reached, caution is still advised when BYL719 is co-administered with CYP3A4 sensitive or narrow therapeutic index drugs such as opioid analgesics. Inhibition of opioid metabolism by CYP3A4 can lead to opioid toxicity, including fatal respiratory depression, or an enhanced risk for QTc prolongation. Patients receiving BYL719 and opioid analgesics should therefore be carefully monitored. Synthetic opioids with clinically relevant interactions with CYP3A4 inhibitors include, but are not limited to, propoxyphene, fentanyl, alfentanyl and sufentanil. Use of alfentanyl, a sensitive CYP3A4 substrate with narrow therapeutic window, should be fully avoided whenever possible. The use of methadone and levomethadyl is prohibited (refer to Table 14-4 in Appendix 1).

While the weak reversible *in vitro* inhibition potential of BYL719 towards CYP2C-family enzymes is unlikely to translate into clinical significance based on normal clinical exposure, BYL719 may inhibit the metabolic clearance of co-medications metabolized by CYP2C8, CYP2C9, CYP2C19, if sufficiently high BYL719 concentrations are achieved *in vivo*.

Investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19 (refer to Table 14-2 in Appendix 1). Patients receiving such medications must be carefully monitored for potential toxicity due to any individual concomitant medications. Particularly, caution is advised when BYL719 is co-administered with drugs that are sensitive substrates for CYP3A4, CYP2C8, CYP2C9 or CYP2C19 and which have a narrow therapeutic index (Table 14-1 in Appendix 1).

Buparlisib

In vitro metabolism studies performed to examine the reversible and metabolism-dependent inhibition of cytochrome P450 enzymes showed that buparlisib is a weak, reversible inhibitor of CYP3A4/5, CYP2C8, CYP2C9 and CPY2C19. Buparlisib may therefore inhibit the metabolic clearance of co-medications metabolized by CYP3A4, CYP2C8, CYP2C9, CYP2C19, if sufficiently high concentrations are achieved *in vivo*. Investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19 (refer to Table 14-1 in Appendix 1).

[redacted]

Thus, caution should in principle be used in administering concomitantly drugs whose disposition is mainly dependent on these cytochrome P450 isoenzymes and whose therapeutic index is narrow. Patients receiving such medications must be monitored for potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate.

6.4.1.7 Moderate CYP3A4 inhibitors and inducers (Buparlisib only)

As *in vitro* and *in vivo* metabolism studies suggest that oxidative metabolism of buparlisib is at least partially mediated by CYP3A4, moderate CYP3A4 inhibitors and inducers are permitted but should be used with caution (see Table 14-2 in Appendix 1 for a list of moderate CYP3A4 inhibitors and inducers). Please note that this list may not be comprehensive.

6.4.1.8 Drugs with a conditional or possible risk to induce Torsade de Pointes

If a patient, enrolled in the study, requires the concomitant use of any medication with a possible or conditional risk for TdP (see Table 14-5 in Appendix 1 for a list of such medications), then investigators, at their discretion, may co-administer such medications. Patients receiving such medications must however be monitored. Note: please refer also to Table 14-4 in Appendix 1 for a list of prohibited QT prolonging medication.

6.4.1.9 Gastric protection agents

BYL719 and buparlisib are characterized by a pH-dependent solubility. Therefore acid reducing agents (ARAs, e.g. proton-pump inhibitors, H2-antagonists and antacids) may alter the solubility of alpelisib and buparlisib and hence their bioavailability. A drug-drug interaction study in human healthy volunteers confirmed that co-administration of alpelisib with the H2-antagonist ranitidine after a meal lead to a decrease in exposure by only ~20%, considered to be not clinically relevant. For buparlisib a DDI study showed that co-administration with the proton-pump-inhibitor rabeprazole did not significantly change the exposure of buparlisib, independent of the food condition. Hence both buparlisib and alpelisib can be co-administered with any ARAs.

6.4.1.10 BCRP inhibitors (BYL719 treatment only)

BYL719 was identified as a substrate for the human BCRP. Co-administration of BYL719 with BCRP inhibitors may increase systemic exposure and/or alter tissue uptake of oral BYL719 and should therefore be used with caution. See Table 14-6 in Appendix 1 for a list of BCRP inhibitors.

6.4.1.11 Corticosteroids

Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone are known to induce CYP3A enzymes, thereby increasing the risk of reducing buparlisib. Based on experience from a study which was carried out to assess the impact of a repeated dose of 4 mg dexamethasone on the PK of buparlisib [CBKM120C2106], an equivalent dose of dexamethasone up to 4 mg q.d. can be considered safe in patients receiving buparlisib.

[redacted]

Since corticosteroids may prolong or aggravate hyperglycemia (steroid-induced diabetes), which is a common adverse event for PI3K inhibitors, they should be used with caution and closely monitored.

6.4.2 Prohibited concomitant therapy

6.4.2.1 Strong CYP3A4 inhibitors and inducers (Buparlisib only)

In vitro and *in vivo* metabolism studies suggest that oxidative metabolism of buparlisib is partially mediated by CYP3A4. Coadministration of buparlisib/placebo with strong CYP3A4 inhibitors and inducers is therefore prohibited. Please refer to Table 14-3 in Appendix 1 for a list of prohibited drugs. Please note that this list may not be comprehensive.

6.4.2.2 Other investigational and antineoplastic therapies

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.

6.4.2.3 Drugs with a known risk for QT prolongation or of causing Torsades de Pointes

If a patient, enrolled in the study, requires the concomitant use of any medication included in Table 14-4 of Appendix 1 entitled "List of Prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Advisory Board of the Arizona CERT to have a **known** risk of causing TdP), BYL719 or buparlisib administration must be interrupted as long as the patient requires therapy with the QT prolonging agent.

If the patient requires long term therapy with such a QT prolonging agent, leading to study treatment interruption of > 28 days, the patient must be permanently discontinued from BYL719 or buparlisib.

Co-administering QT prolonging drugs (or any other drug with the potential to increase the risk of drug-related QT prolongation e.g. via a potential drug-drug interaction increasing the exposure of the study drugs or the exposure of the QT prolonging drug) should be avoided. If during the course of the study, concomitant administration of drugs with a known potential to cause Torsades de Pointes is required and cannot be avoided, study drug must be interrupted until an assessment of the potential safety risk has been performed. A definitive list of drugs associated with QT prolongation and/or TdP is available online at www.qtdrugs.org. If, based on the investigator assessment and clinical need study treatment is resumed, close ECG monitoring is advised.

6.4.2.4 Herbal medications

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 14 days prior to first dose of study drug.

[redacted]

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

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

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

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

6.5.2 Treatment assignment or randomization

Once eligibility criteria have been confirmed, patients will be assigned to one of the two cohorts (i.e. PIK3CA mutated and PIK3CA wild-type). Within each cohort, patients will be randomized to one of the two arms (i.e. BYL719+letrozole or placebo+letrozole) in a 1:1 ratio. Within the placebo+letrozole arm, newly randomized patients will receive matching BYL719 placebo (see Section 4.1 and Section 6.1). Randomization will be stratified according to centrally measured Ki67 level (<14% or ≥14%) and lymph node status (positive or negative). The PIK3CA mutation status and Ki67 results will not be communicated at time of the randomization in order to avoid any potential bias.

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

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of BYL719 or matching placebo to be dispensed to the patient. The randomization number will not be communicated to the caller.

[redacted]

6.5.3 Treatment blinding

This is a multi-center randomized, double-blind study. Due to the different appearances of BYL719 and buparlisib the active treatment arms A and B are only blinded against placebo arm C but not against each other (see Figure 4-1 for more details on study design). The identity of the investigational drugs (BYL719 and buparlisib) vs. matching placebos will be concealed by identical packaging, labeling and schedule of administration. Randomization data are kept strictly confidential from patients, investigators, local radiologists, study team, or anyone involved in the study conduct until database lock.Treatment group information will be accessible to the DMC if required during their periodic safety reviews. The independent statistician and programmers producing outputs for the DMC will remain semi-blinded to the treatment groups. Details are presented in the DMC charter [DMC Charter].

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

6.6 Study drug preparation and dispensation

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

6.6.1 Study drug packaging and labeling

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

Medication labels will be in the local language and comply with the legal requirements of each country.

Table 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
BYL719 or BYL719 matching placebo	Tablets in bottle 50 mg 200 mg	Labeled as BYL719 50mg/ placebo and BYL719 200mg/placebo Once daily dosing
buparlisib or buparlisib matching placebo	Capsules in bottle 10 mg 50 mg	Labeled as BKM120 10mg/placebo and BKM120 50mg/placebo 5 days on/2 days off dosing
letrozole	Refer to local product information	Refer to local product information

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and

[redacted]

designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the BYL719 or buparlisib Investigator's Brochures.

Table 6-7 Supply and storage of study treatments

Study treatments	Supply	Storage
BYL719 or BYL719 matching placebo	Centrally supplied by Novartis	Refer to study drug label
buparlisib or buparlisib matching placebo	Centrally supplied by Novartis	Refer to study drug label
letrozole	Locally	Refer to local product information

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

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

6.6.3.2 Study drug accountability

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

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

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source

[redacted]

documentation. Visit windows of +/- 3 days are allowed (except at cycle 1 Day 1 and where specified in Table 7-1).

The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening phase			Treatment phase									Post-Treatment Follow up phase
Cycle			**Molecular Pre-Screening**	**Screening**		**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4 to Cycle 6**	**End of study treatment (EoT) – before surgery**	
Days			**Any time after the site initiation to -1**	**-28 to -1**	**-7 to-1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**1**	**N/A**	**N/A**
Obtain molecular pre-screening Informed Consent	D	7.1.1	X												
Collection of tumor sample from diagnosis biopsy	D	7.1.1	X (≥ 14 days before randomization)												
Acknowledgment of Receipt of adequate tumor tissue quantity from Novartis designated laboratory	S	7.1.1	X (≥3 days after tumor receipt												
PIK3CA mutation and Ki67 status results entered in IRT	S	7.1.1	X (before randomization)												
Obtain main study Informed Consent	D	7.1.2		X											
IRT registration	S	6.5.1	X	X		X				X		X	X	X	
IRT randomization	D	6.5.2				X									
End of phase disposition	D	7.1.4		X										X	
Demography	D	7.1.2.3	X												
Inclusion/exclusion criteria	D	5.2/5.3		X											

[redacted]

	Category	Protocol Section	Screening phase			Treatment phase									Post-Treatment Follow up phase
Cycle			**Molecular Pre-Screening**	**Screening**		**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4 to Cycle 6**	**End of study treatment (EoT) – before surgery**	
Days			**Any time after the site initiation to -1**	**-28 to -1**	**-7 to-1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**1**	**N/A**	**N/A**
Relevant medical history/current medical conditions	D	7.1.2.3		X											
Diagnosis and extent of cancer	D	7.1.2.3		X											
Intended breast surgery type	D	7.1.2.3		X											
Prior antineoplastic therapy (Surgery)	D	7.1.2.3		X											
Physical Examination	S	7.2.2.1		X		X		X		X	X	X	X	X	
ECOG Performance status	D	7.2.2.4		X		X				X		X	X	X	
Height	D	7.2.2.3		X											
Weight	D	7.2.2.3		X		X				X		X	X	X	
Vital signs	D	7.2.2.2		X		X	X	X	X	X	X	X	X	X	
Pulmonary function tests	D	6.3.2.1				As clinically indicated									
Hematology	D	7.2.2.5.1			X	X*		X		X	X	X	X	X	
Biochemistry (partial)	D	7.2.2.5.2					X**	X	X**		X**				
Fasting Biochemistry (full)	D	7.2.2.5.2			X	X*		X		X	X	X	X	X	
Hepatotoxicity follow-up testing/procedures	D	7.2.2.5.6				As clinically indicated									

[redacted]

	Category	Protocol Section	Screening phase			Treatment phase									Post-Treatment Follow up phase
Cycle			**Molecular Pre-Screening**	**Screening**		**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4 to Cycle 6**	**End of study treatment (EoT) – before surgery**	
Days			**Any time after the site initiation to -1**	**-28 to -1**	**-7 to-1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**1**	**N/A**	**N/A**
Coagulation	D	7.2.2.5.4			X					X		X	X	X	
Fasting plasma glucose	D	7.2.2.5.3			X		X	X	X	X	X	X	X	X	
Fasting C-peptide, Insulin	D	7.2.2.5.3			X		X	X	X	X	X	X	X	X	
HbA1c	D	7.2.2.5.3			X							X		X	
Fasting Lipase	D	7.2.2.5			X					X		X	X	X	
Fasting Amylase	D	7.2.2.5			X					X		X	X	X	
Fasting Lipid profile	D	7.2.2.5.2			X					As clinically indicated					
Urinalysis	D	7.2.2.5.5			X					As clinically indicated					
Tumor evaluation	D	7.2.1		X		See Table 7-2									
Pathological Response	D	7.2.1													X
*Hematology and Fasting Biochemistry (full) should be repeated on cycle 1 day 1 only if the screening assessment has been done more than 7 days before. **Partial biochemistry will be performed at the local laboratory and is restricted to the parameters described in Section 7.2.2.5, Table 7-4.															
ECG	D	7.2.2.6.		X		X				X		X	X		
Cardiac imaging	D	7.2.2.6.1		X		As clinically indicated								X	
Adverse events	D	8		Continuous											Up to 30 days after last dose of treatment

[redacted]

	Category	Protocol Section	Screening phase			Treatment phase									Post-Treatment Follow up phase
Cycle			**Molecular Pre-Screening**	**Screening**		**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4 to Cycle 6**	**End of study treatment (EoT) – before surgery**	
Days			**Any time after the site initiation to -1**	**-28 to -1**	**-7 to-1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**1**	**N/A**	**N/A**
Surgical and Medical Procedure	D	7.1.2.3		Continuous											Up to 30 days after last dose of treatment
Prior/concomitant medications	D	7.1.2.3 / 6.4		Continuous											Up to 30 days after last dose of treatment
New Antineoplastic Therapies since discontinuation of study treatment	D	7.1.6				To be collected, if applicable, until surgery is performed.									N/A
Patient self-reported questionnaires : PHQ-9 / GAD-7 (buparlisib/placebo)	D	7.2.2.7		See Table 7-6											
Biomarkers Assessment	D	7.2.4		See Table 7-9 and Table 7-10											
Tumor Biopsy				X				X							X
PK sampling (for PK subset)	D	7.2.3				See Table 7-8									
Meal record (PK subset)	D	7.2.3				X							X (C4D1 only)		

[redacted]

	Category	Protocol Section	Screening phase			Treatment phase									Post-Treatment Follow up phase
Cycle			**Molecular Pre-Screening**	**Screening**		**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4 to Cycle 6**	**End of study treatment (EoT) – before surgery**	
Days			**Any time after the site initiation to -1**	**-28 to -1**	**-7 to-1**	**1**	**8**	**15**	**22**	**1**	**15**	**1**	**1**	**N/A**	**N/A**
Patient Diary	S	7.1.3				Daily Continuous									
BYL719 / Placebo administration	D	6.1				Daily Continuous Dosing									
Buparlisib /Placebo administration	D	6.1				5 days on/2 days off									
Letrozole administration	D	6.1				Daily Continuous Dosing									

[redacted]

7.1.1 Molecular pre-screening

The molecular pre-screening may occur well in advance of the other screening phase assessments (any time after the site is initiated and provided the molecular pre-screening ICF has been signed) or can occur in parallel with the other screening assessments (provided that the main ICF has been signed).

Once the patient signs the molecular pre-screening ICF, demography should be collected and the tumor sample should be shipped to the Novartis designated laboratory as soon as possible but no later than 14 days before the planned randomization date. The PIK3CA mutation status based on tumor tissue assessment, as well as Ki67 results, will need to be determined by the Novartis designated laboratory. These results will be entered directly to the IRT prior to randomization to confirm patient eligibility and allow stratification.

The IRT system will notify sites when Ki67 results and PIK3CA mutation status have been entered. Only patients meeting minimum criteria listed below will undergo the molecular pre-screening:

- Patient has a confirmed diagnosis of early breast cancer (non-metastatic)
- Patient has estrogen-receptor and/or progesterone positive breast cancer as per local laboratory testing
- Patient has HER2 negative breast cancer defined as a negative in situ hybridization test or an IHC status of 0 or 1+ as per local laboratory testing
- Patient is postmenopausal at the time of breast cancer diagnosis
- Patient has not previously received a treatment, either systemic or local for the current diagnosis of breast cancer

The PIK3CA mutation status and Ki67 status are assessed centrally; the steps required for patient enrollment are as follows:

1. Upon patient signature on the molecular pre-screening ICF, the tumor sample from diagnosis biopsy should be immediately collected and shipped to a Novartis designated laboratory. The sample should be shipped at least 14 days prior to the planned randomization date to allow proper time for the analysis.
2. The site should get confirmation of receiptby Novartis designated laboratory within 3 days of sample receipt. The site will also be informed if the sample quality is not appropriate.
3. The Novartis designated laboratory will generate the PIK3CA mutation status and Ki67 results before the planned randomization date and enter them directly into the IRT system
4. The sites will be informed by the IRT system that the results have been entered.

7.1.2 Screening

Written molecular pre-screen and main informed consent must be obtained before any study specific assessments are performed.

The screening assessments must be performed within maximum 28 days to confirm patient's eligibility and before the start of the first study treatment dose (BYL719/placebo in combination with letrozole).

[redacted]

Patients who fail to be started on treatment may be re-screened one time, provided the patient was not registered previously in IRT as having entered the Treatment Period. In this situation, the Patient No. which was previously assigned to the patient will be re-applied to the same patient throughout her entire study participation.

Radiographic tumor assessments should be performed within 28 days prior to randomization. Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to randomization, including before signing the main study ICF can be considered as the baseline images for this study.

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

For details of assessments, refer to Table 7-1.

7.1.2.1 Eligibility screening

While the investigator is responsible to ensure that each patient meets all inclusion/exclusion criteria prior to randomization, a subset of those criteria have been identified as key eligibility criteria and will also be verified by the sponsor through IRT prior to permitting the patient to be randomized. The eligibility checklist form must be completed in IRT by the investigator or designee at the following study timepoints:

- at molecular pre-screening, for minimum criteria details refer to Section 7.1.1
- at cycle 1 day 1 prior to starting the treatment phase and receiving the first dose of study drug (letrozole and BYL719/placebo). Verification of all eligibility criteria must be done prior to contacting IRT. After the eligibility has been checked in IRT and confirmed that the patient is eligible for the trial, then the patient can be enrolled into the treatment phase of the study.

Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screen failures

Patients who sign the main informed consent, but fail to be started on treatment for any reason as well as patients who sign the molecular pre-screening informed consent but do not have a tumor sample which can be analyzed (insufficient amount of tumor tissue was present in the patient's archival sample) will be considered screen failures.

The following data must be collected in the eCRF for any patient that signs any ICF

- Informed Consent Dates,
- Demography,
- Screening Phase Disposition eCRF page (including reason for not being started on treatment),
- Serious Adverse Events (see Section 8.2 for details around SAE collection and requirements),

[redacted]

- Death, if applicable,
- Biomarker assessment page – tumor biopsy,
- Inclusion/Exclusion Criteria,
- Withdrawal of consent, if applicable,
- PIK3CA mutation status based on tumor tissue and Ki67 results (reported via data transfer), if applicable.

If a screen failure patient experiences an AE which does not meet the SAE criteria, details about the AE will be recorded only in the investigator's source documents. In case of an SAE after signing of main study informed consent, data must be recorded on both the AE and SAE forms.

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

If the patient fails to start the study, then IRT must be notified within 2 days of the screen fail that the patient was not enrolled (Section 7.1.2.2).

7.1.2.3 Patient demographics and other baseline characteristics

Patient information to be collected at screening will include:

- Demography (Date of Birth and Initials (where permitted), sex, race, ethnicity, source of patient referral).
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade.
- Diagnosis and Extent of Cancer (including staging, histology/cytology and sites of disease at study entry).
- Intended breast surgery type (i.e. the type of surgery intended prior to treatment should be recorded for all patients.)
- Prior antineoplastic surgical interventions prior to the administration of study drug.
- All medications and significant non-drug therapies (including physical therapy, oxygen and blood transfusions) taken within 28 days before the first dose is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.

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

- PIK3CA mutation status
- Ki67 status
- HER2 status
- ER/PR status

[redacted]

- Physical Examination (See Section 7.2.2.1)
- Vital signs (See Section 7.2.2.2)
- Height and weight (See Section 7.2.2.3)
- ECOG performance status (See Section 7.2.2.4)
- Laboratory evaluations (e.g., hematology, coagulation, chemistry, urinalysis) (See Section 7.2.2.5)
- ECG (See Section 7.2.2.6)
- Cardiac imaging (See Section 7.2.2.6.1)

7.1.3 Treatment period

Within each of the two cohorts (PIK3CA mutated and PIK3CA wild-type), patients will be randomized using Ki67 results and lymph node status for stratification (see Section 4). Study treatment should be started as soon as possible and no later than 3 days after the randomization of the patient.

Patients will be assigned to one of the treatment arms to be treated at cycle 1 day 1 with letrozole plus BYL719 or letrozole plus placebo. Patients will receive treatment until week 24, surgery, disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason.

Patients will come to the site for assessments at a minimum of every 2 weeks for the first 2 cycles of treatment, then every cycle thereafter. A biopsy will be taken at week 2 for Ki67 and other biomarkers assessment. A sample will also be collected at the time of surgery for Ki67 and other biomarkers assessment.

Patients will be fasting at each site visit when fasting clinical laboratory parameters have to be assessed.

Patients will be instructed to complete a daily patient diary that will be reviewed at each site visit by site staff for study drug compliance at PK days and during the course of the study participation.

For details of assessments, refer to Table 7-1.

7.1.4 Discontinuation of Study Treatment

Patients may voluntarily discontinue from the buparlisib/Placebo plus Letrozole or BYL719/Placebo plus Letrozole treatment arm for any reason at any time. If a patient decides to discontinue from study treatment, the investigator must make a reasonable effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they

- state an intention to withdraw,
- fail to return for visits,
- become lost to follow-up for any other reason.

[redacted]

The investigator should discontinue buparlisib/placebo plus letrozole or BYL719/placebo plus letrozole treatment arm for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

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

- Adverse Event
- Non-compliance with study treatment
- Progressive Disease
- Study terminated by sponsor
- Technical problems
- Use of prohibited treatment and medications refer to Section 6.4.1 and Section 14.1
- Any protocol deviation that results in a significant risk to the patient's safety
- Death

The appropriate personnel from the site and Novartis will assess whether buparlisib/placebo plus letrozole or BYL719/placebo plus Letrozole treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue buparlisib/placebo or BYL719/placebo study treatment should NOT be considered withdrawn from the study. They should continue taking Letrozole as per investigators' clinical judgment, in which case the patient must and return for the assessments indicated in Section 7.2.1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7.

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

Patients who discontinue study treatment (e.g. letrozole, BYL719/placebo and buparlisib/placebo) should be scheduled for an EOT visit as soon as possible, and within 14 days after the date study treatment is permanently discontinued, at which time all of the assessments listed for the EOT visit will be performed. Known information on intended surgery and pCR should be collected on the eCRF for these patients. Patients who discontinue but do NOT withdraw consent and have surgery within 30 days post-discontinuation should have pCR data collected at the time of surgery.

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

The investigator must contact IRT to register the patient's treatment discontinuation.

7.1.5 Withdrawal of Consent

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

[redacted]

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

If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision while respecting the subject's rights and record this information.

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

7.1.6 Follow up for Safety Evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

All patients will be followed for AEs and serious adverse events for at least 30 days following the last dose of study treatment. At the end of this period, the investigator should assess and discuss with the patient any AE observed/concomitant medication taken since discontinuation of study treatment.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate End of treatment Disposition CRF.

7.1.8 Breast Cancer Surgery

Definitive breast surgery will be performed as early as possible, but no later than 14 days after the last dose of BYL719/placebo or buparlisib/placebo or letrozole. If a patient discontinues from BYL719/placebo or buparlisib/placebo, letrozole treatment will be maintained until the day of surgery.

Surgical management of the primary tumor and axilla is left at the discretion of the surgeon. Patients with involved or close surgical margins after breast conserving surgery may undergo additional surgery to obtain negative margins.

After the study treatment period (i.e. 24 weeks) or if the patient prematurely discontinues for any reason other than withdrawal of consent, the investigator will report if patient undergoes breast surgery, and the type of surgery performed. The investigator will receive the pathological response report generated by the local lab that assessed the tumor following the protocol mandated by Novartis. A separate tissue sample from the surgery will also be sent to

the Novartis designated laboratory for Ki67 and other biomarkers assessment (see Section 7.2.4)

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor evaluation will be determined locally according to the Novartis guideline (Appendix 2) on the Response Evaluation Criteria in Solid Tumors (RECIST), based on RECIST Version 1.1 unless otherwise specified below. The investigator's assessment of ORR will be used for the primary efficacy analysis.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study.

Magnetic Resonance Imaging (MRI) or ultrasound (US) of breast will be performed at screening, cycle 4 day 1 (+/- 7 days) and prior to surgery (maximum 7 days before). The same technique should be used throughout the duration of the trial. Additional radiological assessments may be performed when needed as per investigator judgment e.g. at screening (to exclude metastasis) or during the course of the study (to rule out clinical progression).

All patients who discontinue from study treatment due to disease progression must have their progression clearly documented according to the criteria specified in Appendix 2 (RECIST v1.1). Further treatment is left up to the investigator's discretion.

Table 7-2 Imaging collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Ultrasound or MRI of Breast	Mandated	At C4D1; after C6D28, before surgery
CT or MRI (Chest, Abdomen, Pelvis or other organ as indicated)	As clinically indicated	As clinically indicated
Bone Scan	As clinically indicated	As clinically indicated
Other Radiological Assessments	As clinically indicated	As clinically indicated

Pathological complete response assessment:

Pathological Complete Response (pCR) is one of the two primary endpoints and is based on local assessment. Surgical breast and axillary node resection specimens will be evaluated for pathologic tumor response within 2 weeks of surgery following the pCR guidelines distributed by Novartis. Patients will be considered pathological complete responders if there is no invasive cancer remaining in the breast and lymph nodes specimens (whether or not there is in remaining in situ component) according to the FDA definition of pCR: ypT0/Tis ypN0 (AJCC staging system).

7.2.2 Safety and tolerability assessments

Safety will be monitored by physical examination, vital signs, weight, performance status evaluation, ECG, laboratory evaluations including glucose monitoring and the assessment of

[redacted]

patient rated mood scales, as well as collecting all serious and non-serious Adverse Events (AE).

Prior ECGs and/or echocardiogram/MUGA scan(s) performed as part of the regular work-up of the patient within 28 days prior to randomization can be considered as baseline safety assessments for this study.

For details on AE collection and reporting, please refer to Section 8.1.

If one of the study drug is being held due to toxicity, scheduled visits and assessments should still be performed (with the exception of the dosing of the held study drug) as described in Table 7-1, unless otherwise specified.

7.2.2.1 Physical examination

The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site.

Physical examination is to be performed according to the visit schedule as outlined in Table 7-1.

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

7.2.2.2 Vital signs

Vital signs (pulse rate, blood pressure) will be monitored as per the visit schedule (see Table 7-1). Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for five minutes.

Clinically significant findings that were present prior to the signing of informed consent must be included in the "Medical History" page on the patient's eCRF at Screening. Significant new findings that begin or worsen after informed consent and meet the definition of an AE must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.3 Height and weight

Height and body weight will be measured as outlined in the visit schedule (see Table 7-1).

7.2.2.4 Performance status

The performance status will be assessed according to the ECOG performance status scale (Oken 1982). ECOG performance status will be assessed as per the visit schedule (see Table 7-1).

[redacted]

Table 7-3 ECOG performance status

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

7.2.2.5 Laboratory evaluations

As outlined in Table 7-4, fasting plasma glucose, AST, ALT, ALP, total bilirubin and creatinine, will be performed both centrally and locally for rapid availability for safety evaluation and dose adjustments. Clinical laboratory analyses (Hematology, Biochemistry, coagulation, HbA_{1C}, C-Peptide, and Urinalysis) are to be performed by central laboratory according to the Visit Schedule outlined in Table 7-1. If a local laboratory is used for any unscheduled laboratory assessments, Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

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

Hepatotoxicity follow-up testing will be performed when needed (refer to Section 6.3.2.1. Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BYL719/placebo or buparlisib/placebo).

[redacted]

Table 7-4 Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Fasting Biochemistry (full)	Albumin, Alkaline phosphatase (ALP), ALT (SGPT), AST (SGOT), GGT, Bicarbonate, Calcium, Chloride, Creatinine, Creatine kinase, potassium, sodium, magnesium, Total Bilirubin (direct must be collected only in case total bilirubin is elevated > ULN), Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Biochemistry (partial)	Creatinine, ALT, AST, Total bilirubin, ALP, fasting plasma glucose
Urinalysis	Dipstick analysis (WBC, blood, protein and glucose)
Coagulation	Prothrombin Time (PT) or International normalized ratio [INR], Partial thromboplastin time (PTT) or activated Partial thromboplastin time (aPTT)
Additional tests	Fasting Plasma Glucose, Fasting Lipase, Fasting Amylase, C-peptide, Insulin, Glycosylated Hemoglobin (HbA_{1c})
Fasting Lipid profile	Total Cholesterol, HDL, LDL, Triglycerides
*Viral hepatitis serologic tests and other tests for hepatotoxicity follow-up	HAAb, HBsAg, HBsAb HBcAb, HCV RNA or HDV RNA (where needed), HEAb, CMVAb, EBcAb, ALP, CPK, LDH, WBC (eosinophilia), and others.
All laboratory analysis will be performed centrally; however fasting plasma glucose, ALT, AST, ALP, total bilirubin, and Creatinine will be performed both locally and centrally (for rapid availability for safety evaluation and dose adjustments). Any unscheduled laboratory assessment can be done locally but should be sent to the central laboratory as well for central analysis. The central results will be electronically transferred to the database. All local laboratory parameters results should be entered on eCRF. *Hepatotoxicity follow-up testing/procedures will be performed locally (refer to Section 6.3.2.1. Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BYL719/placebo or buparlisib /placebo and Section 7.2.2.5.6 Viral hepatitis serology and other tests for hepatotoxicity follow-up).	

7.2.2.5.1 Hematology

Hematology tests are to be performed by the central laboratory according to the Visit Schedules outlined in Table 7-1. For details of the Hematology panel refer to Table 7-4.

7.2.2.5.2 Biochemistry

Biochemistry tests are to be performed by the central laboratory according to the Visit Schedule outlined in Table 7-1. For details on the Biochemistry panel refer to Table 7-4.

Lipid panel is to be performed according to the Visit Schedule outlined in Table 7-1. For details on the Lipid Profile panel refer to Table 7-4.

7.2.2.5.3 Monitoring FPG, C-peptide, and HbA1C

Fasting Plasma Glucose (FPG), C-peptide, and HbA1C will be assessed according to the visit schedule in Table 7-1. Patients must be fasting overnight for at least 10 hours prior to the blood draw. The study personnel will ask the patient whether he or she has been fasting, which will be captured in the eCRF as well.

HbA_{1c} will be measured at screening, Cycle 3 Day 1 and at EOT.

[redacted]

7.2.2.5.4 Coagulation

Prothrombin Time (PT) or International normalized ratio (INR), and partial thromboplastin time (PTT) or aPTT, will be measured according to the visit schedule in Table 7-1.

7.2.2.5.5 Urinalysis

Urinalysis includes dipstick analysis will be performed as outlined in Table 7-1.

7.2.2.5.6 Viral hepatitis serology and other tests for hepatotoxicity follow-up

During study treatment, viral hepatitis serologic and other tests will be performed as per the guidelines of management of hepatotoxicity (ALT or AST >3.0x ULN and total bilirubin > 2.0x ULN) in patients receiving BYL719/placebo or buparlisib/placebo, refer to Section 6.3.2.3.6 Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving BYL719/placebo or buparlisib/placebo for details.

Viral hepatitis serology includes the following:

- Hepatitis A IgM antibody and hepatitis A serology total
- Hepatitis B surface antigen, Hepatitis B Core Antibody (IgM) and viral DNA
- Hepatitis C serology and viral RNA
- Hepatitis D RNA (where needed)
- Hepatitis E IgM and IgG antibody and viral RNA

Obtain fractionated bilirubin, serum Alkaline Phosphatase (ALP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and blood count with differential to assess eosinophilia.

Additional viral serology tests may include:

- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Herpes Simplex Virus

7.2.2.6 Electrocardiogram (ECG)

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

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

[redacted]

Table 7-5 Local ECG collection plan

Cycle	Day	Time	ECG Type
Screening	-28 to -1	Any time	12 Lead
1	1	Pre-dose	12 Lead
2	1	Pre-dose	12 Lead
3 – n*	1	Pre-dose	12 Lead
Unscheduled sample		Anytime	12 Lead

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

The left ventricular heart function will be evaluated by ECHO or MUGA at Screening to confirm eligibility and either after C6D28 or study treatment discontinuation (whatever occurs first) if last assessment was done more than 6 weeks before. Additional cardiac imaging during treatment is to be performed if indicated by clinical signs or symptoms. The same imaging modality should be used.

7.2.2.7 Patient self-reported Mood Questionnaires

The Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) are validated (Kroenke 2001, Spitzer 2006, Spitzer 1999), patient self-administered questionnaires developed for use in clinical practices.

The PHQ-9 (Appendix 4, Figure 14-1) consists of 9 questions that assess anhedonia, depressed mood, sleep, energy, appetite, guilt and worthlessness, concentration, feeling slowed down or restlessness, and suicidal thoughts. For each of these questions, patients are asked to rate how much over the past 2 weeks they have been bothered by the symptom. Scoring of the PHQ-9 is based on a Likert-type scale from 0 to 3 (0 indicates not at all; 1, several days; 2, more than half the days; 3, nearly every day). The sum of all nine questions is used to determine a total PHQ-9 score ranging from 0 to 27.

The GAD-7 (Appendix 4, Figure 14-2) is a one-dimensional questionnaire consisting of 7 questions. Similarly to the PHQ-9, in the GAD-7, patients are asked to indicate how often, over the past 2 weeks, they have been bothered by each of the seven core symptoms of generalized anxiety disorder as referenced in the DSM IV. Response options are ‘‘not at all,’’ ‘‘several days,’’ ‘‘more than half the days,’’ and ‘‘nearly every day,’’ scored as 0, 1, 2, and 3, respectively. The sum of all seven questions calculates the total GAD-7 score. Therefore, GAD-7 scores range from 0 to 21.

Questionnaires will only be completed by patients in the buparlisib+letrozole and buparlisib matching placebo+letrozole arms at Cycle 1 Day 15, Cycle 2 Day 1 and Day 15, and Cycle 3 Day 1 and at Day 1 of each subsequent cycle in addition to the EOT visit. An additional assessment at Cycle 3 Day 15 is also required if any psychiatric disorder is present at Cycle 3 Day 1 (See Table 7-6). Additional assessments may be done according to the clinical judgment of the investigator.

All questionnaires should be given by the site to the patient in the patient’s local language and reviewed for completeness and possible AEs.

[redacted]

Table 7-6 Patient self-reported mood questionnaire collection plan (buparlisib/placebo+letrozole arms only)

Patient Questionnaires	Visit/ Cycle*	Day	Time
PHQ-9 GAD-7	Cycle 1	Day 15	Prior to any clinical assessments, study drug dosing or diagnostic testing.
	Cycle 2	Day 1, Day 15	
	Cycle 3	Day 1 (Day 15 only if any psychiatric disorder at C3D1)	
	Every Cycle	Day 1	
	End of treatment	Day of end of treatment assessment	
	End of treatment	Day of end of treatment assessment	

The severity classification table described in Table 7-7 for the PHQ-9 and GAD-7 will be used in this study to increase the sensitivity of identifying potential anxiety and/or depression disorders. During the study, questionnaire scores and corresponding severity classification can be used to aid the investigator in identifying new or worsening of events. However, grading must be based on the clinical interpretation of severity according to the NCI- CTCAE (v 4.03).

Table 7-7 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

During the treatment phase, patients randomized to buparlisib or buparlisib-matching placebo, who indicate a positive response by selecting '1, 2, or 3' to question number 9 in the PHQ-9, must omit treatment with study drug (buparlisib or matching placebo) and must be referred for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient PHQ-9 self-assessment.

Investigators must not encourage the patients to change responses reported in questionnaires. Guidelines on how to instruct the patient to complete the questionnaires as well as how to determine the scores will be provided with each instrument. Guidance on scoring questionnaires is also provided in Appendix 4. Dosing modification guidelines for buparlisib/placebo are provided in Table 6-4. For additional information on AE reporting, please refer to Section 8.1.

7.2.3 Pharmacokinetics

Blood samples for plasma concentrations measurements for BYL719 and letrozole will be collected from at least 15 patients in each treatment arm from selected centers. The blood sampling regimen for determining PK is given in Table 7-8. One sample of blood will be drawn for two potential analytes and plasma samples will be split for BYL719/placebo and

[redacted]

letrozole analysis depending on the treatment arm. Post dose PK-samples are calculated from the start of BYL719/placebo or letrozole administration (tablets or capsules).

Exact dates and clock times of drug administration and actual blood draw will be collected on the appropriate eCRF. The time of the breakfast prior to PK sampling, where post dose timepoints are collected, should be recorded in the appropriate eCRF page. If a patient treated with either combination of treatments experiences an AE that fits the criteria of a SAE as determined by the Investigator, every attempt should be made to take a blood sample for measurement of plasma concentrations of study treatment.

If vomiting occurs within 4 hrs following study-drug administration on the day of PK sampling, where post-dose time points are collected, the time (using the 24 hrs clock) of vomiting should be recorded in a separate section of the eCRF and on the transmittal forms, which accompany the sample. No additional study medication should be taken in an effort to replace the material that has been vomited. If gastric protection agents were taken, this should be recorded in a separate section of the eCRF and on the transmittal forms, which accompany the sample.

If a patient withdraws prematurely from the study, a PK blood sample must be obtained whenever possible. This will be considered as an unscheduled. PK sample should be collected at any time, preferably within 2 weeks post-last BYL719 dose, and the date and time of the last dose recorded.

Whenever an ECG with a QTcF change from baseline > 60 msec or a new absolute QTcF ≥ 501 msec result is obtained for patients treated with the drugs combination, a blood sample to assess concentrations of BYL719, buparlisib and letrozole should be obtained and the time of sample collection noted.

7.2.3.1 Pharmacokinetic blood sample collection and handling

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Blood should be collected in accordance with institutional guidelines. On days and time points when pharmacokinetics, biochemistry, hematology or other blood samples are to be performed, the pharmacokinetic sample must be drawn first. Complete instructions for sample processing, handling and shipment will be provided in the [CBYL719A2201 Laboratory Manual]. No time window for full PK sampling on Cycle 1 Day 1 is allowed (other than specified in Table 7-8), while, other PK samples may be obtained ± 1 day from the scheduled date. Dosing information of the last 3 or 7 days before the PK sampling may be recorded, if feasible at every PK visit (except at Cycle 1 Day 1) for PK analysis. Any sampling problems should be noted on the eCRF and on appropriate source documentation

[redacted]

Table 7-8 Pharmacokinetic blood collection log

			BYL719 / placebo			buparlisib / placebo			Letrozole			
Cycle	**Day**	**Time**	**Dose Reference ID**		**PK Sample Number**	**Dose Reference ID**		**PK Sample Number**	**Dose Reference ID**		**PK Sample Number**	**Blood Volume (mL)**
1	1	Pre-dose*	301		301	401		401	501		501	2
1	1	0.5 hour post dose ± 10 min	301		302	401		402	501		502	2
1	1	1 hour post dose ± 10 min	301		303	401		403	501		503	2
1	1	3 hour post dose ± 15 min	301		304	401		404	501		504	2
1	1	6 hour post dose ± 30 min	301		305	401		405	501		505	2
1	1	9 hour post dose ± 30 min**	301		306	401		406	501		506	2
1	2	24 hour post dose* ± 120 min	301	3012	307	401	4012	407	501	5012	507	2
1	8	Pre-dose*	302	3021	308	402	4021	408	502	5021	508	2
1	15	Pre-dose*	303	3031	309	403	4031	409	503	5031	509	2
1	22	Pre-dose*	304	3041	310	404	4041	410	504	5041	510	2
2	1	Pre-dose*	305	3051	311	405	4051	411	505	5051	511	2
3	1	Pre-dose*	306	3061	312	406	4061	412	506	5061	512	2
4	1	Pre-dose*	307	3071	313	407	4071	413	507	5071	513	2
4	1	0.5 hour post dose ± 10 min	307		314	407		414	507		514	2
4	1	1 hour post dose ± 10 min	307		315	407		415	507		515	2
4	1	3 hour post dose ± 15 min	307		316	407		416	507		516	2
4	1	6 hour post dose ± 30 min	307		317	407		417	507		517	2
4	1	9 hour post dose ± 30 min**	307		318	407		418	507		518	2
4	2	24 hour post dose* ± 120 min	307	3072	319	407	4072	419	507	5072	519	2
5 to n	1	Pre-dose*	308+	3081+	320+	408+	4082+	420+	508+	5081+	520+	2
Unscheduled sample		---	---	---	3001+		---	4001+	---	---	5001+	2

* Take sample immediately prior to study treatment dose
** Optional sampling time
\+ Refer to Lab manual for naming conventions

[redacted]

7.2.3.2 Analytical method

Refer to the [CBYL719A2201 Laboratory Manual] for detailed instructions for the collection, handling and shipping of samples.

Plasma concentrations of BYL719, buparlisib and letrozole will be measured at Novartis or designated CRO using validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) assays. The lower limits of quantitation (LLOQ) are currently 5.0 ng/mL, 1.0 ng/ml and 2.0 ng/ml.

Residual plasma samples used for PK analysis may also be used for exploratory analysis. [redacted]

7.2.4 Biomarkers

7.2.4.1 Biomarker assessments and biomarker sample collection plan

A summary of biomarker assessments and biomarker sample collection plan has been provided in Table 7-9.

For all biomarker samples, the sample collection information must be captured on the relevant eCRF page(s) and laboratory requisition form(s). Biomarker data will be sent electronically to Novartis. See laboratory manual for detailed sample collection, storage and shipment information

Table 7-9 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Mandatory collections			
Tumor samples			
Tumor Tissue (referred as Specimen 1, specimen 2, C1D15 biopsy and surgical specimen)	N/A	Screening, C1D15, and post treatment follow up	Screening (day -28 to day-1), C1D15 and /surgical specimen/ tumor progression
Blood Samples			
Blood for circulating tumor DNA	2x10 mL	Screening	Screening (day -28 to day-1)
	10ml	Treatment	C1D15, C3D1, C4D1, C5D1, C6D1
	10ml	End of treatment	after last dose of study treatment
Blood for germline DNA	6 mL	Treatment	Any time before first dose of study treatment
Optional collections			
Skin Biopsy	N/A	Anytime	At time of rash

[redacted]

7.2.4.2 Biomarker assessment for randomization

7.2.4.2.1 Tumor tissue

The biopsy collected for initial diagnosis of breast cancer will be used to assess PIK3CA mutation and Ki67. Diagnostic biopsy or a minimum of 7 to 9 slides need to be provided at the earliest possible time. However, if initial diagnostic biopsy is insufficient, a new biopsy can be collected if feasible and acceptable to the patient (see [Laboratory Manual] and Table 7-10 for details on tissue collection).

Assessment of PIK3CA mutation status will be performed to allow proper allocation of patients to a given cohort (PIK3CA mutated or wild-type). Ki67 will be used for stratification purpose (to differentiate luminal A – Ki67<14% - and luminal B – Ki67 ≥14% - breast cancer patients).

7.2.4.3 Biomarkers assessment for pathway inhibition and efficacy

7.2.4.3.1 Assessments at baseline

Tumor tissue:

Collection and shipment of specimen 1 (i.e. the tumor tissue acquired at the initial diagnosis of breast cancer) to a Novartis designated laboratory must occur as soon as possible and at least 14 days prior to the planned randomization date. The Novartis designated laboratory must provide acknowledgment of receipt of adequate tumor tissue quantity within 3 days of receipt of sample receipt. The PIK3CA mutation status as well as Ki67 status must be determined by the Novartis designated laboratory and entered into the IRT system prior to randomization (see Section 7.1.1).

Specimen 2 will be obtained from either the diagnostic material submitted at molecular pre-screening (i.e. part of Specimen 1 if material had sufficient quantity and quality) (see Section 4.1) or prospectively collected (i.e. a newly collected biopsy) from the patients, if Specimen 1 material had sufficient quantity and/or quality, prior to initiation of treatment. This specimen will be primarily used to assess ER and Ki67status centrally; as these parameters are needed for calculating the PEPI score (secondary endpoint of the study). It will also be used to assess molecular alterations of many genes associated with the PI3K pathway in Breast Cancer (Cancer Genome Atlas Network 2012). In the event of a previously unidentified mutation, germline DNA will be used to confirm the tumor origin of the given mutation.

Blood:

Circulating tumor DNA: This will be utilized to test for mutations in genes that are relevant for PI3K signaling (e.g. PIK3CA). The mutation profile obtained from the circulating tumor DNA will be compared with the mutation profile obtained from the diagnostic biopsy collected at entry on trial. This is a required assessment which will provide a validation on the use of circulating tumor DNA mutation analysis in neoadjuvant context. The blood sample (2x10 mL) will be collected during screening or at cycle 1 day 1 (when patient is eligible and before first dose of treatment).

[redacted]

7.2.4.3.2 Assesments during treatment

Tumor Tissue:

A new biopsy will be taken at C1D15, following 2 weeks of treatment: "C1D15 Biopsy" (see [Laboratory Manual] and Table 7-10 for details on tissue collection).

Ki67 will be measured to evaluate the dynamics of its variation under treatment (Dowsett 2007). Markers of cell death [redacted] will be measure to assess the percentage of cell death in response to treatment.

Finally, PI3K-driven intracellular signaling is typically driven by binding of ligand to a tyrosine kinase receptor followed by phosphorylation of several intracellular components ultimately activating of the PI3K function such as cell survival. The day-15 biopsy (Biopsy 3) will be analyzed for markers shown to be closely associated with the PI3K pathway using a phosphoprotein multiplex approach to assess tumor response to the treatment and compared to baseline level assessed in specimen 2. [redacted]

Blood:

Circulating tumor DNA*:* In addition to a screening sample, blood samples (10 mL) for circulating tumor DNA will be collected at cycle 1 day 15, C3D1, C4D1, C5D1, C6D1 during treatment, . These samples will be utilized to test for mutations in genes that are relevant for PI3K signaling (e.g. PIK3CA and ESR1).

7.2.4.3.3 At the time of surgery

Tumor tissue (Surgical specimen):

Tumor tissue (Surgical specimen): 4 samples from the surgical specimen (or tumor bed in cases of pathological complete response) will be sent within 4 weeks of surgery to the Novartis designated laboratory for central analysis of ER and Ki67 levels, together with other pathological features, in order to determine the PEPI score (Ellis 2008). Two of these samples should be formalin-fixed and shipped in ethanol; and the other two samples should be snap-frozen and shipped on dry ice (for tissue preparation, please refer to the [CBYL719A2201 Laboratory Manual]).

In addition, tumor cell death marker analysis and molecular characterization of the tumor, by mutation and/or expression analysis, may be performed in order to assess the effect of treatment on the PI3kinase pathway and other cancer and cell signaling related pathways.

Blood:

Circulating tumor DNA: The mutation profile obtained from the circulating tumor DNA at the end of treatment will be assessed.

For all tumor samples, the sample collection information must be captured on the relevant eCRF page(s) and laboratory requisition form(s).

[redacted]

[redacted]

[redacted]

7.2.4.5 Optional additional biomarker studies

If the patient agrees, the tumor and blood samples remaining after analysis will be stored under the control of Novartis for up to 15 years for additional exploratory biomarker assessments and/or the development of biological/diagnostic test(s) related to BYL719/buparlisib/letrozole and/or Cancer. The decision to perform such analyses will depend on the outcome data, emerging internal or external data and sample availability.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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

For patients whose PIK3CA mutation status is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event eCRF.

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.

[redacted]

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

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

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

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

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

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

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia

instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.1.3 Adverse events of special interest

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

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

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

[redacted]

8.2.2 Reporting

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

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

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

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

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

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

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

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

[redacted]

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

8.3 Emergency unblinding of treatment assignment

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

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

Study treatment must be discontinued once emergency unblinding has occurred.

8.4 Pregnancies

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

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

8.5 Warnings and precautions

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

[redacted]

8.6 Data Monitoring Committee

An internal Data Monitoring Committee (DMC) composed of Novartis personnel who are not directly involved with the BYL719 program will be constituted. The primary responsibility of the DMC will be to periodically review ongoing unblinded safety data from the study and advise whether the study should be stopped. Responsibilities of the DMC are included in the DMC charter.

8.7 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results. The details of the role of the Steering Committee will be defined in a Steering Committee charter. The SC will be blinded to the trial data.

Periodic review of safety data aggregated by blinded treatment group (BYL719+Letrozole and BYL719-placebo + Letrozoleor buparlisib/placebo) will be performed and results will be shared with study steering committee.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

[redacted]

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

9.2 Site monitoring

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

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

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

9.3 Data collection

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

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

Pharmacokinetic (PK) and Biomarker (blood and tissue) samples drawn during the course of the study will be collected from the investigator sites and analyzed by a central lab contracted by Novartis. The site staff designated by the investigator will enter the information required by the protocol onto the PK and Biomarker Sample Collection eCRFs, as well as onto the designated CRO's requisition form. One copy of the requisition form will be forwarded to the

central lab along with the corresponding samples with required information (including study number, subject ID, etc.) and one copy will be retained by the site.

9.4 Database management and quality control

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

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

Pharmacokinetic and biomarker samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Laboratory samples for hematology, biochemistry, Urinalysis, coagulation, lipid profile and others assessments (HbA1c, fasting plasma glucose, fasting lipase and amylase, insulin and c-peptide) will be performed by a Central Laboratory. However fasting plasma glucose, ALT, AST, ALP and Creatinine and total bilirubin will be performed both locally and centrally. Results of analysis tested centrally will be reconciled and sent electronically to Novartis (or a designated CRO). Unscheduled laboratory analysis performed locally will be collected directly in e-CRF by the sites.

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

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

10 Statistical methods and data analysis

Data will be summarized by Novartis and/or designated CRO. Any data analysis carried out independently by the investigators must be submitted to Novartis before publication or presentation. It is planned that the data from the participating centers in this protocol will be combined so that an adequate number of patients will be available for analysis. Analysis will

[redacted]

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 due to any reason.

10.1 Analysis sets

10.1.1 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 and strata they have been assigned to during the randomization procedure.

The FAS will be the primary population for all the efficacy analyses.

10.1.2 Safety Set

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

10.1.3 Per-Protocol Set

The per-protocol set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the protocol. It will constitute of all randomized patients who receive at least one dose of study drug, have completed 24 weeks of therapy have undergone surgery and have at least one tumor assessment. Other major protocol deviations may be considered for exclusion from the PPS and will be listed in the study reporting and analysis plan (RAP).

The PPS may be used to carry out sensitivity analyses of primary efficacy endpoint if the FAS and the PPS are different in the population the PoC is established.

10.1.4 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who received at least one dose of BYL719, buparlisib or letrozole and have at least one evaluable post-treatment concentration measurement.

Due to the variability in the PK of BYL719, buparlisib and letrozole, at least 12 out of 15 patients providing blood samples from each of the combinations are needed to be evaluable for a Full Sampling Pharmacokinetic Analysis Set to provide an estimate on the magnitude of the drug-drug interaction and assess PK parameters for BYL719 and buparlisib.

10.1.4.1 BYL719 Pharmacokinetic Analysis Set (BYL PAS)

The BYL PAS will include all patients who received at least one dose of study medication BYL719 and had at least one evaluable post-treatment BYL719 concentration measurement.

10.1.4.2 BYL719 Full Sampling Pharmacokinetic Analysis Set (BYL FPAS)

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

[redacted]

- received all planned doses of BYL719 for the last consecutive 3 days preceding full PK profile assessment on Cycle 4 Day 1
- did not vomit within 4 hours of BYL719 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)

10.1.4.3 Buparlisib Pharmacokinetic Analysis Set (BKM PAS)

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

10.1.4.4 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).

10.1.4.5 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.

10.1.4.6 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

10.1.5 Other analysis sets

Not applicable.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline disease characteristic/prognostic data will be summarized by cohort and treatment the patient was randomized to and pooled on cohorts for the FAS.

[redacted]

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

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

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

The actual cumulative dose and duration of exposure to BYL719, buparlisib, placebo and letrozole treatment, as well as dose intensity (computed as the ratio of actual cumulative dose received to actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity to planned dose intensity), will be listed and summarized using descriptive statistics. The summary data will be presented for each treatment, by cohort and pooled on cohorts. The duration of exposure will also be presented for the study treatment by arm and by cohort and pooled on cohorts. The total daily doses of BYL719, buparlisib, placebo and letrozole for each patient will be summarized using descriptive statistics (e.g. mean, median, and mode).

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized by treatment arm and by cohort and pooled on cohorts. And all dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by ATC (Anatomical therapeutic chemical) classification system term for each treatment arm. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions.

10.4 Primary objective

The primary objectives of the study are:

- To assess the anti-tumor activity of BYL719 QD plus letrozole QD versus letrozole alone in increasing the pathologic complete response (pCR) rate 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.
  and
- To assess the anti-tumor activity of BYL719 QD plus letrozole QD versus letrozole alone in increasing the Objective Response rate (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.

10.4.1 Variable

The primary efficacy endpoints are:

- pathologic complete response (pCR) defined as 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.
- Objective Response Rate (ORR) defined as the proportion 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 (Appendix 2). No confirmation of CR/PR is required.

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)

10.4.2 Statistical hypothesis, model, and method of analysis

The primary objectives of this study are to assess the anti-tumor activity of BYL719 plus letrozole vs. letrozole alone based on pCR rate or ORR in each of the following two cohorts of HR+, HER2-negative breast cancer patients: (i) PIK3CA mutated and (ii) PIK3CA wild type based on tumor tissue.

There is no formal plan to compare the BYL719 and buparlisib combination arms.

Since this study is double-blinded with respect to placebo but not whether a patient is on BYL719 or buparlisib, some patients in the control arm of letrozole will receive letrozole plus BYL719 placebo and some patients will receive letrozole plus buparlisib placebo. Letrozole plus BYL719 placebo and letrozole plus buparlisib placebo will be combined together within a cohort for all analyses.

Pathologic complete responseBased 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:

[redacted]

- 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%

To determine the first criteria for PoC, the posterior distribution of the difference in the pCR rates (in the ORR respectively) between the combinations arm and letrozole will be estimated assuming binomial distribution of the pCR rates (of the ORR respectively) and using non-informative beta priors. Details will be specified in the RAP.

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

The pCR rates and ORR in each of the treatment arms will be summarized by cohort using descriptive measures including 90% confidence intervals using Clopper and Pearson (1934) exact method. The pCR and ORR rates will also be summarized by each stratum.

10.4.3 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.

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.

10.4.4 Supportive and sensitivity analyses

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 these population(s).

Additional supportive analyses may be performed if appropriate and will be specified in the RAP.

Subgroup analyses in a given cohort may be performed based on age, race, and other demographic and disease characteristics (e.g. ER status, PR status, Ki67, Lymph node status) in an exploratory manner in the population(s) if the PoC is established. Details about other subgroups and additional subgroup analysis will be specified in the RAP.

[redacted]

10.5 Secondary objectives

10.5.1 Key secondary objective(s)

None.

10.5.2 Other secondary efficacy objectives

The treatment effect of BYL719 plus letrozole vs. letrozole alone on pCR rate and ORR will be assessed in each of the following two cohorts: (i) PIK3CA mutated and (ii) PIK3CA wild type, based on ctDNA (assessed in hotspots from exons 9 and 20). The same statistical hypothesis, model, and method of analysis will be used as for PIK3CA cohorts based on tumor tissue. Patients with unknown mutation status based on ctDNA assessment will be excluded from the analysis.

Descriptive statistics (N, % and 90% confidence intervals using Clopper and Pearson (1934) method) will be used to summarize breast conserving surgery (BCS) rate. Summary statistics will also be presented for Ki67 changes under treatment (at day 15 and surgery) and PEPI score by treatment arm. The above analyses will be performed separately for the i) PIK3CA mutated and ii) PIK3CA wild type cohorts based on tumor tissue.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

All safety analyses will be carried out on the Safety set. All listings and tables will be presented by treatment arm irrespective of PIK3CA mutational status.

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

The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation. Those collected later than 30 days after study treatment discontinuation will be flagged in listings.

The safety data will be summarized and listed by treatment arm on pooled cohorts. Therefore, the safety assessment will be performed following the completion of both cohorts. Some safety analyses may be also performed separately for the continuous schedule and for the 5 days-on / 2 days-off schedule of buparlisib.

1. The overall observation period for all safety analyses will be divided into three mutually exclusive segments:pre-treatment period: from day of patient's informed consent to the day before first dose of study medication.
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication.
3. post-treatment period: starting at day 31 after last dose of study medication.

Periodic review of safety data aggregated by blinded treatment group (BYL719/placebo or buparlisib/placebo) will be performed and results will be shared with study steering committee.

[redacted]

In addition, selected safety analyses will be performed by an independent statistician not involved with the conduct of the study. Details regarding the safety analysis review by DMC are provided in Section 8.6. Further details are described in the DMC charter.

10.5.3.2 Adverse events (AEs)

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades version 4.03), type of AE, relation to study treatment.

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

All deaths (on-treatment and post-treatment) will be summarized. Deaths reportable as SAEs and non-fatal serious AEs will be listed by patient and tabulated by type of AE.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). SEC will be defined at project level and may be regularly updated. For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

10.5.3.3 Laboratory abnormalities

Laboratory data will be graded according to CTCAE version 4.03, if applicable. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

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

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

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

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

For laboratory tests where CTCAE v4.03 grades are not defined,

- shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on- treatment value
- listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges

[redacted]

10.5.3.4 Other safety data

Other safety data collected will be listed and summarized using descriptive statistics as appropriate. Notable values may be flagged. Notable/abnormal values for safety data will be further specified in the statistical analysis plan.

ECG

The following summaries will be generated by parameter and treatment arm:

- Notable ECG parameters change from baseline to worst on-treatment result
- listing of ECG evaluations for all patients with at least one abnormality

Cardiac imaging

Summary for the change from baseline to worst post-baseline in LVEF values

Vital signs

Definitions of notably abnormal results will be included in the statistical plan. The following summaries will be generated by parameter and treatment arm:

- Descriptive statistics for the change from Baseline to the worst post-baseline visit.
- Listing of patients with clinically notable vital sign abnormalities. Notable values will be flagged

ECOG Performance Status

- ECOG data will be listed for the safety set separately by treatment arm.

Mood Assessment

Mood assessment includes two self-rating mood questionnaires, the GAD-7 Anxiety scale and PHQ-9 Depression scales and is being administered to patients in the buparlisib/placebo arms only. The primary variable for the analyses of patient-reported outcomes will be the total scores of each of the two scales. Shift tables comparing the baseline severity score to worst post- baseline severity score will be provided by treatment arm (buparlisib plus letrozole vs buparlisib placebo + letrozole).

10.5.3.5 Tolerability

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

10.5.4 Pharmacokinetics

Pharmacokinetic parameters will be determined for all PK-evaluable patients using non-compartmental method(s) using Phoenix WinNonlin (Version 6.4 - Pharsight, Mountain View, CA). PK parameters listed in Table 10-1 will be estimated and reported, when feasible. Exploratory PK analysis may be conducted using compartmental modeling if appropriate.

Pharmacokinetic parameters for BYL719, buparlisib (BKM120) and letrozole after single oral dose at Cycle 1 Day1 (single agent PK) will include Tmax, Cmax, AUCinf, AUClast, AUC0-

[redacted]

24, CL/F, Vz/F and T1/2 (only BYL719 as T1/2 cannot be properly estimated for buparlisib due to its long half-life). Pharmacokinetic parameters for BYL719, buparlisib (BKM120) and letrozole after multiple oral doses at Cycle 4, Day 1 will include Tmax, Cmax, AUClast, AUC0-24, CLss/F, T1/2 (for BYL719), effective half-life (T1/2,eff for buparlisib only) and RAcc. For both compounds Clast and Tlast will be listed but not summarized. PK parameters will be used to determine the magnitude of the drug-drug interaction by determining Cmax and AUC ratios for letrozole.

PK parameters on Cycle 4 Day 1 will be compared between 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 + BYL719, letrozole + buparlisib) as a fixed effect. The treatment difference between letrozole + BYL719 and letrozole alone and between letrozole + buparlisib and letrozole alone will be calculated and back transformed to produce point estimates and 90% CI for the ratios of the geometric means as described above.

Table 10-1 Non-compartmental PK parameters

Term	Definition
Cmax	Maximum observed plasma concentration after drug administration (ng/mL)
Tmax	Time to reach Cmax (hr)
$Tlast_t$	Last measurable concentration sampling (hr)
Clast	Last measurable concentration (ng/mL)
AUClast	Area under the concentration-time curve from time zero to the last measurable concentration sampling time (Tlast) (h x ng/mL)
AUC0-24	Area under the concentration-time curve from time zero to 24 hours post dose (h x ng/mL)
AUCinf	The area under the plasma concentration-time curve from time zero to infinity (h x ng/mL)
AUCex[1]	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/hr)
CLss/F	Apparent oral total drug total plasma clearance calculated from stead-state exposure data (L/hr)
Vz/F	The apparent volume of distribution during terminal phase (associated with lambda_z) (volume)
T1/2	Elimination half-life associated with the terminal slope (lambda_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 lamda_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.

10.5.4.1 Data handling principles

10.5.4.1.1 Analysis sets

The plasma samples will be assayed for BYL719 or buparlisib (BKM120) and letrozole concentrations by Novartis or subcontractor using validated LC-MS/MS methods described in the [Laboratory Manual].

[redacted]

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 BYL719, 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 or missing data 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. Exploratory PK analysis may also be conducted based on preliminary data prior to database lock, and nominal time instead of actual elapsed time may be used.

10.5.4.1.1 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 timepoint.

Descriptive graphical plots of individual plasma concentration by time will be generated, as will mean concentration time profiles for BYL719, buparlisib and letrozole. Further graphical exploratory analyses will be carried out if deemed appropriate and specified in the RAP. Any other exploratory analyses will be conducted if necessary.

10.5.5 Resource utilization

Not Applicable.

10.5.6 Patient-reported outcomes

None.

10.6 Exploratory objectives

10.6.1 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 that preclude the analysis of

[redacted]

samples). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

Further details regarding exploratory analyses of biomarker and efficacy data are presented in Section 10.6.

10.6.1.1 Outline of the 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.

10.6.1.2 Data handling principles

For IHC variables the H-score will be calculated using the following standard algorithm H-score = Low level stain *1+ medium level stain *2+ high level stain*3. IHC is also used to assess Ki67, which is measured by percent positive cells, thus does not require an H-score computation.

Further details will be provided in the study RAP.

10.6.1.3 Data analysis principles

10.6.1.3.1 Analysis sets

The FAS set will be used for all biomarker analysis depending on the study phase to be analyzed. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

10.6.1.3.2 Basic tables, figures and listings

The biomarker data analysis will include the following:

Description of distribution of baseline level by using mean, standard deviation, median, minimum and maximum of raw data for quantitative biomarker data collected only at baseline. Categorical markers, such as mutation or amplification status, will be summarized using frequency and percentages for all baseline and post baseline time points.

Mean, standard deviation, median, minimum, and maximum of raw data, absolute change from baseline and percent change from baseline for IHC measured at baseline and at different time points.

The concordance/discordance of the PIK3CA mutation status between ctDNA and tumor tissue measured at study entry may be summarized.

All these analyses will be outlined in full in the RAP.

[redacted]

[redacted]

10.6.1.3.3 Advanced analysis methods

None.

10.6.2 Efficacy

Exploratory analyses will be performed to assess the anti-tumor activity of buparlisib versus letrozole alone in increasing the pathologic complete response (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 and based on ctDNA. Additional exploratory analyses may be performed using the subpopulation of patients who receive the intermittent schedule if the PoC is established with buparlisib plus letrozole in at least one cohort

Exploratory analyses will also be performed to assess the anti-tumor activity of BYL719 plus letrozole and buparlisib plus letrozole versus letrozole alone regardless of PIK3CA mutational status, or between the combined group of patients treated with BYL719 or buparlisib plus letrozole versus those treated with letrozole alone.

10.7 Interim analysis

No interim efficacy analysis will be performed.

10.8 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. BYL719+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 BYL719+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 BYL719 (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 BYL719+letrole and Placebo+letrozole within each cohort, the assessment of the PoC for BYL719 will have the following operating characteristics, using the PoC criteria described in Section 7.2.1 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

[redacted]

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
	0.3	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
	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

10.9 Power for analysis of key secondary variables

Not Applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

11.3 Informed consent procedures

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

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

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

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

Additional consent form

Sub-studies and studies with an optional Exploratory Biomarker component will have a separate consent form covering those studies. This form will be adapted for each Study based on a standard template used globally for all Studies. These informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a subject opts not to participate in the optional assessments, this in no way affects the subject's ability to participate in the main research study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.3.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

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

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

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

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

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12 Protocol adherence

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

12.1 Amendments to the protocol

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

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14 Appendices

14.1 Appendix 1 - List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or BYL719 and/or buparlisib and/or letrozole. Please note that all lists in Appendix 1 are not comprehensive. Please refer to regular updated online sources and the label of a concomitant drug to decide whether a drug is permitted (with caution) or prohibited based on Section 6.4. In doubt please the contact medical monitor with any questions.

14.1.1 Cytochrome P450 Substrates

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. This list only meant to be used as a guide.

Table 14-1 List of CYP450 substrates to be used with caution

Category	Drug Names
CYP2C8	
Narrow Therapeutic index substrates of CYP2C8	Paclitaxel
Sensitive substrates of CYP2C8	Repaglinide
Other Substrates of CYP2C8	Amodiaquine, Benzphetamine, Carbamazepine, Cerivastatin, Docetaxel, Everolimus, Febuxostat, Fluvastatin, Isotretinoin, Phenytoin, Pioglitazone, Retinol, Repaglinide, Rosiglitazone, Tolbutamide, Torsemide, Verapamil, Zopiclone
CYP2C9	
Narrow Therapeutic index substrates of CYP2C9	(S)-Warfarin, Phenytoin
Sensitive substrates of CYP2C9	(S)-Warfarin
Other Substrates of CYP2C9	Amitriptyline, Carvedilol, Celecoxib, Chlorpheniramine, Chloramphenicol, Clomipramine, Clopidogrel, Desogstrel, Diclofenac, Dronabinol, Febuxostat, Fluoxetine, Flurbiprofen, Fluvastatin, Formoterol, Glibenclamide, Glimepiride, Glipizide, Hexobarbital, Ibuprofen, Imipramine, Indomethacin, Irbesartan, Irinotecan, Ketamine, Lomoxicam, Losartan, Mefenamic acid, Meloxicam, Mephenytoin, Montelukast, Nateglinide, Omeprazole, Phenylbutazone, Piroxicam, Quetiapine, Rosiglitazone, Sertraline, Sildenafil, Sulfamethoxazole, Sulfinpyrazone, Suprofen, Tamoxifen, Tienilic acid, Tolbutamide, Torsemide, THC, Testosterone, Valdecoxib, Vardenafil, Valsartan, Voriconazole, Zafirlukast, Zileuton

[redacted]

Category	Drug Names
CYP2C19	
Narrow Therapeutic index substrates of CYP2C19	(S)-Mephenytoin (also sensitive)
Sensitive substrates of CYP2C19	Clobazam, Dexlansoprazole, Diazepam, Gliclazide, (R)-Mephobarbital, Lansoprazole, (R)-Lansoprazole, (S)-Lansoprazole, Omeprazole, (R)-Omeprazole, Pantoprazole, (+) Pantoprazole, Rabeprazole, Tilidine,
Other Substrates of CYP2C19	Antipyrine, Bosentan, Dapasone, Dexloxiglumide, Diclofenac, Esomeprazole, Flurbiprofen, Glyburide, Losartan, Moclobemide, Ospemifene, Phenytoin, Pitavastatin, Proguanil, Quinidine, Rabeprazole, Rosuvastatin, Sildenafil, Tolbutamide, Voriconazole
CYP3A	
Narrow Therapeutic index substrates of CYP3A	Alfentanil, Cyclosporine, Diergotamine, Ergotamine, Fentanyl, Pimozide, Quinidine, Sirolimus, Tacrolimus
Sensitive substrates of CYP3A	Alfentanil, Almorexant, Alpha-dihydroergocryptine, Aplaviroc, Aprepitant, Atazanavir, Atorvastatin, Avanafil, Bosutinib, Brecanavir, Brotizolam, Budesonide, Buspirone, Capravirine, Casopitant, Conivaptan, Danoprevir, Darifenacin, Darunavir, Dasatinib, Dronedarone, Ebastine, Eletriptan, Elvitegravir, Eplerenone, Everolimus, Felodipine, Fluticasone, Ibrutinib, Indinavir, Ivacaftor, Levomethadyl, Lomitapide, Lopinavir, Lovastatin, Lumefantrine, Lurasidone, Maraviroc, Midazolam, Midostaurin, Naloxegol, Neratinib, Nisoldipine, Perospirone, Quetiapine, Ridaforolimus, Saquinavir, Sildenafil, Simeprevir, Simvastatin, Sirolimus, Tacrolimus, Ticagrelor, Terfenadine, Ticagrelor, Tilidine, Tipranavir, Tolvaptan, Triazolam, Ulipristal, Vardenafil, Vicriviroc, Voclosporin
Other Substrates of CYP3A	Alprazolam, Ambrisentan, Amlodipine, Antipyrine, Aripiprazole, Artemether, Avosentan, Boceprevir, Bosentan, Buprenorphine, Carbamazepine, Dexloxiglumide, Dextromethorphan, Diazepam, Docetaxel, Enzalutamide, Gemigliptin, Halofantrine, Imipramine, Lansoprazole, Lidocaine, Linagliptin, Loperamide, Loratadine, Losartan, Lurasidone, Macitentan, Methadone, Mirodenafil, Montelukast, Morphine, Nelfinavir, Netupitant, Nevirapine, Nifedipine, Nilotinib, Nitrendipine, Omeprazole, Ospemifene, Oxycodone, Paclitaxel, Pazopanib, Pioglitazone, Quinine, Ranolazine, Repaglinide, Rifabutin, Ritonavir, Roflumilast, Saxagliptin, Selegiline, Sertraline, Sibutramine, Sotrastaurine, Telaprevir, theophylline, tirilazad, tolterodine, udenafil, Vincristine, Voriconazole

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. Please note that this may not an exhaustive list. Dated July 2015.

[1] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsades de Pointes, QT prolongation).

[3] Other substrates are these that have shown an in vivo ≥2-fold increase in AUC with co-administration of an inhibitor based on the UW database.

[redacted]

14.1.2 Cytochrome P450 Inhibitors and Inducers

This list of CYP inhibitors and inducers was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. This list only meant to be used as a guide.

Table 14-2 List of moderate CYP3A4 inducers and inhibitors used with caution (buparlisib treatment arm)

Category	Drug Name
Moderate CYP3A Inhibitors	ACT-178882, Amprenavir, Aprepitant, Atazanavir, Casopitant, Cimetidine, Ciprofloxacin, Crizotinib, Cyclosporine, Darunavir, Diltiazem, Dronedarone, Erythromycin, FK1706, Fluconazole, Grapefruit juice (citrus paradisi fruit juice 240 mL QD), Imatinib, Ledipasivir, Netupitant, Schisandra sphenanthera[1], Tofisopam, Verapamil
Moderate CYP3A Inducers	Bosentan, Efavirenz, Etravirine, Genistein, Lersivirine, Lopinavir, Modafinil, Nafcillin, Ritonavir and St. John's wort, Semagacestat, Talviraline, Thioridazine, Tipranavir and Ritonavir
[1]Herbal product, [2]P-gp inducer	

Table 14-3 List of prohibited strong CYP3A4 inducers and inhibitors (buparlisib treatment arm)

Category	Drug Name
Strong CYP3A Inhibitors	Boceprevir, Clarithromycin, Cobicistat, Conivaptan, Danoprevir, Grapefruit juice (citrus paradisi fruit juice, 240 mL TID), Elvitegravir, Idealisib, Indinavir, Itraconazole, Ketoconazole, LCL161, Lopinavir, Mibefradil, Nefazodone, Nelfinavir, Posaconazole, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Tipranavir, Troleandomycin, Voriconazole
Strong CYP3A Inducers	Avasimibe[1,2], Carbamazepine, Enzalutamide, Mitotane, Phenobarbital, Phenytoin, Rifabutin, Rifampin (Rifampicin)[2], St. John's wort (hypericum perforatum)[2]
[1]Herbal product; [2]P-gp inducer	

14.1.3 Drugs that prolong the QT interval and/or induce Torsades de Pointes

The Arizona Center for Education and Research on Therapeutics (CERT) keeps a comprehensive list of drugs that prolong the QT interval and/or induce Torsades de Pointes. Because the quality of the evidence for QT prolongation/TdP risk varies, drugs are further classified into three categories:

- **Known Risk of TdP:** Substantial evidence supports the conclusion that these drugs prolong QT intervals and have a risk of TdP when used as directed in labeling.
- **Possible risk of TdP:** Substantial evidence supports the conclusion that these drugs can cause QT prolongation but there is insufficient evidence that the drugs, when used as directed in labeling, have a risk of causing TdP.

[redacted]

- **Conditional risk of TdP:** Substantial evidence supports the conclusion that these drugs prolong QT and have a risk of developing TdP but only under certain known conditions.

All QT-prolonging drugs with known risk (Table 14-4) are prohibited for all patients from screening through permanent discontinuation of study treatment in this study. For a complete and most updated drug list, please check the website https://crediblemeds.org/healthcare-providers/drug-list.

Please always refer to the QTDrug Lists database to double-check the QT risk classification of a drug before administration as drugs may be subject to reclassification!

Table 14-4 List of prohibited QT prolonging drugs

Drug	QT risk*	Comment
Anagrelide	known risk	
Amiodarone	known risk	Females>Males, TdP risk regarded as low
Arsenic trioxide	known risk	
Astemizole	known risk	No Longer available in U.S.; Substrate for 3A
Azithromycin	known risk	
Bepridil	known risk	No Longer available in U.S.; Females>Males
Chloroquine	known risk	
Chlorpromazine	known risk	
Cilostazol	known risk	
Ciprofloxacin	known risk	Drug metabolism inhibitor- Risk for drug interactions
Cisapride	known risk	No longer available in the U.S.; Substrate for 3A
Citalopram	known risk	
Clarithromycin	known risk	Substrate for 3A4
Disopyramide	known risk	Females>Males
Dofetilide	known risk	
Domperidone	known risk	Not available in the U.S.
Donepezil	known risk	
Dronedarone	known risk	Substrate for 3A
Droperidol	known risk	
Escitalopram	known risk	
Erythromycin	known risk	Females>Males. Substrate for 3A
Flecainide	known risk	
Fluconazole	known risk	Drug metabolism inhibitor- Risk for drug interactions
Halofantrine	known risk	Females>Males
Haloperidol	known risk	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases. Substrate for 3A4
Ibutilide	known risk	Females>Males
Levofloxacin	known risk	
Levomethadyl	known risk	No longer available in U.S.
Mesoridazine	known risk	
Methadone	known risk	Females>Males. Substrate for 3A4
Moxifloxacin	known risk	
Ondansetron	known risk	

[redacted]

Drug	QT risk*	Comment
Pentamidine	known risk	Females>Males
Pimozide	known risk	Females>Males. Substrate for 3A4
Probucol	known risk	No longer available in U.S.
Procainamide	known risk	Not available in the U.S. (oral)
Propofol	known risk	
Quinidine	known risk	Females>Males. Substrate for 3A4
Sevoflurane	known risk	
Sotalol	known risk	Females>Males
Sparfloxacin	known risk	No longer available in U.S
Sulpiride	known risk	Not available in the U.S.
Terfenadine	known risk	No longer available in U.S.; Substrate for 3A4
Thioridazine	known risk	
Vandetanib	known risk	
Classification according to https://crediblemeds.org/ - Dated July 2015		

Table 14-5 List of QT prolonging drugs to be used with caution

Drug	QT risk*	Comment
Alfuzosin	possible risk	
Amantadine	conditional risk	
Amisulpride	conditional risk	
Amitriptyline	conditional risk	Risk of TdP with overdosage; Substrate of CYP2C19
Apomorphine	possible risk	
Aripiprazole	possible risk	
Atazanavir	possible risk	
Atomoxetine	possible risk	
Bedaquiline	possible risk	
Bortezomib	possible risk	
Bosutinib	possible risk	
Chloral hydrate	conditional risk	
Ceritinib	possible risk	
Clomipramine	possible risk	
Clozapine	possible risk	
Crizotinib	possible risk	
Dabrafenib	possible risk	
Dasatinib	possible risk	
Degarelix	possible risk	
Desipramine	possible risk	Risk of TdP with overdosage
Dexmedetomidine	possible risk	
Dihydroartemisinin + piperaquine	possible risk	
Diphenhydramine	conditional risk	Risk of QT increase/TdP in overdosages
Dolasetron	possible risk	
Doxepin	conditional risk	
Eribulin	possible risk	
Famotidine	possible risk	

[redacted]

Drug	QT risk*	Comment
Felbamate	possible risk	
Fingolimod	possible risk	
Fluoxetine	conditional risk	
Foscarnet	possible risk	
Furosemide	conditional risk	
Galantamine	conditional risk	
Gatifloxacin	possible risk	No longer available in U.S.
Gemifloxacin	possible risk	
Granisetron	possible risk	
Hydrochlorothiazide	conditional risk	
Hydroxychloroquine	conditional risk	
Hyroxyzine	conditional risk	
Iloperidone	possible risk	
Imipramine	possible risk	Risk of TdP in overdosage
Indapamide	conditional risk	
Isradipine	possible risk	
Itraconazole	conditional risk	Drug metabolism inhibitor- Risk for drug interactions
Ivabradine	conditional risk	not available in the United States
Ketoconazole	conditional risk	Drug metabolism inhibitor
Lapatinib	possible risk	
Leuprolide	possible risk	
Lithium	possible risk	
Metoclopramide	conditional risk	
Metronidazole	conditional risk	
Mifepristone	possible risk	
Mirabegron	possible risk	
Mirtazapine	possible risk	
Moexipril/HCTZ	possible risk	
Nelfinavir	conditional risk	
Nicardipine	possible risk	
Nilotinib	possible risk	
Norfloxacin	possible risk	
Nortriptyline	possible risk	
Ofloxacin	possible risk	
Olanzapine	possible risk	
Oxytocin	possible risk	
Paliperidone	possible risk	
Panobinostat	possible risk	
Pantoprazole	conditional risk	
Paroxetine	conditional risk	
Pasireotide	possible risk	
Pazopanib	possible risk	
Perflutren lipid microspheres	possible risk	
Pipamperone	possible risk	not available in the United States

[redacted]

Drug	QT risk*	Comment
Posaconazole	conditional risk	
Promethazine	possible risk	
Quetiapine	possible risk	Substrate for 3A4
Quinine sulfate	conditional risk	
Ranolazine	possible risk	
Rilpivirine	possible risk	
Risperidone	possible risk	
Ritonavir	conditional risk	Substrate for 3A4
Roxithromycin	possible risk	not available in the United States
Saquinavir	possible risk	
Sertindole	possible risk	not available in the United States
Sertraline	conditional risk	
Solifenacin	conditional risk	
Sorafenib	possible risk	
Sunitinib	possible risk	
Tacrolimus	possible risk	Substrate for 3A4
Tamoxifen	possible risk	
Telaprevir	conditional risk	
Telavancin	possible risk	
Telithromycin	possible risk	Substrate for 3A4
Tetrabenazine	possible risk	
Tizanidine	possible risk	
Tolterodine	possible risk	
Toremifene	possible risk	
Toresemide	conditional risk	
Trazodone	conditional risk	Substrate for 3A4
Trimethoprim-Sulfa	conditional risk	
Trimipramine	conditional risk	
Tropisetron	possible risk	
Vardenafil	possible risk	Substrate for 3A4
Vemurafenib	possible risk	
Venlafaxine	possible risk	
Voriconazole	possible risk	
Vorinostat	possible risk	
Ziprasidone	possible risk	
Classification according to https://crediblemeds.org/ - Dated July 2015		

14.1.4 BCRP inhibitors

As clinical BCRP inhibition has been investigated and/or formally shown only in selected cases in the past the table encompasses also drugs and molecular entities for which inhibition of BCRP was only shown *in vitro*. Please note that this is not an exhaustive list. This list only meant to be used as a guide.

[redacted]

Table 14-6 BCRP inhibitors to be used with caution

Category	Drug Name
BCRP inhibitors – DDI potential shown *in vivo*	Atazanavir, Cyclosporine, Eltrombopag, Gefitinib
BCRP inhibitors – Inhibition shown *in vitro*	A number of different compound and chemical classes such as steroid(-like) compounds, antivirals, immunosuppressant, estrogen agonists and antagonists, diketopiperazines, (dihydro)pyridines, azoles (e.g. PPIs and anti-infectives), statins and P-gp inhibitors have shown the potential to inhibit BCRP *in vitro*. Examples include*:* Afatinib, Abacavir, Amprenavir, Aripiprazole, Atorvastatin, Axitinib, Cerivastatin, Curcumin, Daunomycin, Delavirdine, Efavirenz, Elacridar, Erlotinib, Fluvastatin, Fumitremorgin C, Ivermectin, Lapatinib, Lansoprazole, Lopinavir, Nelfinavir, Nilotinib, Omeprazole, Pantoprazole, Pitavastatin, Regorafinib, Rosuvastatin, Saquinavir, Simvastatin, Sulfasalazine, Sunitinib, SN-38 (irinotecan), Tacrolimus, Teriflunomide

[redacted]

14.2 Appendix 2: Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

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Glossary

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

[redacted]

14.2.1 Introduction

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

The efficacy assessments described in Section 14.2.2 and the definition of best response in Section 14.2.16 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.17 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.2.27 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.2.2 Efficacy assessments

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

14.2.3 Definitions

14.2.3.1 Disease measurability

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

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

For patients without measurable disease see Section 14.2.25.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.

[redacted]

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

14.2.4 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.2.25.

14.2.5 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

[redacted]

- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such

techniques can be useful in confirming complete pathological response when biopsies are obtained.

- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.2.6 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.2.3.1.
- **Nodal target**: See Section 14.2.3.1.

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

[redacted]

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

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-7) and non-target lesions (Table 14-8) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-9) as well as the presence or absence of new lesions.

14.2.8 Follow-up and recording of lesions

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

14.2.9 Non-nodal lesions

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

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

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

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

[redacted]

14.2.10 Nodal lesions

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

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

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

14.2.11 Determination of target lesion response

Table 14-7 Response criteria for target lesions

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

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See Section 14.2.5.

Notes on target lesion response

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

[redacted]

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-7 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.

[redacted]

- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
  - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
  - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
  - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.2.12 Determination of non-target lesion response

Table 14-8 Response criteria for non-target lesions

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

[1]. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

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

[redacted]

one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.2.11 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.2.13 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.2.14).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.2.5.

14.2.14 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-9.

Table 14-9 Overall lesion response at each assessment

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

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 14.2.7.

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

[redacted]

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

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

14.2.15 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.2.25 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.2.16 Best overall response

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

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required

- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

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

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

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

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

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

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

- Investigator overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator)

[redacted]

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

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

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

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

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

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

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

14.2.17 Time to event variables

14.2.18 Progression-free survival

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

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

14.2.19 Overall survival

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

[redacted]

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

14.2.20 Time to progression

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

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.2.21 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.2.22 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such

as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

14.2.23 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.2.22. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

[redacted]

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

14.2.24 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

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

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.2.25).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.

- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

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

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-10.

Table 14-10 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.2.7.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses

[redacted]

which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.2.26 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.2.24, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-11 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 14.2.24
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.2.24.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

[redacted]

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-11 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.2.27 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

[redacted]

14.2.28 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.2.29 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

14.2.30 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

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

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

[redacted]

- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.2.31 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

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

14.2.32 Programming rules

The following should be used for programming of efficacy results:

14.2.33 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.2.34 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and

assessment date is calculated as outlined in Section 14.2.24). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.2.35 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.2.36 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.2.37 Study/project specific programming

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

14.2.38 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-11)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.2.24. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor

assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

14.2.39 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005

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

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

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

14.3 Appendix 3: Guidelines on Calculating PEPI Score

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 14-12).

Table 14-12 The preoperative endocrine prognostic index (PEPI) score

Pathology, biomarker Status	RFS Points
Pathological tumor size	
T1/2	0
T3/4	3
Node status	
Negative	0
Positive	3
Ki67 level	
0% – 2.7% (0 – 1†)	0
>2.7% – 7.3% (1 – 2 †)	1
>7.3% – 19.7% (2 – 3 †)	1
>19.7% – 53.1% (3 – 4 †)	2
>53.1% (>4 †)	3
ER status, Allred score	
0 – 2	3
3 – 8	0

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

[redacted]

14.4 Appendix 4: Patient Self-Reported Mood Questionnaires

14.4.1 Scoring the PHQ-9 and GAD-7

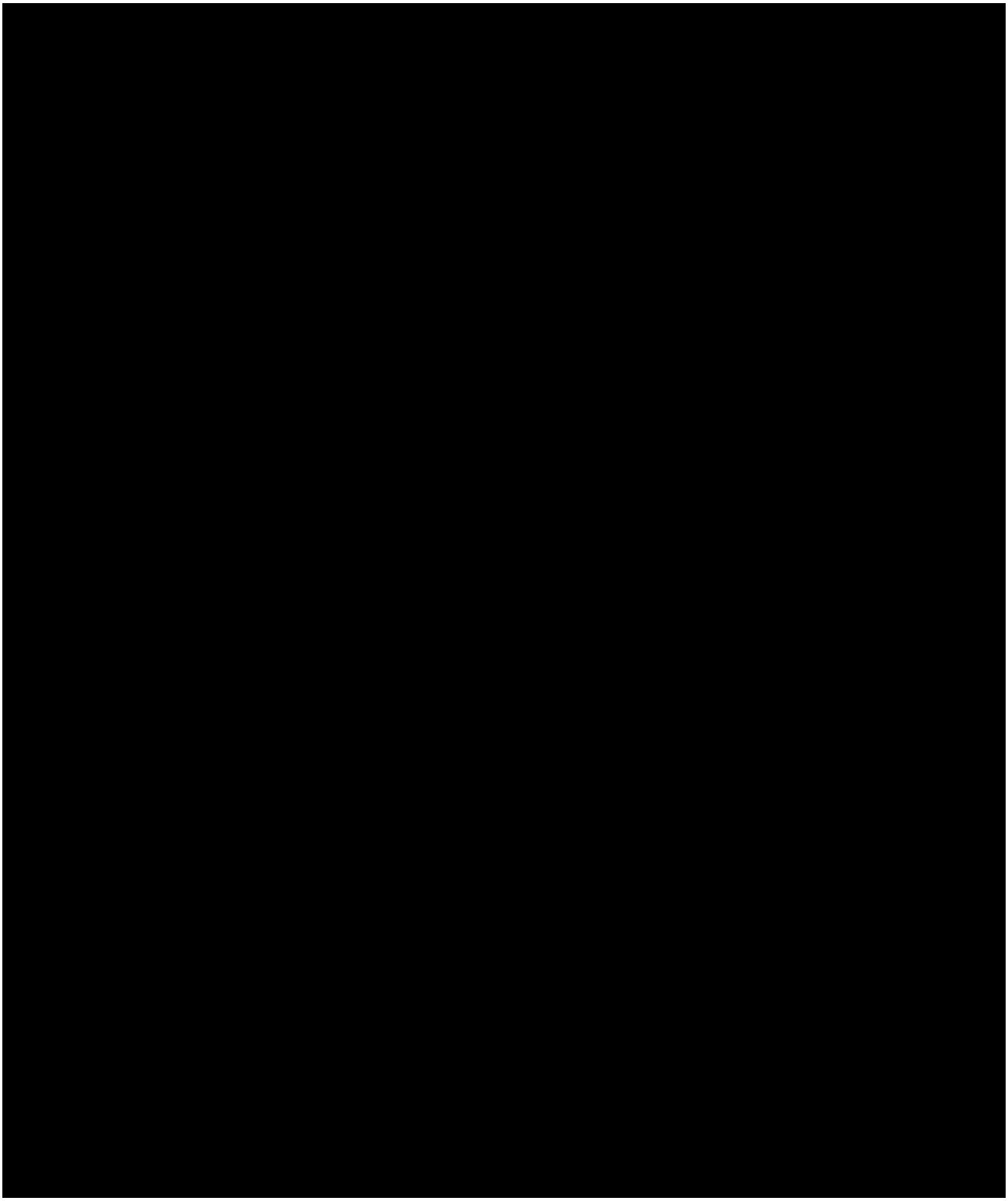
14.4.1.1 Calculating the Total Score for the PHQ-9

Total scores from the PHQ-9 will be calculated to assess depression severity according to the developer's guidelines [Instruction Manual: Instructions for PHQ and GAD-7 Measures. Accessed on 2010 Sept 9 from: //phqscreeners.com]. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. PHQ-9 total score for the nine items ranges from 0 to 27.

PHQ-9 Scoring Example:

In the example below, the Total Score for the PHQ-9 depression severity is 8, where the score is the sum of four items scored "0" (questions: #3, 7, 8, 9), three items scored "1" (questions: #1, 4, 6), one item scored "2" (question: #2), and one item scored "3" (question: #5).

[redacted]



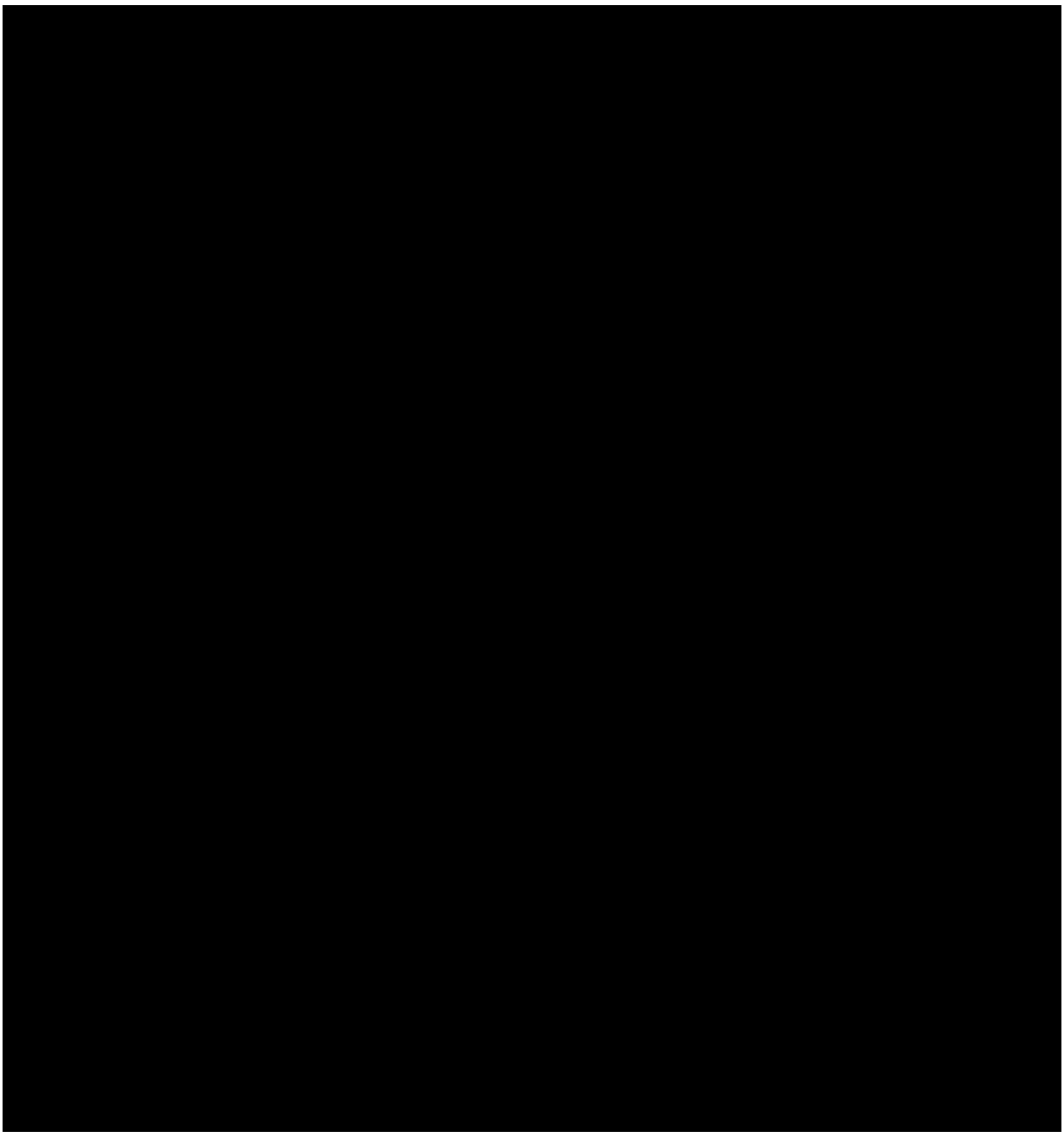
14.4.1.2 Calculating the Total Score for the GAD-7

Similar to the PHQ-9, scores for the GAD-7 will calculated to assess anxiety severity according to the developer's guidelines [1]. This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all," "several days," "more than half the days," and "nearly every day," respectively. A total score for the GAD-7 can range from 0 to 21.

GAD-7 Scoring Example:

In the example below, the Total Score for the GAD-7 anxiety severity is 9, where the score is the sum of two items scored "0" (questions: #6, 7), two items scored "1" (questions: #2, 3), two items scored "2" (questions: #1, 5), and one item scored "3" (question: #4).

[redacted]



14.5 Appendix 5: Guidelines for the treatment of study drug combination induced diarrhea

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

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

Patient history of diarrhea

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

- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;
- Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;
- Instruct patients regarding risk of developing diarrhea;
- Perform baseline clinical/laboratory studies according to the trial protocol (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients);
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading (Table 14-13).

Table 14-13 NCI CTCAE version 4.03 grading of diarrhea for patients without colostomy

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

First report of diarrhea

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

[redacted]

- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)

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

Management of diarrhea

General recommendations:

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

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

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

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

[redacted]

Treatment of diarrhea CTCAE grade 1 or 2

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

12-24 hrs later:

Diarrhea resolved

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

Diarrhea unresolved

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

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

After 12-24 hrs:

Diarrhea resolved

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

Diarrhea unresolved

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

[redacted]

Treatment of diarrhea CTCAE grade 3 or 4

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

After 12-24 hrs:

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

Diarrhea workup

Perform appropriate tests (Fine et al 1999).

Spot stool analysis

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

Endoscopic examinations

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

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

[redacted]