NOVARTIS

Clinical Development

BYL719

Clinical Trial Protocol CBYL719X2101

A phase IA, multicenter, open-label dose escalation study of oral BYL719, in adult patients with advanced solid malignancies, whose tumors have an alteration of the *PIK3CA* gene

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List of abbreviations

ADL	Activity of Daily Life
ADA	American Diabetic Association
AE	Adverse Event
Akt	see PKB (protein Kinase B)
ALT	Alanine aminotransferase/Glutamic Pyruvic Transaminase/GPT
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time (also known as PTT)
AR	Accumulation Rate
AST	Aspartate aminotransferase/Glutamic Oxaloacetic Transaminase/GOT
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the curve
BCRP	Breast Cancer Resistant Protein
b.i.d.	*bis in diem*/twice a day
BLRM	Bayesian Logistic Regression Model
BM	Bone Marrow
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
Cmax	Maximum concentration
CR	Complete Response
CrCl	Creatinine Clearance
CRD	Clinical Research and Development
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DDS	Dose Determining Set
DLT	Dose Limiting Toxicity
DS&E	Drug Safety & Epidemiology
DSMB	Drug Safety Monitoring Board
p-4EBP1	phospho-Eukaryotic translation initiation factor 4E-Binding Protein 1
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGF/EGFR	Epithelial Growth Factor/ Epithelial Growth Factor Receptor
ELISPOT	Enzyme-Linked Immunosorbent Spot
ER	Estrogen receptor
EWOC	Escalation With Overdose Control

[redacted]

^{18}F-FDG	^{18}F-Fluorodeoxyglucose
FAS	Full Analysis Set
bFGF	basic Fibroblast Growth Factor
F / M	Female / Male
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GLP	Good Laboratory Practice
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
HbA1c	Hemoglobin A1c
Hct	Hematocrite
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
HER2+	Human Epidermal Growth Factor Receptor 2 Positive
hERG	human Ether-a'-go-go-Related Gene channel
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HNSTD	Highest Non Serious Toxic Dose
HR+	Hormone Receptor Positive
IB	Investigators' brochure
IC50	Inhibitor concentration, 50%
IC / ICF	Informed Consent / Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF1	Insulin Growth Factor 1
IHC	Immunohistochemistry
IRB	Institutional Review Board
i.v.	Intravenous(ly)
LC-MS/MS	Liquid Chromatography and tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
LLN	Lower Limit Of Normal
LLOQ	Lower Limit Of Quantification
LVEF	Left Ventricular Ejection fraction
MAPK	Mitogen Activated Protein Kinase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
M-CSF	Macrophage Colony Stimulating Factor
MCV	Mean Corpuscular Volume

[redacted]

MDR	Multi Drug Resistance
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTOR	mammalian Target of Rapamycin
MUGA	Multiple Gated Acquisition Scan
MVD	Mean Vascular Density
NK Cells	Natural Killer Cells
NOAEL	No-Observable-Adverse Effect Level
NOEL	No-Observable-Effect Level
NVP	Novartis Product
o.d.	*omnia die*/once a day
ORR	Overall Response Rate
PARP	Poly(ADP-ribose)Polymerase
PD	Pharmacodynamic
PD	Progressive Disease
PDK1	Pyruvate Dehydrogenase Kinase isozyme 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
P-gp	P-glycoprotein
PH	Pleckstrin Homology
PI	Principal Investigator
PI3K	Phosphatidylinositol-3-Kinase
PIK3CA	Gene which encodes the p110alpha catalytic subunit of PI3K
PIKKs	Phosphatidylinositol-3-Kinase related Kinases
PK	Pharmacokinetic
PKB	Protein Kinase B (or Akt)
PlGF	Placental Growth Factor
p.o.	*Per Os*/by mouth/orally
PR	Partial Response
PSA	Prostate-Specific Antigen
PT	Prothrombin Time
PTEN	Phosphatase and Tensin homolog
PTT	Partial Thromboplastin Time (also known as APTT)
q.d.	quaque die / once daily
QTcF	QT interval corrected according to Fridericia
RBC	Red Blood Cells
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Serious Adverse Event
S / D	Source / Data
SEC	Study Evaluation Completion

S6K	Protein Kinase S6
SLD	Sum of the Largest Diameters
SS	Safety Set
SOP	Standard Operating Procedure
SUV	Standardized Uptake Value
T/C	Tumor volume over Control volume
TTP	Time to Progression
ULN	Upper Limit of Normal
VEGF/VEGFR	Vascular Endothelial Growth Factor / Vascular Endothelial Growth Factor Receptor
WBC	White Blood Count
WCBP	Women of Childbearing Potential
WHO	World Health Organization

[redacted]

Amendment 9

Amendment rationale

The primary objective of this study has been reached and interim database lock for the primary data analysis has taken place. The ongoing patients have now been on treatment for between 18 and 33 months and information about the safety of BYL719 in these patients is available. The purpose of this amendment is to reduce the protocol assessments to allow the patients to follow local standard of care, whilst maintaining access to study treatments and continuing to monitor safety.

[redacted]

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 6.6.4.2 has been amended to update the reference of the list of drugs causing QT prolongation
- Section 7 has been amended as follows:
  - Table 7-2 has been added to Section 7
  - Section 7.4.1 (Efficacy) has been amended to inform that no efficacy assessments are required by the protocol
  - Section 7.5 (Safety) has been amended to inform that only safety related events will be collected
  - Section 7.9 (Pharmacokinetics) has been amended to inform that no assessments are required by the protocol
  - Section 7.10 (Biomarkers) has been amended to inform that no assessments are required by the protocol

Review requirements by IRB/IEC and Health Authorities

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, changes herein affect the Informed Consent and 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]

Amendment 8

Amendment rationale

The purpose of this amendment is to include guidelines for management of pneumonitis.

Changes to the protocol

- Added Section 6.6.3 Management of pneumonitis and added management of pneumonitis to Table 6-4 Criteria for interruption and re-initiation of BYL719.

Review requirements by IRB/IEC and Health Authorities

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

Amendment 7

Amendment rationale

The purpose of this amendment is to add blood sampling for an additional exploratory investigation into the molecular mechanisms of rash observed with BYL719. Grade 3 rash has been observed in some patients participating in this study and the clinical course of these adverse reactions varied among patients. The objective is to investigate the underlying causal mechanisms and parameters associated with the predictability of rash. Current scientific knowledge suggests that genetic variants such as certain HLA subtypes can play a role in drug-related high-grade skin rash (Tsuchiya 2012). Polymorphisms of transporters such as MDR1 (ABCB1) or ABCG2 may have an effect on disease susceptibility, for example to breast cancer, and on drug disposition and toxicity, for example of telaprevir or gefitinib (Turgut 2007, Roujeau 2012, Cusatis 2006). Cytotoxic T-cells against drugs or metabolites, macrophages and the associated cytokine release, i.e., of interferon gamma, may be relevant in drug hypersensitivity (Rozieres 2009). Toxic skin reactions are also hypothesized to be associated with infections and viral load.

[redacted]

[redacted]

Other exploratory tests, for example measurement of other cytokines or detection cytotoxic T-cells or macrophages may be conducted using existing blood or tissue samples if such tests become available.

Furthermore, to better understand the mechanisms of resistance being investigated in this study, additional blood samples for circulating DNA will be taken at baseline and at end of treatment, to be paired with tumor biopsies taken at the same time points. This will enable a comparison of mutations detected in tumor with those in the plasma sample.

For patient convenience, a reduced assessment schedule will be used once a patient has completed 6 cycles of study treatment. This is because patients have received multiple cycles of therapy with study treatment and have demonstrated tolerability the study treatment and require a less intensive treatment schedule. The day 15 visits (vital signs, hematology, biochemistry, and fasting plasma glucose) after the end of 6 cycle need no longer be performed. However, the visits may continue at the discretion of the Investigator.

The pregnancy monitoring in Section 8 has been clarified and updated.

Changes to the protocol

- The study synopsis has been updated to reflect the changes listed below.
- Section 3.3.1 (End-points for exploratory objectives) has been updated to include the tests for mechanisms of immunological response
- Section 4 (Study design) has been updated to include a sentence that patients who continue on study for more than 6 cycles will undergo a reduced schedule of assessments
- Table 7-1 has been updated
- Section 7.5.7.1 (ECGs) has been updated to indicate that ECGs need not be performed once all patients have completed at least 6 cycles of study treatment
- Section 7.9 (Pharmacokinetics) has been updated to remove references to ‘once every other day’ dosing, and it has been updated to indicate that PK sampling need not be performed once all patients have completed at least 6 cycles of study treatment
- [redacted]
- Section 7.10.3 (Exploratory biomarker assessments) has been updated [redacted]
- Section 8.2 (Pregnancies) has been updated to include sentence that pregnant female partners of male study participants will be consented to provide the outcome of the pregnancy.

The following change to the protocol has been made and is a non-substantial amendment. Following patient consent, an exploratory analysis of fulvestrant PK will be performed on remaining samples already collected for BYL719 PK.

- The sentence “No PK assessment will be done for fulvestrant” has been removed.

[redacted]

Amendment 6

Amendment rationale

The purpose of this amendment 6 is to include patients with *PIK3CA* wild type estrogen positive (ER+), HER2 receptor negative, locally advanced or metastatic breast cancer in the BYL719 plus fulvestrant treatment group of this clinical trial. To ensure homogeneity in the population treated, this amendment will add that patients with ER+ breast cancer enrolled into both the single agent and fulvestrant combination expansion cohorts will have HER2 negative breast cancer. The rationale for the amendment is based on the following:

- [redacted]
- Profiling of BYL719 in a large panel of cancer cell lines, the Cancer Cell Line Encyclopedia (CCLE) showed that cell lines responsive to BYL719 are enriched for ER+ breast cancer.
- The presence of a *PIK3CA* mutation is associated with increased sensitivity to BYL719 across many cancer types; however 106 out of 339 cell lines of different cancers characterized as wild type for *PIK3CA* were also sensitive to BYL719 (Huang 2012). It is possible that other molecular features may be involved in the activation of the PI3K pathway in ER+ breast cancer and other cancers.
- Since luminal breast cancer cell lines were found to be sensitive to BYL719 and approximately 30% of *PIK3CA* wild type cancer cell lines were also responsive to BYL719 in vitro, it is justified to investigate a possible synergy of BYL719 combined with fulvestrant also in patients with *PIK3CA* wild type ER+ metastatic breast cancer.

A sample size of approximately 20 patients is considered sufficient to observe preliminary activity in this patient population and to further evaluate the safety of BYL719. This will also allow to further evaluate the safety of BYL719 plus fulvestrant.

Changes to the protocol

- The study synopsis has been updated to reflect the changes listed below.
- Section 2 (Study rationale/purpose) has been updated to state that *PIK3CA* wild type breast cancer patients will also be enrolled in the BYL719 and fulvestrant combination cohort.
- Section 3.2 (Secondary objectives). The fourth secondary objective is now also to assess preliminary antitumor activity of BYL719 and fulvestrant in *PIK3CA* wild type breast cancer patients
- Figure 4-1 (Study design) has been updated
- Section 4 (Study rationale/purpose) has been updated to state that *PIK3CA* wild type breast cancer patients will also be enrolled in the BYL719 and fulvestrant combination cohort.

[redacted]

- Section 5 (Study rationale/purpose) has been updated to state that *PIK3CA* wild type breast cancer patients will also be enrolled in the BYL719 and fulvestrant combination cohort.
- Throughout the text it has been clarified that the ER positive breast cancer patients enrolled into this study will also be HER2 negative.

Amendment 5

Amendment rationale

The purpose of this amendment is to include patients with *PIK3CA* wild type estrogen positive (ER+) locally advanced or metastatic breast cancer in the single agent BYL719 treatment group of this clinical trial.

[redacted]

- Profiling of BYL719 in a large panel of cancer cell lines, the Cancer Cell Line Encyclopedia (CCLE) showed that cell lines responsive to BYL719 are enriched for luminal and HER2+ breast cancer (luminal breast cancer cell lines are representative for ER+ breast cancer).
- The presence of a PIK3CA mutation is associated with increased sensitivity to BYL719 across many cancer types; however 106 out of 339 cell lines of different cancers characterized as wild type for PIK3CA were also sensitive to BYL719 (Huang 2012). It is possible that other molecular features may be involved in the activation of the PI3K pathway in ER+ breast cancer and other cancers.
- Since luminal breast cancer cell lines were found to be sensitive to BYL719 and approximately 30% of PIK3CA wild type cancer cell lines were also responsive to BYL719 in vitro, it is justified to investigate BYL719 in patients with PIK3CA wild type ER+ metastatic breast cancer.

A sample size of approximately 20 patients is considered sufficient to observe preliminary activity in this patient population and to further evaluate the safety of BYL719.

Changes to the protocol

- The study synopsis has been updated to reflect the changes listed below
- Section 1.3 (Overview of BYL719) now includes a summary of the pre-clinical data of the *PIK3CA* wild type cell lines
- Section 3.2 (Secondary objectives) now includes *PIK3CA* wild type ER+ breast cancer patients
- Section 4 (Study design): Figure 4-1 (study design) and the text have been updated to reflect inclusion of *PIK3CA* wild type ER+ breast cancer patients
- Section 5 (Populations) has been updated to include *PIK3CA* wild type ER+ breast cancer patients and an explanation of the pre-screening process

[redacted]

- Section 5.1 (Inclusion criteria), inclusion criteria #1 now includes *PIK3CA* wild type ER+ breast cancer patients
- Section 7.10 includes clarifications to the biomarker sections
- Section 10.7.2 (Dose expansion arm) of the statistical methods section has been amended to include the *PIK3CA* wild type ER+ breast cancer patients
- Minor changes were made for clarification and consistency throughout the protocol

Amendment 4

Amendment rationale

The purpose of this amendment is to introduce a combination arm of BYL719 and fulvestrant; to introduce a modified formulation of BYL719; and to provide further detail regarding the investigation of twice daily (b.i.d.) BYL719 schedule.

- A combination arm of BYL719 and fulvestrant is introduced into this protocol, to be conducted in post-menopausal breast cancer patients whose tumors are estrogen receptor (ER) positive and have a PIK3CA alteration.
  - PI3K is involved in ligand-independent estrogen receptor signaling and PIK3CA mutations have been observed in 28-48% of ER positive primary or metastatic tumors, with the PI3K pathway upregulated in endocrine therapy-resistant cells (Sanchez 2011; Gonzalez-Angulo 2011; Miller 2011). PI3K pathway activation has been associated with resistance to anti-estrogen receptor therapy (Miller 2011). PIK3CA mutated ER+ breast cancer cells are sensitive to inhibition of PI3K under estrogen deprivation; and treatment with fulvestrant is sensitizing ER+ breast cancer cells (i.e., MCF7 LTED) to PI3K inhibition (Sanchez 2011).
  - In an in vitro study, the combination of BYL719 and fulvestrant was synergistic in PIK3CA mutated breast cancer cell lines (data on file). Inhibiting both the PI3Kα receptor and the estrogen receptor may offer a promising combined approach to the treatment of such breast cancer patients.
  - A confirmed partial response has been observed in this study in a ER+/PR+/HER- breast cancer patient treated with BYL719 at 270mg/d who had previously received fulvestrant, aromasin and tamoxifen. In addition, 3 ER+ breast cancer patients in this study are each ongoing in month 8 with stable disease.
  - The provisional starting dose of BYL719 will be 300mg q.d. This starting dose meets the overdose control criteria principle applied to the Bayesian Logistical Regression model presented in Section 10.4.2. Immediately before beginning the combination part, the statistical model will be run to take into consideration new data from recent cohorts. Should the predicted starting dose no longer meet the overdose control criteria, a lower starting dose will be implemented that does satisfy the overdose criteria.
- A modified formulation of BYL719 has been developed [redacted]
  - [redacted]

[redacted]

- In addition, further clarification has been provided as to the investigation of a b.i.d. schedule of BYL719.

Changes to the protocol

- The study synopsis has been updated accordingly
- Section 1.4 has been added to provide an introduction and overview of fulvestrant.
- Section 2 (Study rationale/purpose) has been updated with the rationale for the introduction of a fulvestrant - BYL719 combination arm.
- Section 3 (Objectives) have been amended to include the combination into the study objectives.
- Section 4 (Study design) has been updated to include a dose escalation phase followed by a dose expansion phase in the combination arm and to clarify the investigation of the b.i.d. schedule of BYL719.
- Section 5 (Population)
  - Inclusion criteria 1 now includes the following sub-paragraph: Patients participating in the combination arm of BYL719 and fulvestrant must be post-menopausal women with estrogen receptor positive locally advanced or metastatic breast cancer whose tumors have an alteration of the *PIK3CA* gene and have had disease progression following anti-estrogen therapy, or whose disease has relapsed following adjuvant anti-estrogen therapy.
  - Inclusion criteria 6 now includes an additional sentence: Child Pugh classification of A
- Exclusion criteria 15 and 16 have been updated to reflect the latest Novartis contraception guidelines
- Section 4 and Section 6.1.2 (How applied) now include a paragraph describing the introduction of the modified formulation
- Section 6.1.2.1 (Study combination) now includes how fulvestrant is supplied and reference to the package insert.
- Section 6.2 (Treatment arms) includes sentence describing the combination arm.
- Section 6.6.1.4 (Starting dose for cycle 1) includes the starting dose of BYL719 and fulvestrant

- Section 6.6.1.7 (Dose-limiting toxicity) has been amended to which toxicities are applicable in the combination arm.
- Table 6-4 (Dose Modification Guidelines) has been modified to include the fulvestrant dose reduction guidelines for liver toxicity.
- Section 10 – the statistical model has been updated to incorporate the modified BYL719 formulation and the fulvestrant combination.
- Some of the sections pertaining to biomarkers have been modified to further reflect the changes introduced in protocol amendments 2 and 3.

Amendment 3

Amendment rationale

The rationale of the amendment is as follows:

The design of the expansion phase has been modified to further assess the safety and preliminary efficacy of BYL719 by enrolling at least 45 patients at the MTD (or RP2D). This arm will now contain approximately 22 patients with head and neck cancer or esophageal cancer carrying PIK3CA gene alterations, and the remaining patients will have other solid tumors with PIK3CA alterations. In preclinical experiments head and neck cancer cell lines were proved to be among the most sensitive to BYL719 treatment. BYL719 also showed pronounced activity against esophageal cancer cell lines, both in vitro and in vivo. [redacted]

The number of biomarkers originally planned to be evaluated have been reduced. The purpose of this amendment is to focus the biomarker analysis on key biomarker parameters. Results of preclinical and clinical investigations conducted with PI3K inhibitors indicate that measurement of downstream biomarkers such as pAKT or pS6 may provide valuable information about the inhibition of the PI3K pathway. Therefore it was decided to focus on the analysis of such biomarkers which according to current knowledge are most relevant to understand the pharmacodynamic effects of BYL719. The analysis of other biomarkers which may not bring significant value to understand the activity of BYL719 is no longer mandated.

The following biomarkers are no longer mandated:

- Cellular markers of proliferation or angiogenesis in tumor, such as Ki-67 and PARP
- All markers in skin, such as p-S6

Although the protocol already permits use of the b.i.d. schedule, this amendment clarifies that it may be instead of, or in parallel with, the once daily schedule. The decision whether to adopt it will be determined based on the safety and pharmacokinetic data available at the time, the starting dose will be established based on DLT data. Expansion part of the study will be conducted for one dose regimen only.

[redacted]

Changes to the protocol

- The synopsis has been amended accordingly
- Section 1.3.4 (Biomarker Development) has been reduced according to the biomarkers removed from the protocol
- Section 2 (Study Rationale/Purpose) has been modified to add rationale text for the enlarged expansion arm.
- Section 3 (Objectives) has been modified according to the biomarkers removed from the protocol or moved as part of exploratory endpoints.
- Section 4 (Study Design) has been modified to clarify how b.i.d. dosing may be adopted and to permit the MTD expansion arm to include 45 patients (22 patients with head and neck cancer or esophageal cancer, and 23 patients with other solid tumors).
- Section 6.2 (Treatment Arms) has been modified to clarify how b.i.d. dosing may be adopted.
- Section 6.6.1.1 (Study Drug Administration) has been modified to provide instruction of how BYL719 should be taken if the b.i.d. dosing is adopted.
- Section 6.6.1.6 (Criteria for dose escalation and determination of MTD) has been modified to add how the BLRM will be used to model a b.i.d. starting dose
- Section 7 (Schedule of Assessments) has been reduced according to the biomarkers removed from the protocol
- In Section 10, the statistical model has been updated in order to permit the evaluation of data generated from different dosing schedules, e.g. the currently used once daily (o.d.) schedule, and a twice daily (b.i.d.) schedule, which may potentially be used in the future.
- To ensure consistency, and make minor corrections, some text describing biomarker collection has been modified to further reflect the previous protocol amendment 2.
- Following new technical information, the single blood sample taken for genetic analysis (Section 7.10.2.2) has been changed from a volume of approximately 2mL to 5mL.

Amendment 2

Amendment rationale

The rationale of the amendment is as follows:

- The eligibility criteria have been amended to also include patients whose tumors have an amplification of the *PIK3CA* gene as the tumors of these patients may also be sensitive to BYL719.
- To update the guidelines for the treatment of study drug induced hyperglycemia in Post-text Supplement 3. The modification ensures more consistency with the Dose Limiting Toxicity criteria and clinical practice.
- To update the definition of hypertension as dose-limiting toxicity to clarify that an isolated abnormal blood pressure value does not constitute a DLT, but rather the extent of medical intervention (more than one drug or more intensive therapy than previously) should also be taken into account.

[redacted]

- To change the timepoints of the fresh tumor biopsies. The Cycle 1 Day 8 and Cycle 1 Day 28 samples are removed, and samples will now be taken at Cycle 2 Day 28 and at the time of tumor progression, matching the time of radiological tumor assessment. The fresh skin biopsies and non-fasting glucose metabolism samples will now be obtained according to the same schedule. We anticipate that understanding the molecular mechanisms of resistance to BYL719 will play a critical role in drug development and might offer new treatment modalities to patients.
- To amend the eligibility criteria pertaining to prior treatment. Prior treatment with PI3K, mTOR or AKT inhibitors may lead to resistance to the PI3K pathway signaling in such a way that potential BYL719 benefit may be changed. Therefore, enrolment of such patients requires approval by the Novartis Clinical Project Leader.
- To add a blood sample for germline DNA analysis in order to identify novel mechanisms of resistance to treatment with BYL719
- To remove biomarker assessments in blood of circulating angiogenic markers and markers of cellular death, circulating DNA, and circulating Tumor Cells. The effects of BYL719 on PI3K signaling can be adequately assessed using the tissue samples. To remove the FDG-PET scans from the protocol assessments. It is anticipated that the efficacy of BYL719 can be adequately assessed by conventional CT/MRI methods, and FGD-PET data will no longer add value to this assessment.
- To add that the pre-screening analysis for the *PIK3CA* mutation is now able to be performed at a Novartis approved laboratory.
- To update the pharmacokinetic sections to permit analysis of BYL719 metabolites should the need arise.

Changes to the protocol

- The study title and all relevant subsequent sections have been amended to include the enrollment of patients with PIK3CA amplification.
- Synopsis: The synopsis of the protocol has been updated
  - To exclude FDG-PET scans
  - To permit the pre-screening analysis of the *PIK3CA* mutation to be performed at a Novartis approved laboratory
  - To clarify that enrollment of patients with prior treatment with PI3K, mTOR, or AKT inhibitors requires approval from the Novartis Clinical Program Leader
  - To modify the exploratory biomarker objectives to include resistance mechanisms.
- Section 1.3.6 has been modified to reference the Investigators Brochure for clinical data.
- Section 3.3 Exploratory Objectives: FDG-PET scans have been removed and the biomarker objectives modified to include investigation of resistance mechanisms.
- Section 5 Population: Text has been changed to permit central pre-screening analysis for the *PIK3CA* mutation at a Novartis approved laboratory.
- Section 5.1 Inclusion Criteria: The criterion stating that patients must be eligible to have FDG-PET scans performed has been removed.

[redacted]

- Section 5.2 Exclusion Criteria: The criterion excluding prior treatment with PI3K inhibitors has been changed to state that early disease progression on prior treatment with PI3K, mTOR or AKT inhibitors may lead to resistance to the PI3K pathway signaling in such a way that potential BYL719 benefit may be changed. Therefore, enrolment of such patients requires approval by the Novartis Clinical Project Leader.
- Table 6-2 Criteria for dose limiting toxicities: A foot note has been added to clarify that hypertension will only be considered DLT if it requires more than one drug or more intensive therapy than previously.
- Table 7-1 Visit Evaluation Schedule: The schedule has been modified to move the fresh tumor biopsy, skin biopsy and non-fasting glucose metabolism samples to time of radiological tumor assessment at C2D28 and tumor progression. FDG-PET scans have also been removed. A blood sample for germline DNA analysis has been added. A footnote has been clarified to add that a fresh tumor biopsy need not be taken at screening/baseline if a fresh tumor biopsy was already taken for the pre-screening analysis, this sample can be sent instead.
- Section 7.1 Information collected on screening failures. The demographics of patients who fail screening are now collected on the CRF.
- Section 7.9.2 Analytical method: Text has been modified to state that, in addition to BYL719 analysis, exploratory BYL719 metabolite analysis on remaining plasma material may be performed.
- [redacted]
- Section 7.10 Biomarker. This section has been modified throughout to move the fresh tumor biopsy, skin biopsy and non-fasting glucose metabolism samples to time of radiological tumor assessment at C2D28 and tumor progression. Section 7.10.3.5 has been added to describe the additional blood sample for pharmacogenetic analysis.
- Post-text Supplement 3: The treatment modification guidelines for hyperglycemia have been modified.
- Post-text Supplement 4: Typographical errors have been corrected and operating characteristics added.

[redacted]

Amendment 1

Amendment rationale

- This amendment addresses the decrease of the starting dose from 60 mg/person/day to 30 mg/person/day based on feedback from a regulatory authority. This included:
  - Revision of the “starting dose level for cycle 1” section and provisional dose level Table 6-1 so that the 30 mg/day dose will be used as starting dose.

[redacted]

  - Revision of the "statistical hypothesis, model, and method of analysis" section to update the statistical model using a starting dose of 30 mg/person/day.
- The availability of archival tumor tissue for study enrollment is clarified in inclusion criterion 2 and in corresponding/referring text throughout the protocol. As for some patients archival tumor tissue is not available, the availability of a fresh tumor biopsy instead would also allow study enrollment.
- The preclinical dog safety data was updated based on feedback from a regulatory authority, for information to the patients to be treated in this study and possible study drug related effects expected.
- Study update: The study was not yet commenced in any participating country.

Changes to the protocol

- Section 6.6.1.4 has been amended as follows-
  - The starting dose has been reduced from 60 mg/day to 30 mg/day
  - The rational to use a starting dose of 60 mg/day has been removed and replaced by the rational to use a starting dose of 30 mg/day. The safety factor was modified to derive at the current starting dose of 30 mg/day. The expected exposure at the updated starting dose was corrected.
- Table 6-1 has been amended as follows –
  - Provisional dose level -1 was updated from 30 mg to 20 mg. The provisional dose level 30 mg/day was added as dose level 1 (i.e. starting dose) and dose level 60 mg/day was updated to dose level 2 and all following dose levels accordingly. The dose level increment from previous dose was updated accordingly.
  - As one dose level was added in the table of provisional dose levels, fresh tumor biopsies must, as consequence be collected in at least one patient per cohort from the **fourth** dose cohort and onwards, instead of from the third dose cohort. Changes were implemented throughout the protocol.
- Section 10 has been amended as follows –
  - The text under 'prior specification' in Section 10.4.2 has been updated for the reduced starting dose and its implications to the BLRM statistical model. In addition the following text was added for clarification *"The prior for the 'High toxicity' component assumes that the increase in probability of DLT as dose increases is high, and is derived as follows:*
    - *Median prior probabilities of DLT were set to be approximately 5% and 33% at dose 10mg/person/day and 100mg/person/day, respectively*
    - *For the remaining doses, the prior medians of probability of DLT were assumed linear in log-dose on the logit-scale*
    - *Based on the above medians for the probability of DLT at each dose and wide prior credible intervals, obtained from minimally informative Beta distributions, (Neuenschwander 2008), the optimal parameters of the individual bivariate normal distributions belonging to the "high toxicity" component were obtained."*

  The corresponding text in PTS 4 was also amended.

[redacted]

- [redacted]

- Section 5.1, text of inclusion criterion 2 has been amended to clarify that *"If archival tumor tissue is not available, a fresh tumor biopsy must be provided instead."* Changes to corresponding/referring text throughout the protocol were implemented.
- [redacted]

- Section 6.2, the following text was added for clarification *"The statistical model will be amended to include a covariate defining the new schedule at this time using all available PK information to define the potential relationship to the continuous daily schedule. The new total dose per 24h must not exceed the last dose that was determined to be safe using the daily dosing schedule and must satisfy the EWOC criteria under the amended statistical model."*
- Other minor changes/corrections in the protocol text were made for consistency and/or clarifications.
- The changes in this protocol amendment should be considered as substantial, in Member States of the European Union and European Economic Area (Directive 2001/20/EC).

[redacted]

Oncology clinical study protocol synopsis

Investigational drug	BYL719
Protocol no.	CBYL719X2101
Study phase	IA
Study title	A phase IA, multicenter, open-label dose escalation study of oral BYL719, in adult patients with advanced solid malignancies, whose tumors have an alteration of the *PIK3CA* gene
Background	NVP-BYL719 (BYL719), the investigational drug in this study, is an oral class I α-specific phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. BYL719 inhibits strongly the PI3Kα isoform and much less strongly the β, δ, and γ isoforms. The BYL719 biological activity correlates with inhibition of various PI3K/Akt downstream signaling pathway components. *In vitro*, BYL719 inhibits the proliferation of breast cancer cell lines harboring *PIK3CA* mutations ± ErbB2 amplifications (GI_{50}= 139 to 2331 nM). Luminal and HER2+ breast cancer cell lines are particularly sensitive to BYL719. Presence of PIK3CA mutation or amplification was associated with increased sensitivity to BYL719. However, 106 out of 339 PIK3CA wild type cell lines across various cancers were also sensitive to BYL719. *In vivo*, BYL719 shows statistically significant dose-dependent anti-tumor efficacy in *PIK3CA* mutant xenograft models in rodents. BYL719 was well tolerated in the repeated-dose toxicity studies (daily dosing of up to 4 weeks) at dosages at which tumor growth control was achieved. BYL719 affected rapidly dividing tissues which resulted in pharmacologically relevant observations (lymphoid tissue depletion and other bone marrow related toxicity except neutropenia, and GI toxicity) in the animals exposed to a BYL719 dose close to or at the maximal tolerated dose. 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 affected at higher doses in dogs. Changes in bone/cartilage and tooth-forming structures were observed in rats. Epithelial effects were seen in the cornea in dogs and mainly at the lower dose. Abnormal clinical chemistry (mainly insulin elevation) and histopathology (pancreatic islets) findings indicated an altered glucose metabolism. In both rats and dogs, histopathology and clinical pathology findings generally occurred at higher doses that were also associated with strong effects on body weight development (in the growing animals) and food uptake, but all were reversible or showed a tendency to reversibility after a 4-week treatment-free recovery period. BYL719 showed no effect on neuronal or pulmonary function. No evidence of a phototoxic potential was found in a 3T3 neutral red uptake test *in vitro*. BYL719 is not genotoxic *in vitro*. For the preliminary clinical experience of BYL719 please refer to the IB. Please refer to Section 1 for further details.

[redacted]

Purpose/rationale	This is a first-in-man trial, in which BYL719 will be administered to adult patients with advanced solid tumors, whose tumors have an alteration of the *PIK3CA* gene and whose disease has progressed despite standard therapy or for whom no standard therapy exists. The trial has been designed as a Phase IA dose-escalation trial with a MTD dose expansion arm. The single agent MTD dose expansion cohort and the fulvestrant combination MTD dose expansion cohort will also include ER+/HER2- breast cancer patients whose tumors have the wild type *PIK3CA* gene. The purpose of the trial is: (i) To determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) of BYL719; (ii) To assess the safety and tolerability of this dosage; (iii) To assess preliminary antitumor activity; (iv) To assess the pharmacokinetic profile (PK) of BYL719; and (v) To assess the pharmacodynamic (PD) effect, measured by the impact of the drug on various biomarkers. Once MTD (or RP2D) has been defined, an expansion arm will open at the MTD level to further characterize the safety, PK and PD profile of BYL719 at this dose (for details please see Section 2).
Objectives	**Primary** • To determine MTD (or RP2D) of oral BYL719 as single agent in adult patients with advanced solid malignancies whose tumors have an alteration of the *PIK3CA* gene, and in combination with fulvestrant in post-menopausal patients with estrogen receptor positive metastatic breast cancer whose tumors have an alteration of the *PIK3CA* gene **Secondary** • To assess the overall safety and tolerability of BYL719 treatment both as single agent and in combination with fulvestrant • To characterize the full pharmacokinetic profile of oral BYL719 after single (Cycle 1 Day1) and multiple administrations (Cycle 1 Day 8 and 28) both as single agent and in combination with fulvestrant • To assess the preliminary efficacy of oral BYL719 as single agent in patients with relapsing/refractory *PIK3CA* mutant solid malignancies and in combination with fulvestrant in ER+ breast cancer patients • To assess the preliminary anti-tumor activity of oral BYL719 as single agent and with fulvestrant in patients with locally advanced or metastatic *PIK3CA* wild type ER+/HER2- breast cancer **Exploratory** • To assess downstream effects of PI3K pathway inhibition • To assess markers that may correlate with prediction of response and/or resistance: altered molecular status (e.g. gene mutation, amplification, deletion and/or protein over-expression or activation) • To assess pre- and post-treatment changes in circulating tumor markers (as relevant for the respective cancer types), if applicable, as potential surrogate for indication of efficacy • To perform additional analysis on remaining material from samples collected during the study (blood, tumor) that could help in the understanding of BYL719 drug action and/or identify potential biomarkers that may correlate with efficacy and safety

[redacted]

Endpoints (efficacy, safety)	**Primary Endpoint**
	• Incidence rate of dose limiting toxicities (DLT) (in the first cycle (of 28 days) of each investigated dose level).
	Secondary Endpoints
	• Safety and tolerability: type, intensity, severity and seriousness of adverse events (AE) according to NCI CTCAE v. 4.0.
	• Pharmacokinetics of BYL719 as single agent or in combination with fulvestrant: plasma concentration-time profiles and derived basic PK parameters of BYL719, including but not limited to $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, CL/F, Vz/F and the terminal half-life (t1/2) and other PK parameters if deemed appropriate.
	• Objective tumor response rate (ORR), defined as the sum of complete response and partial response as best reported response by RECIST 1.0 criteria (Novartis v2.0 guideline)
	• Progression Free Survival (at MTD/RP2D only)
	Exploratory Endpoints
	• Inhibition of the PI3K pathway assessed by:
	  • Pre- and post-treatment changes in glucose metabolism (i.e. of fasting glucose, fasting c-peptide in blood)
	  • Levels of pS6 and pAkt in tumor tissue.
	• Pre- and post-treatment changes in circulating tumor markers (as relevant for the respective cancer types, if any) as a measure of tumor response
	• Additional analysis on remaining material from samples collected during the study (blood, tumor) that could help in the understanding of BYL719 drug action.
	• Whole exome sequencing, RNA and proteomic profiling of tumor tissue in order to detect changes in molecular (e.g. acquired mutations), RNA and proteomic (e.g. upregulation of tyrosine kinase) profiles from patients at baseline, on treatment and at tumor progression. If potential tumor-specific findings are detected, these might warrant a comparison with non-tumorous normal tissue (blood sample). [redacted]
	New biomarkers will be integrated if developed during this trial and considered appropriate for judgment of efficacy and safety.

Study design	This is a multi-centre, open-label phase IA dose-escalation study with dose escalation arms for q.d. or b.i.d. administration. Oral BYL719 will be administered daily on a continuous schedule. Provisional dose levels are given in Table 6-1. **Once daily single agent BYL719** At first, dose escalation will be conducted investigating a once daily (q.d.) administration of BYL719. In the initial stage of the dose escalation arm, at least one patient will be enrolled to each cohort to evaluate the next dose level. If this one patient has not experienced a clinically relevant ≥ CTCAE grade 2 toxicity, then one patient will be considered sufficient for decision making on the next dose level. However, in case this one patient does experience a clinically relevant ≥ CTCAE grade 2 toxicity, then an additional patient must be enrolled at that dose-level. All evaluable patients in the initial dose cohort have to be

[redacted]

	assessed for decision making on dose escalation. Once the 2nd patient experiences clinically relevant CTCAE grade 2 toxicity or the first clinically relevant CTCAE ≥ grade 3 toxicity has occurred in the study, the minimum cohort size will be 3 patients for that cohort and all further cohorts. Similarly, for all dose levels for which anti-tumor efficacy has been observed in the animal setting (assumed lowest dose at which an impact on the tumor growth has been observed) at an equivalent dose (considered to be 120mg/d and onwards), at least 3 patients will be enrolled per dose level. In addition paired pre- and post-treatment fresh tumor samples should be collected for all patients unless not feasible and/or accessible according to the investigator's judgment, while it will be mandatory in at least 1 patient per cohort from the fourth cohort onwards. In the expansion arm, fresh pre- and post-treatment biopsies will be collected for all patients, unless not feasible and/or accessible according to the investigator's judgment. A minimum of 8 analyzable matched pairs must be obtained in the expansion. Cohorts may be expanded at any dose level below MTD (or RP2D) for further investigation of safety, pharmacokinetic and/or pharmacodynamic parameters as required. As such, additional eligible patients from who the investigator considers it feasible to obtain paired fresh tumor biopsies, can be enrolled at any time during dose escalation in the cohort explored at that point in time. An adaptive Bayesian logistic regression model (BLRM) for dose escalation with overdose control (EWOC), will guide the dose escalation arm to determine the MTD. Before a drug dosage can be declared to be the MTD, at least 21 evaluable patients should have been treated. with at least six evaluable patients treated at the MTD. Once MTD has been declared, for the purpose of evaluating safety with sufficient accuracy, the MTD (or RP2D) cohort will be expanded to at least 65 patients (for example, if 6 patients are enrolled to establish the MTD (or RP2D), an additional approximately 60 patients will be added – see Section 10.7.2 for justification). Approximately 20 of these patients will have head and neck, or esophageal, cancer carrying an alteration (mutation or amplification) of *PIK3CA*. Approximately 20 patients will be *PIK3CA* wild type locally advanced or metastatic ER+/HER2- breast cancer patients, and the remaining patients will have other solid tumors carrying a molecular alteration of *PIK3CA* (including, for example, metastatic breast, ovarian, colorectal, or gastric cancer). (for further details please see Section 4 and Section 5). **Twice daily single agent BYL719** Once the MTD of BYL719 using a q.d. schedule is determined, a b.i.d. dosing schedule will be investigated in parallel by the addition of a new arm. Before the b.i.d. MTD can be declared at least 12 patients must be treated in rhe b.i.d. dose escalation, with at least 6 patients treated at the MTD. It is possible that two MTDs (q.d. and b.i.d.) will be established. Once the MTD is determined for the b.i.d. schedule, a safety expansion arm may be opened. PK and safety data will be analyzed to determine whether any of the expansion arms may be discontinued. **BYL719 and fulvestrant combination** A combination of BYL719 with fulvestrant will be investigated in post-menopausal patients with locally advanced or metastatic ER+ breast cancer whose tumors have an alteration of the PIK3CA gene. Before the MTD can be declared at least 12 patients must be treated in the combination dose escalation, with at least 6 evaluable patients treated at the MTD. When the MTD (or RP2D) has been established after dose escalation, a dose expansion

[redacted]

	cohort will enroll approximately 20 patients with ER+/HER2- breast cancer whose tumors have an alteration of the PIK3CA gene, and 20 patients with ER+/HER2- breast cancer whose tumors are PIK3CA wild type. The dose escalation phase will begin using BYL719 with the q.d. schedule. A b.i.d. schedule may be opened for the combination, if suggested by PK and safety data of BYL719 as single agent. The expansion of the combination will be carried out with only one of the q.d. or b.i.d. regimens, a decision which will be taken prior to initiating the expansion. **Modified Formulation** As of Protocol Amendment 4, a modified formulation of BYL719 has been developed[redacted](See Section 6.1.2) No formal comparison between both formulations will be conducted, but a minimum of 6 patients will be enrolled in the q.d. expansion cohort using the modified formulation and followed for one cycle. If the observed PK is comparable and the overdose control criteria are met then the study will continue with the modified formulation. Otherwise dose adjustments (escalation or de-escalation) may be made in accordance with the recommendations of the BLRM until a dose level fulfilling the overdose control criteria and/or achieving comparable PK is reached. If the study continues with the modified formulation any patient receiving the previous formulation may switch over to the modified formulation after they have completed at least one cycle.
Population	This study will be conducted in adult patients with advanced solid tumors, whose tumors have an alteration (mutation or amplification) of the *PIK3CA* gene and whose disease has progressed despite standard therapy or for whom no standard therapy exists. An additional set of *PIK3CA* wild type locally advanced or metastatic ER+/HER2- breast cancer patients will be treated in the single agent MTD dose expansion cohort. The combination of BYL719 and fulvestrant will be investigated in patients eligible for fulvestrant treatment (post-menopausalER+ locally advanced or metastatic breast cancer) whose tumors have an alteration of the PIK3CA gene. Prior to the formal screening period for this protocol, potential eligible patients will be asked to sign a “Pre-screening Informed Consent”. This will allow the use of already available mutational status information or to allow determination of the molecular status (mutation or amplification) of the tumor. This can be done while the patient is still on standard treatment or whenever possible. This will ensure that the molecular status of the tumor is known when the patient may be screened for enrollment into the study. Only once the status of the *PIK3CA* gene of the patient’s tumor is determined/identified the patient may sign the study’s main Informed Consent (IC) and begin the screening/baseline visit. If the sites are unable to establish the *PIK3CA* gene status, the sample can be sent to a Novartis approved laboratory (for further details please see Section 5).
Inclusion/exclusion criteria	**Inclusion** (see also Section 5.1) • Patients with histologically-confirmed, advanced unresectable solid tumors who have progressed (documented as per RECIST 1.0 criteria (Novartis v2.0) on the last line of therapy before entering this trial) within three months before screening/baseline visit on (or not been able to tolerate) standard therapy or for whom no standard anticancer therapy exists • The single agent expansion arm will enroll the following:

[redacted]

	• Approximately 22 patients with either head and neck cancer, or esophageal cancer carrying a molecular alteration (mutation or amplification) of the *PIK3CA* gene. • Approximately 20 *PIK3CA* wild type ER+/HER2- locally advanced or metastatic breast cancer patients. • Patients with other solid tumors carrying a *PIK3CA* alteration. • Patients participating in the combination arm of BYL719 and fulvestrant must be eligible for treatment with fulvestrant with estrogen receptor positive, HER2 negative, locally advanced or metastatic breast cancer and have had disease progression during or following anti-estrogen therapy, or whose disease has relapsed following adjuvant anti-estrogen therapy. Patients with ER+ HER2- breast cancer, either with a PIK3CA alteration or PIK3CA wild type, may enter this combination expansion cohort. • Availability of a representative formalin fixed paraffin embedded tumor tissue sample. Archival tissue and documented PIK3CA status will be mandatory for study enrollment. If archival tumor tissue is not available, a fresh tumor biopsy must be provided instead. Fresh (paired) tumor biopsies must be collected whenever feasible and accessible according to the investigator's judgment. • At least one measurable or non-measurable (as per RECIST 1.0 criteria) lesion • Age ≥ 18 years • World Health Organization (WHO) Performance Status ≤ 2 • Good organ (hepatic, kidney, BM) function at screening/baseline visit as defined by: • Serum total Bilirubin ≤ 1.5 x ULN and AST/SGOT and ALT/SGPT ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases are present • Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 ml/min • Platelets ≥ 100 x 10^9/L, Hemoglobin (Hgb) ≥ 9 g/dL (which may be reached with transfusion), Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L • Calcium within normal limits • Potassium within normal limits • Magnesium ≥ the lower limit of normal • Fasting glucose < 140 mg/dL / 7.8 mmol/L • Negative serum pregnancy test within 72 hours before starting study treatment in all pre-menopausal women (except those who have undergone hysterectomy, sterilization, irreversible castration) and women < 12 months after onset of menopause. • Able to sign informed consent and to comply with protocol requirements. **Exclusion** (see also Section 5.2) • Brain metastasis unless treated and free of signs/symptoms attributable to brain metastasis in the absence of corticosteroid therapy (anti-epileptic therapy is allowed). Brain scan is mandatory in case of clinical evidence of brain metastatic disease. • Prior treatment with PI3K, AKT or mTOR inhibitor at clinically relevant doses and failure to benefit. Enrolment of patients previously treated with

[redacted]

	such agents requires approval by the Novartis Clinical Project Leader • Patient with peripheral neuropathy NCI-CTC Grade ≥ 3. • Patient with diarrhea NCI-CTC Grade ≥ 2. • Patient with acute or chronic pancreatitis • Any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study: 1. Impaired cardiac function or clinically significant cardiac disease, including any of the following: • Clinical significant heart disease such as CHF requiring treatment (NYH grade ≥ 2), LVEF < 45% as determined by MUGA scan or ECHO, or uncontrolled hypertension (please refer to WHO-ISH guidelines) • ST depression or elevation of ≥ 1.5 mm in 2 or more leads • QTcF > 480 msec on screening ECG • Congenital long QT syndrome • History or presence of clinically significant ventricular arrhythmias or atrial fibrillation • Clinically significant resting bradycardia (< 50 beats / min) • Complete left bundle branch block (LBBB) • Right bundle branch block (RBBB) + left anterior hemiblock (LAHB - bifascicular block) • Unstable angina pectoris ≤ 3 months prior to starting study drug • Acute Myocardial Infarction (AMI) ≤ 3 months prior to starting study drug 2. Patients with clinically manifest diabetes mellitus (treated and/or clinical signs or with fasting glucose ≥ 140 mg/dL / 7.8 mmol/L), history of gestational diabetes mellitus or documented steroid-induced diabetes mellitus. 3. Patients in the combination arm: hepatic impaitrment of Child-Pugh status of B or C 4. Patients in the combination arm: bleeding disorders interfering with I.M. administration 5. Other concurrent severe and/or uncontrolled concomitant medical condition (e.g. active or uncontrolled infection incl. known diagnosis of HIV) that could cause unacceptable risks or compromise compliance with the protocol guidelines. • Patients who are currently receiving treatment with medication that has the potential to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug. • Patients in the combination arm: known hypersensitivity to fulvestrant or to any components of the drug product. • Patients who are currently receiving treatment with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants. • Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BYL719 (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption

[redacted]

	syndrome, or small bowel resection), or patients unable to take oral medication.
	• Patients treated with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin is allowed for as long as it has been initiated at least 2 week prior to study enrollment.
	• Patient who have received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
	• Patients who have received chemotherapy, targeted therapy, endocrine therapy or immunotherapy ≤ 4 weeks (6 weeks for nitrosourea and mitomycin-C) prior to starting study drug or have not recovered from side effects of such therapy.
	• Patients who have received radiotherapy ≤ 4 weeks prior to starting study drug, who have not recovered from side effects of such therapy and/or from whom ≥ 30% of the bone marrow was irradiated.
	• Patients who have undergone major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery
	• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are not allowed to participate in this study UNLESS they are using highly effective methods of contraception during dosing and for 5 weeks after study drugs discontinuation. Highly effective contraception methods include:
	  • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
	  • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least five weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
	  • Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
	  • Combination of the following (a+b):
	  a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
	  b. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
	Oral contraceptives (OC), injected or implanted hormonal methods are not allowed as the sole method of contraception, as BYL719 has not been characterized with respect to its potential to interfere with the PK and/or the effectiveness of OCs.
	Post menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six

[redacted]

	months of spontaneous amenorrhea with serum Follicle-Stimulating Hormone (FSH) levels > 40 mIU/mL [**for US only:** and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. • Sexually active males must use a condom during intercourse while taking the drugs and for 5 weeks after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. • History of another malignancy within 2 years, except cured basal cell carcinoma of the skin or excised carcinoma *in situ* of the cervix.
Patient numbering	Each patient in the study will be uniquely identified by a 9-digit number which is a combination of his/her 4-digit center number and a 5-digit subject number (for further details please see Section 6.3)
Investigational and control drugs	Study Drug: BYL719 (for the single agent part) Study Treatment: BYL719 combined with fulvestrant (for the combination part)
Dose, regimen, treatment cycle	The proposed starting dose of 30 mg/day is based on preclinical data and is deemed safe. BYL719 will be given orally, daily until disease progression or unacceptable toxicity, or until investigator's decision or patient refusal. For the purposes of scheduling and evaluations, a treatment cycle is defined as 28 days. Please see Section 6.6.1.7 for criteria for defining DLTs. Please refer to Section 6.6.2.1 for criteria for interruption and re-initiation of BYL719 treatment. Intra-patient dose escalation is not permitted at any time within the first 4 cycles of treatment. The provisional starting dose of the BYL719 in combination with fulvestrant is 300mg q.d. Fulvestrant is given by intra-muscular injection administered at 500mg/month, with one additional 500mg administration after 2 weeks of the first dose (Section 6.6.1.4)
Supply, preparation, and administration	BYL719 is supplied to the investigational sites as 10 mg, 50 mg and 200 mg tablets (other strengths may be made available). BYL719 will be dosed on a flat scale of mg/day and not adjusted to body weight or body surface area. BYL719 will be taken on a continuous daily dosing schedule. BYL719 tablets should be taken as specified in Section 6.1 and Section 6.6.1.1. Commercially available fulvestrant will be supplied according to the local regulations.
Visit schedule and assessments	Please refer to Table 7-1.
Efficacy assessment(s)	Measurement of changes in tumor size by CT or MRI using RECIST criteria. For details please see Section 7.4. Tumor markers (PSA, CEA, CA19-9, soluble mesothelin peptides, etc.) will be assessed as relevant for the respective cancer type, if any.

[redacted]

Special safety assessment(s)	**Biochemistry:** • Glucose monitoring: fasting plasma glucose, fasting insulin and fasting c-peptide, hemoglobin A1c & fructosamine • Lipids: total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides • Amylase, lipase, AST, ALT, alkaline phosphatase, bicarbonate, total bilirubin, urea or BUN, creatinine, sodium, potassium, phosphorus, magnesium, calcium, total protein, albumin, LDH, CRP and basal cortisol • TSH, free T3 and free T4 • Testosterone (for male pts only), FSH and LH (for female pts only) • CTX -1 to assess bone turnover **Hematology:** • Complete blood count consisting of red blood cells (RBCs), a total white blood cell count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, basophil counts and others), hemoglobin (Hgb), hematocrite (Hct), MCH, MCHC, MCV, reticulocyte and platelet counts. **Cardiovascular system:** • 12-lead ECG • Monitoring of blood pressure • Cardiac imaging (MUGA scan or echocardiogram). For further details please see Section 7.5.
Patient reported outcomes	Not applicable
Pharmacokinetics	Pharmacokinetic blood samples will be collected from all patients enrolled in the study by either direct venipuncture or an indwelling cannula inserted in a forearm vein (3ml of blood for BYL719 determination in plasma) according to the following schedules: 24-h profile: Sampling will be performed on Day 1 and Day 8 of Cycle 1 and Day 1 of Cycle 2 at pre-dose and at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 24h (at pre-dose of the following dosing) post-dose (daily dosing schedule). Trough level: Sampling will be performed at pre-dose on Day 1 of every cycle starting at Cycle 3. For further details please see Section 7.9.

[redacted]

Biomarker assessments	**Laboratory biomarkers:** Tumor: Mandatory tumor specimens and/or pre-treatment and post-treatment fresh biopsies where feasible and accessible (mandatory fresh tumor biopsies, see Section 4 and Section 7.10 for further details). • Markers for pre-screening: *PIK3CA* mutation or amplification • Markers of pathway inhibition: e.g. p-S6, p-Akt, p-4EBP1 • Markers that may correlate with prediction of response and/or resistance: altered molecular status (e.g. gene mutation, amplification, deletion and/or protein over-expression or activation) of markers relevant to PI3K signaling, other pathways that may interact with the *PI3K* pathway, or are thought to be important in cancer (e.g. *PIK3CA*, PTEN, KRas, BRaf) **Blood:** • Markers of pathway inhibition: e.g. glucose metabolism markers (i.e. fasting glucose, fasting c-peptide) For further details please see Section 7.10.
Exploratory Biomarker studies	To allow exploratory investigation for the molecular mechanisms of skin rash [redacted] See Table 7-6 for scheduling details. Patients who have discontinued from this study may also be asked for consent to provide a blood sample for these analyses. Any remaining material after the above specified analyses of blood, and tumor biopsy samples may, upon the patient's consent be used for additional studies that would extend the search for other potential relevant biomarkers for BYL719 effect, disease and/or safety of the patient and they would be decided upon clinical outcome, reagent and sample availability. For further details please see Section 7.10.2.2.
DSMB	Not applicable

[redacted]

Statistical methods and data analysis	An adaptive Bayesian logistic regression model guided by the escalation with overdose control (EWOC) principle will be used. All information currently available about the dose-toxicity curve of BYL719 is summarized in a prior distribution. For this study, this includes pre-clinical data including the starting dose and the predicted MTD of BYL719. This prior distribution is then updated after each cohort of patients with the DLT data from the current trial. Once updated, the distribution summarizes the probability that each dose combination (as single agent or in combination for a given schedule) falls into the following categories: 1. Under dosing: DLT rate under 16% 2. Target toxicity: DLT rate between 16% and 33% 3. Excessive toxicity: DLT rate between 33% and 100% The overdose control mandates that any dose of BYL719 as single agent or in combination with fulvestrant that has more than a 25% chance of being in the excessive toxicity categories is not considered for dosing. All patients will be treated until disease progression or unacceptable toxicity. In general, a minimum of 3 patients will be enrolled onto each dose cohort and evaluated for decision making on dose selection for the next cohort. However, until a 2nd patient experiences a toxicity of CTC grade 2 or the first occurrence of a CTC toxicity ≥ grade 3 in the trial, data from one evaluable patient may be considered sufficient for decision making. At least 21 evaluable patients in the dose-determining set should be enrolled in the dose-escalation part of the study. Before a drug dosage can be declared to be the MTD, at least 12 patients have to be treated with a given treatment regimen (i.e. b.i.d, combination), including at least 6 evaluable patients will have to be treated at this dose level for one treatment cycle. The MTD cohort in solid malignancies, will be expanded by enrolling additional patients to a total of at least 65 patients including approximately 20 patients with head and neck, or esophageal, cancer, approximately 20 patients with PIK3CA wild type ER+ breast cancer and the remaining with other solid tumors and including at least 8 patients with paired fresh biopsies (pre- and post treatment) to be evaluated for safety, tolerability, preliminary efficacy, pharmacokinetics, and biologic activity of BYL719. The RP2D or MTD of BYL719 in combination with fulvestrant will be expanded by enrolling additional patients to a total of at least 20 patients whose breast cancer is ER+/HER2- PIK3CA altered and eligible for the safety set (including those treated at the RP2D or MTD in the dose-escalation arm of the study who are eligible for the safety set). Additionally, 20 patients whose breast cancer is ER+/HER2- and PIK3CA wild type and eligible for the safety set will be enrolled into the combination expansion cohort. With a sample size of 40 there is a 99% probability of detecting an AE with a true incidence rate of 10% (see Table 10-7). For detailed information, please see Section 10.

[redacted]

1 Background

PI3Ks are lipid kinases that are important in controlling signaling pathways involved in cell proliferation, motility, cell death and cell invasion (Cantley 2002, Katso 2001, Markman 2009).

The PI3K lipid kinase family comprises eight enzymes divided into three classes (I, II, and III) based on sequence homology comparisons. Two subclasses of Class I PI3Ks have been described. Class IA enzymes are composed of catalytic subunits whose enzymatic activities are completely dependent on their binding to regulatory subunits. Human cells contain three genes (*PIK3CA*, *PIK3CB* and *PIK3CD*) that encode the catalytic subunits of class IA PI3K enzymes, termed PI3Kα, PI3Kβ and PI3Kδ. The major polypeptides produced by these three genes are p110α, p110β and p110δ. P110α and p110β are expressed in most tissues, whereas p110δ is expressed primarily in leukocytes and in a small number of other cell types. The regulatory subunits of class IA enzymes are collectively referred to as p85. The p110 subunits of class IA PI3Ks have five domains: an N-terminal domain called p85BD that binds to the regulatory p85 family members, a Ras binding domain (RBD), a C2 domain that has been proposed to bind to cellular membranes, a helical domain of unknown function and a kinase catalytic domain.

The class IB PI3K consists of only one enzyme, PI3Kγ. It does not contain the same N-terminal p85-binding motif and does not need to interact with the regulatory subunit in order to be enzymatically active. Instead it appears to be activated by G- protein-coupled receptors and regulated by hetero-trimeric G proteins. The catalytic subunit of PI3Kγ, p110γ, is encoded by *PIK3CG* and is expressed in leukocytes and in a small number of other tissues.

While both p110α and p110β appear to play specific roles in insulin signaling, studies suggest that glucose homeostatis is predominantly mediated by p110α. Inhibitors of p110α, but not p110β or p110δ, have been shown to inhibit insulin-stimulated glucose uptake in adipocytes and to block insulin-mediated glucose regulation in mice (Knight 2006). In addition, recent data suggest that p110α might be the predominant catalytic isoform in vasculogenesis and that specific p110α inhibitors might block angiogenesis (Graupera 2008).

The p110δ isoform plays a major role in the B cell receptor signaling (Randis 2008), the transplanted lymphoma rejection and on NK cells, not in the cell-kill activities (Saudemont 2007) but in the extravasation towards the tumor cells (Saudemont 2009). The p110γ isoform is a key player in leukocyte chemotaxis (Randis 2008). This overall suggests the p110δ and p110γ isoforms to be key modulators of the innate and adaptive immune response (Ghigo 2008).

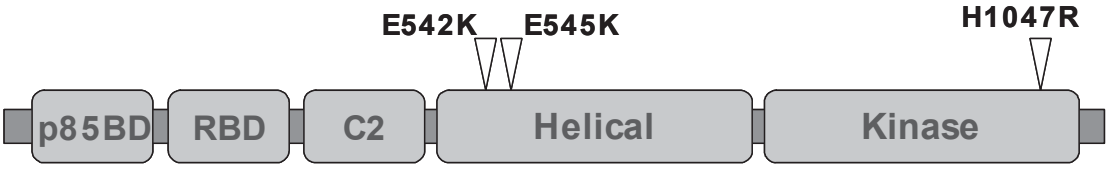
1.1 PI3K Alpha signaling in malignant cells

The dysregulation of the PI3K signaling pathway is implicated in many human cancers (Samuels 2004, Hennessy 2005, Markman 2009, 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 2009).

[redacted]

In addition, *PIK3CA* has received a great deal of attention since the discovery that somatic missense mutations occur at high frequency in this gene in many human cancer types (Samuels 2004, Markman 2009). Sequencing of the entire gene revealed that *PIK3CA* is somatically mutated in a number of cancers as specified in Section 1.2. From these mutation frequencies, *PIK3CA* is one of the most commonly mutated genes identified in human cancers. These mutations are clustered in hot spots within the helical (exon 9) and kinase (exon 20) domains of p110α. Among these hot spot mutations, the three most common tumor-derived alleles of p110α are E542K, E545K (exon 9) and H1047R (exon 20), which represents about 80% of the mutations observed, suggesting that they confer a selective advantage to the cell carrying the mutation.

Figure 1-1 Schematic representation of the major hotspot mutations of PIK3CA



In addition to the hot-spot mutations, numerous rare cancer specific mutations are widely distributed over the coding sequence of p110α (Bader 2005, Samuels 2004). Fifteen of these have been studied, and all except one show a gain of function. Recently, it has been found that the expression of the kinase domain mutant H1047R of p110α in mouse lungs induced adenocarcinomas *in vivo* (Engelman 2008). Mapping the hot-spot mutations and rare cancer-specific mutations of the modeled structure of p110α suggests at least three different molecular mechanisms for the gain of function. First, mutations in the C2 domain are located on the surface patch that interacts with the plasma membrane. The mutations substitute acidic residues with basic residues. This change of p110α surface properties is likely to enhance the affinity of the protein for lipid membrane. Moreover the C2 domain mutations would bring p110α into the immediate proximity of its substrate and thus enhance PI3K activity. Second, mutations in the helical domain are also located on the protein surface and delineate an area that could mediate interactions with other proteins or other domains of p110α. Third, the mutations in the kinase domain pack closely against the hinge region of the activation loop. They could affect the position of the activation loop by locking the loop in the "on" position (Gymnopoulos 2007). More recently, it has been demonstrated that the kinase mutant H1047R depends on p85 binding whereas the E545K and E542K mutants depend on RAS binding (Zhao 2008).

PIK3CA, cancer-specific mutations have not been reported in genes encoding the other class I PI3Ks.

1.2 Overview of chosen cancer indications

A high frequency of "hot spot" mutations have been observed in a number of solid tumors with different incidence rates: 32% of colorectal cancers (Samuels 2004, Markman 2009), 27% of glioblastomas (Samuels 2004, Hartmann 2005, Markman 2009), 25% of gastric cancers (Samuels 2004; Li 2005), 36% of hepatocellular carcinomas (Lee 2005, Markman

[redacted]

2009), 18-40% of breast cancers (Bachman 2004; Campbell 2004; Levine 2005; Wu 2005, Markman 2009), 4-12% of ovarian cancers (Levine 2005; Wang 2005), and 4% of lung cancers (Samuels 2004, Liu 2006; Isakoff 2005; Ikenoue 2005, Fry 2001, Bachman 2004, Lerma 2008, She 2008, Markman 2009), and endometrial cancer (Oda 2005, Salvesen 2009, Engelsen 2009). This trial will focus on head and neck cancer, esophageal cancer, breast cancer, lung cancer, colorectal cancer and endometrium cancer although other indications will be not excluded from this trial.

It is also expected that using PI3K inhibitors in combination with other therapies (like trastuzumab) can improve the efficacy (De Pradip 2010, Markman 2009) and reverse the resistance to existing anti-HER2 therapies (Eichhorn 2008, Serra 2008).

1.3 Overview of BYL719

NVP-BYL719 (BYL719) is an oral class I α-specific phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. BYL719 inhibits strongly the PI3Kα isoform and much less strongly the β, δ and γ isoforms.

[redacted]

The BYL719 biological activity correlates with inhibition of various PI3K/Akt downstream signaling pathway components. *In vitro*, BYL719 inhibits the proliferation of breast cancer cell lines harboring *PIK3CA* mutations ± ErbB2 amplifications (GI_{50}= 139 to 2331 nM). Profiling of BYL719 in a large panel of cancer cell lines (Cancer Cell Line Encyclopedia, CCLE) showed that cell lines responsive to BYL719 are enriched for luminal and HER2+ breast cancer (luminal breast cancer cell lines are representative for ER+ breast cancer). Furthermore, the presence of a PIK3CA mutation is associated with increased sensitivity to BYL719 across many cancer types, while PTEN mutations are associated with lack of sensitivity. On the other hand, 106 out of 339 cell lines of various cancers characterized as wild type for PIK3CA were also sensitive to BYL719 (Huang 2012). This could be related to other molecular features activating the PI3K pathway.

BYL719 *in vivo* translated into a dose-dependent and statistically significant antitumor activity in Rat1-myr-p110α tumor-bearing nude mice while treated with an orally once daily dose (doses of 12.5, 25 or 50 mg/kg). Similar observations were made for the BT474 orthotopic xenografts tumor-bearing nude mice and the NCI-H596 tumor-bearing nude mice. The absence of body weight changes in those animals indicated that BYL719 was well tolerated in all dose groups. The antitumor activity of BYL719 was also explored in the Rat1-myr-p110alpha tumor bearing nude rats. BYL719 was administered at doses of 6.25, 12.5, or 25 mg/kg daily p.o. The growth of the primary tumor was significantly inhibited by treatment with 6.25 mg/kg/day (T/C 22%), 12.5 mg/kg/day (T/C 5%), or 25 mg/kg/day (Regression: 35%). Treatment was well tolerated. Similar observations were also made in the NCI-H596 xenograft disease model in nude rat. The growth of the primary tumor was significantly

[redacted]

inhibited by treatment of BYL719 with 20 mg/kg/day (T/C 25%) or 40 mg/kg/day (Regression: 45%). Treatment was also well tolerated at all tested doses.

Most of the current oncology drug discovery and development work has shifted towards molecularly targeted therapies. A key focus has been on identifying inhibitors against components of pathways that drive tumor cell proliferation, survival, and metastasis such as the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway. PI3Ks are lipid kinases that are important in controlling signaling pathways involved in cell proliferation, motility, cell death and cell invasion.

1.3.1 Non-clinical pharmacokinetics and metabolism

BYL719 had a low plasma CL, a moderate Vss and a good absolute oral bioavailability in all preclinical species tested (Wistar rats, Beagle dogs, mice). The compound is moderately bound to plasma proteins and its protein binding is independent of the concentration. BYL719 showed a rapid distribution to almost all rat tissues, except the brain. BYL719 was found to be preferentially present in melanin containing tissues (such as the choroid and ciliary body of the eye) and declined with time. The highest BYL719 exposures were found in the liver, bile, harderian gland, hair follicles, tactile hair and in the preputial gland.

[redacted]

Results from 4-week GLP BYL719 toxicology studies in dog showed a roughly dose-proportional increase in exposure. The rat exposure (in the GLP toxicology studies) increased until 30 mg/kg beyond which no further increase in exposure was noted following single dose administration. Different studies provided however evidence of higher exposure up to a dose of 50 mg/kg. The toxicology studies provided no clear evidence of increase in exposure following multiple dosing. No gender differences in exposure were observed in rat or dog.

The overall biotransformation of BYL719 in hepatocytes was low in all species tested (i.e. low in the rat, lower in dog and lowest in human hepatocytes). [redacted]

1.3.2 Safety pharmacology and toxicology

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. BYL719 affected rapidly dividing tissues which resulted only in pharmacological relevant observation in the animals exposed to a BYL719 dose close to or at maximal tolerated dose (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

[redacted]

prostate in dogs were also affected at this higher dose. 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 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 as was also seen in the mouse insulin/glucose challenge test. In both rats and dogs, histopathology and clinical pathology findings were generally observed at higher doses which were also associated with strong effects on body weight development (in the growing animals) and food uptake and inhibiting impact on the tumor growth. 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 a electrophysiological risk. [redacted]

BYL719 in the rat safety pharmacology studies showed no effect on neuronal or pulmonary function. No evidence of a phototoxic potential was found in a 3T3 neutral red uptake test *in vitro*.

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

[redacted]

[redacted]

[redacted]

1.3.4 Biomarker development

Multiple potential biomarkers relevant to PI3K signaling modulation have been incorporated into this study to assess the effect of BYL719 at the molecular level and on clinical outcome, and also to potentially help in determining the optimal biological dose.

Table 1-1 Overview of laboratory biomarkers

Biomarker categories	Tumor	Whole blood, serum or plasma
Markers for pre-screening	*PIK3CA* gene status	
Markers to measure pharmacodynamic effects of BYL719	p-S6, p-4EBP1, pAkt	Glucose metabolism (glucose, c-peptide)
Predictive markers to identify responders	PTEN alteration, KRas, BRaf mutations	

1.3.4.1 Pharmacodynamic biomarkers

Pharmacodynamic (PD) markers that reflect target inhibition by BYL719 may aid in dose selection, optimization of therapy, and comparison with other Novartis PI3K inhibitors.

Markers assessed in fresh tumor tissue will be the most important assessment of target inhibition by BYL719.

While the phosphorylation status of Akt/PKB is the most accurate readout for PI3K activity, the phosphorylation of these epitopes is labile. Therefore signaling molecules with a lower tissue processing variability such as p-S6 and p-4EBP1 are considered as potentially relevant PD markers in addition to analysis of p-Akt.

[redacted]

Additional PI3K pathway modulators may be monitored (depending on sample and assay availability) to understand further the drug mechanistic effects: e.g. p-PDK1, FOXO-1/3A, p-GSK-3β, p-mTOR, p-STAT3, p27, cyclin D1 and p-ERK/MEK. This information could potentially aid the comparison of the effects of Novartis PI3K inhibitors for further selection.

PI3K signaling inhibition will be assessed by immunohistochemistry on fresh tumor tissue, preserved in formalin, obtained post-treatment (within 4 to 6 hours of dosing). Phosphorylation status of markers such as S6 (Ser240/244) and Akt will be compared with baseline values obtained in (fresh) tumor samples collected pre-treatment (at screening/baseline).

Previous experience with PI3K inhibitors has shown the glucose metabolism pathway to be a targeted event in several compartments. We therefore will monitor the pre- and post-treatment changes in fasting c-peptide and fasting glucose as potential PD biomarkers for BYL719 activity.

1.3.4.2 Biomarkers to assess anti-tumor effects at molecular and cellular levels

Cellular and tumor effects:

Indication-specific tumor markers such as PSA, CA-125, c-Met, sHER2 (as relevant for the cancer, if any) will be measured as part of the standard of care as per discretion of the investigator.

1.3.4.3 Biomarkers potentially predictive of tumor response

Out of the 16 members of the PI3K family, *PIK3CA* was the only one shown to harbor somatic mutations. Preclinical data suggest that tumor with a mutation and/or amplification in the *PIK3CA* gene will be sensitive to treatment with BYL719. PTEN mutation-PTEN inhibition of the PI3K pathways is thought to depend primarily of the beta subunit. It is therefore likely that patients with a loss of PTEN will not benefit from BYL719 to the same extent as patients with wild type PTEN. We therefore may analyze the PTEN status in patients.

Other mutations commonly associated with PI3K pathway (KRAS, BRAF) may also be investigated as potential predictive markers of response.

During the study, alterations of status (e.g. mutations, amplifications, protein expression/activation etc.) of molecules relevant to PI3K pathway activity - such as PTEN, KRAS, BRAF, other pathways that may interact with the PI3K pathway, or pathways that are thought to be important in cancer - may be investigated, in archival (and/or fresh) pre-treatment tumor samples in patients with paired tumor samples, in the context of responses to therapy.

Furthermore the mechanisms of resistance to PI3K inhibitors are currently not well characterized in clinic. Recently two studies have reported possible ways for the tumor to develop resistance (Serra 2011, Rosen 2010). They report that resistance to PI3Kinhibitors can be acquired through activation of the RAF/MEK/ERK pathway or via activation of alternate Tyrosine Kinase receptors. These results provide new insight on possible resistance

mechanisms and outline the value of having access to tumor samples to further study the relevance of these findings in the clinic.

If feasible, collection of a tumor biopsy at progression is encouraged. This sample will be used to investigate changes in pathway signaling and potential mechanisms of resistance using combination of genomic, proteomic and phosphor-proteomic approaches.

1.3.5 Clinical experience

For more recent clinical data refer to the latest version of the Investigators' Brochure.

1.4 Overview of fulvestrant

Fulvestrant (Faslodex®) is approved for the treatment of post menopausal metastatic breast cancer following disease progression on therapy with an anti-estrogen therapy. For more information, refer to the nationally approved medical professional information (e.g. in the US known as Prescribing Information (PI), resp. EU Summary of Product Characteristics (SmPC)).

1.4.1 Clinical experience with fulvestrant

A phase III clinical trial was completed in 736 post-menopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during anti-estrogen therapy (AE subgroup) and 313 patients whose disease had recurred or progressed during aromatase inhibitor therapy (AI subgroup). This trial compared the efficacy and safety of fulvestrant 500 mg (n=362) with fulvestrant 250 mg (n=374). Progression-free survival (PFS) in the 500mg arm was 6.5 months in all patients, and 8.6 months and 5.4 months in the AE and AI subgroup, respectively (Di Leo et al 2010).

The most common, clinically significant adverse reactions occurring in ≥5 of patients receiving fulvestrant at 500mg were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation. Increased exposure to fulvestrant was observed in patients with moderate hepatic impairment (Child-Pugh class B), therefore a dose of 250 mg is recommended in this case. Fulvestrant has not been administered to patients with severe hepatic impairment (Child-Pugh class C).

1.4.2 Combination of fulvestrant and PI3K inhibitors

PI3K is involved in ligand-independent estrogen receptor signaling and PIK3CA mutations have been observed in 28-48% of estrogen receptor positive primary or metastatic tumors, with the PI3K pathway upregulated in endocrine therapy-resistant cells (Sanchez 2011; Gonzalez-Angulo 2011; Miller 2011). PI3K pathway activation has been associated with resistance to anti-estrogen receptor therapy (Miller 2011). PIK3CA mutated ER+ breast cancer cells are sensitive to inhibition of PI3K under estrogen deprivation; and treatment with fulvestrant sensitizes ER+ breast cancer cells (i.e., MCF7 LTED) to PI3K inhibition (Sanchez 2011). In an in vitro study, the combination of BYL719 and fulvestrant was synergistic in

[redacted]

PIK3CA mutated breast cancer cell lines (data on file). Inhibiting both the PI3Kα receptor and the estrogen receptor may offer a promising combined approach to the treatment of such breast cancer patients. A confirmed partial response has been observed in this ongoing study in a ER+/PR+/HER- breast cancer patient carrying a *PIK3CA* mutation treated with BYL719 at 270mg/d who had previously received fulvestrant.

1.4.3 Anticipated risks and safety considerations of the study drug combination

There may be overlapping toxicity when combining BYL719 with fulvestrant, based on current clinical experience: gastrointestinal disorders (e.g. nausea), asthenia and rash have been observed with both BYL719 and fulvestrant. Increased exposure to fulvestrant is observed in the case of hepatic impairment. Therefore, caution is required when administering the combination of fulvestrant and BYL719 to patients with impaired liver function. To ensure consistency with the fulvestrant label, patients with Child-Pugh status of B and C are excluded from the combination arm.

Drug-drug interaction studies with midazolam, rifampicine and ketoconazole have shown that fulvestrant was not an inhibitor, nor a substrate of CYP3A4. In vitro studies using human hepatocytes suggested that sulphate conjugation was a more predominant metabolism pathway as compared to CYP3A4. Thus the time dependent inhibition of CYP3A4 by BYL719 may not impact fulvestrant clearance. A drug-drug interaction between BYL719 and fulvestrant is considered unlikely.

To ensure the safety of study patients, the starting dose of BYL719 for the combination with fulvestrant will be a fraction of the MTD which is considered safe based on the results of the Bayesian Modeling. Furthermore, appropriate eligibility criteria and DLT definitions, as well as dose modification and stopping rules, are included in this protocol.

2 Study rationale/purpose

The current oncology drug discovery and development work has shifted towards molecularly targeted therapies. The key focus is on identifying inhibitors against components of pathways that drive tumor cell proliferation, survival, and/or metastasis such as the PI3K pathway (p110α mutations and potentially amplification) in an as specific way as possible. The first PI3K inhibitor tested in a clinical trial was the dual pan-class PI3K inhibitor BEZ235, which showed PI3K inhibition as well as mTOR inhibition, while a class I (PI3K) specific inhibitor derived from mTOR activity (BKM120) is currently tested in the clinic. The PI3K isoform which is mutated in tumors is p110α and is present in a number of different tumor types and is assumed to drive the tumor growth; hence the rationale of developing a p110α specific PI3K inhibitor. The alpha specific activity (as compared to δ and β) is expected to reduce the potential for inducing treatment related toxicity.

This trial has been designed as a Phase IA dose escalation trial with a dose expansion arm and aims to recruit adult patients with advanced solid tumors with documented *PIK3CA* alteration (mutation or amplification), who have progressed despite standard therapy or for whom no standard therapy exists. In addition, BYL719 will also be investigated in a limited number of

patients with ER+ breast cancer whose tumor was found to have the wild type *PIK3CA* gene. BYL719 will be taken orally on a continuous daily dosing schedule.

Once MTD (or recommended phase II dose – RP2D) has been defined, an expansion arm will be initiated at the MTD level (or RP2D) to further characterize the safety, preliminary efficacy, as well as PK and PD profile of BYL719 at this dose. The expansion cohort will be enriched with head and neck cancer and esophageal cancer patients. In preclinical experiments head and neck cancer cell lines were proved to be among the most sensitive to BYL719 treatment. BYL719 also showed pronounced activity against esophageal cancer cell lines, both in vitro and in vivo. [redacted]

A combination arm of BYL719 and fulvestrant has been introduced into this protocol, to be conducted in post-menopausal breast cancer patients whose tumors are ER positive, HER2 negative and have a *PIK3CA* alteration. (See details Section 1.4). The aim is to investigate the safety and preliminary efficacy of this combination. Based on current clinical experience with BYL719, patients with ER positive PIK3CA mutant breast cancer seem to benefit from the treatment with [redacted]
Based on the synergistic antitumor effect of BYL719 plus fulvestrant in preclinical experiments, this combination can be expected to further improve the potential antitumor activity in this patient population. The combination of BYL719 and fulvestrant will also be investigated in a limited number of patients with ER+, HER2- breast cancer whose tumor was found to have the wild type *PIK3CA* gene.

3 Objectives

3.1 Primary objective

To determine the MTD (or RP2D) of oral BYL719 as single agent in adult patients with advanced solid malignancies whose tumors have an alteration (mutation or amplification) of the *PIK3CA* gene, and in combination with fulvestrant in post-menopausal patients with ER positive locally advanced or metastatic breast cancer whose tumors have an alteration of the *PIK3CA* gene

3.1.1 End-point for primary objective

Incidence rate of dose limiting toxicities (DLT) (in the first cycle (of 28 days) of each investigated dose level).

3.2 Secondary objectives

1. To assess the overall safety and tolerability of BYL719 treatment both as single agent and in combination with fulvestrant

[redacted]

2. To characterize the full pharmacokinetic profile of oral BYL719 after single (Cycle 1 Day 1) and multiple administrations (Cycle 1 Day 8 and 28) of oral BYL719 both as single agent and in combination with fulvestrant
3. To assess the preliminary efficacy of oral BYL719 as single agent in patients with relapsing/refractory *PIK3CA* mutant solid malignancies and in combination with fulvestrant in ER+ breast cancer patients
4. To assess the preliminary anti-tumor activity of oral BYL719 as single agent and with fulvestrant in patients with locally advanced or metastatic *PIK3CA* wild type ER+, HER2- breast cancer

3.2.1 End-points for secondary objectives

1. Safety and tolerability: type, intensity, severity and seriousness of adverse events (AE) according to NCI CTCAE v. 4.0.
2. Pharmacokinetics of BYL719 as single agent or in combination with fulvestrant: plasma concentration-time profiles and derived basic PK parameters of BYL719, including but not limited to $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, CL/F, Vz/F and the terminal half-life ($t_{1/2}$) and other PK parameters if deemed appropriate.
3. Objective tumor response rate (ORR), defined as the sum of complete response and partial response as best reported response by RECIST 1.0 criteria (Novartis v2.0 guideline)
4. Progression Free Survival (at MTD/RP2D only)

3.3 Exploratory objectives

1. To assess downstream effects of PI3K pathway inhibition
2. To assess markers that may correlate with prediction of response and/or resistance: altered molecular status (e.g. gene mutation, amplification, deletion and/or protein over-expression or activation)
3. To assess pre- and post-treatment changes in circulating tumor markers (as relevant for the respective cancer types), if applicable, as potential surrogate for indication of efficacy
4. To perform additional analysis on remaining material from samples collected during the study (blood and tumor) that could help in the understanding of BYL719 drug action and/or identify potential biomarkers that may correlate with efficacy and safety

3.3.1 End-points for exploratory objectives

1. Inhibition of the PI3K pathway assessed by :
   - Pre- and post-treatment changes in glucose metabolism (i.e. of fasting glucose, fasting c-peptide in blood)
   - Levels of pS6 and pAkt in tumor tissue.
2. Pre- and post-treatment changes in circulating tumor markers (as relevant for the respective cancer types, if any) as a measure of tumor response
3. Additional analysis on remaining material from samples collected during the study (blood, and tumor) that could help in the understanding of BYL719 drug action.
4. Whole exome sequencing, RNA and proteomic profiling of tumor tissue in order to detect changes in molecular (e.g. acquired mutations), RNA and proteomic (e.g. upregulation of

[redacted]

tyrosine kinase) profiles from patients at baseline, on-treatment and at disease progression. If potential tumor-specific findings are detected, these might warrant a comparison with non-tumorous normal tissue (blood sample).

New biomarkers will be integrated if developed during this trial and considered appropriate for judgment of efficacy and safety.

4 Study design

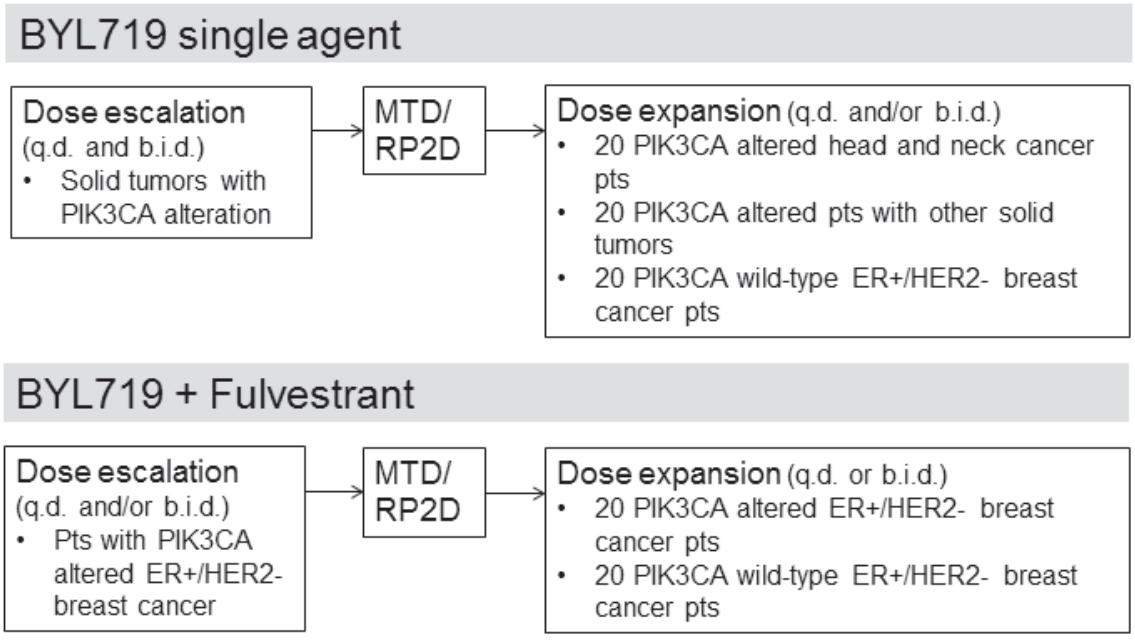
This study has been designed as a multi-center, open-label phase IA study with dose escalation arms for q.d. or b.i.d. dosing. Oral BYL719 will be administered daily on a continuous schedule. Provisional dose levels are given in Table 6-1. A cycle is defined as 28 days.

Depending on the extent of the b.i.d. dose escalation, and depending on the number of patients needed in the dose escalation cohorts, the study will enroll between 110 and 187 patients. Patients who begin on the q.d. regimen will not switch to the b.i.d. regimen, or vice versa.

When all patients have completed at least 6 cycles or discontinued treatment prior to cycle 6 then a Clinical Study Report (CSR) will be generated using all available data. Data gathered from all patients in the continuation segment will be provided in a written summary as an addendum to the CSR.

Once a patient has received 6 cycles of treatment a reduced schedule of assessments will be followed. See Table 7-1 which defines the reduced schedule of assessments.

Figure 4-1 Study design



Once daily (q.d.) single agent BYL719

At first, dose escalation will be conducted investigating a once daily (q.d.) administration of BYL719.

In the initial stage of the dose escalation arm, at least one patient will be enrolled to each cohort to evaluate the next dose level. If this one patient has not experienced a clinically relevant ≥ CTCAE grade 2 toxicity, then one patient will be considered sufficient for decision making on the next dose level. However, in case this one patient does experience a clinically relevant ≥ CTCAE grade 2 toxicity, then an additional patient must be enrolled at that dose-level. All evaluable patients in the initial dose cohort have to be assessed for decision making on dose escalation. Once the 2nd patient experiences clinically relevant CTCAE grade 2 toxicity or the first clinically relevant CTCAE ≥ grade 3 toxicity has occurred in the study, the minimum cohort size will be 3 patients for that cohort and all further cohorts.

Similarly, for all dose levels for which anti-tumor efficacy has been observed in the animal setting (assumed lowest dose at which an impact on the tumor growth has been observed) at an equivalent dose (considered to be 120mg/d and onwards), at least 3 patients will be enrolled per dose level.

In addition, paired pre- and post-treatment fresh tumor samples should be collected for all patients unless not feasible and/or accessible according to the investigator's judgment, while it will be mandatory in at least 1 patient per cohort from the fourth cohort onwards. In the expansion arm fresh pre- and post-treatment biopsies will be collected for all patients, unless not feasible and/or accessible according to the investigator's judgment. A minimum of 8 analyzable matched pairs must be obtained in the expansion arm.

Cohorts may be expanded at any dose level below MTD (or RP2D) for further investigation of safety, pharmacokinetic and/or pharmacodynamic parameters as required. And as such, additional eligible patients from who the investigator considers it feasible to obtain paired fresh tumor biopsies, can be enrolled at any time during dose escalation in the cohort explored at that point in time.

An adaptive Bayesian logistic regression model (BLRM) for dose escalation with overdose control (EWOC), will guide the dose escalation arm to determine the MTD. Before a drug dosage can be declared to be the MTD, at least 21 evaluable patients should have been treated, with at least six evaluable patients treated at the MTD.

Once the MTD is determined, for the purpose of evaluating safety with sufficient accuracy, the MTD (or RP2D) cohort will be expanded to at least 65 patients (for example, if 6 patients are enrolled to establish the MTD (or RP2D), an additional approximately 60 patients will be added – see Section 10.7.2 for justification). Approximately 20 of these patients will have head and neck, or esophageal, cancer carrying molecular alteration (mutation or amplification) of *PIK3CA*. Approximately 20 of these will be *PIK3CA* wild type ER+, HER2- breast cancer patients, and the remaining patients will have other solid tumors carrying a molecular alteration of *PIK3CA* (including, for example, metastatic breast, ovarian, colorectal, or gastric cancer).

[redacted]

Twice daily (b.i.d.) single agent BYL719

Once the MTD of BYL719 using a q.d. schedule is determined, a b.i.d. dosing schedule will be investigated in parallel by the addition of a new arm. Before the b.i.d. MTD can be declared at least 12 patients must be treated in the b.i.d. dose escalation, with at least 6 evaluable patients treated at the MTD. It is possible that two MTDs (for each q.d. and b.i.d.) will be established.

Once the MTD is determined for the b.i.d. schedule, a safety expansion arm may be opened. PK and safety data will be analyzed to determine whether any of the expansion arms may be discontinued.

BYL719 and fulvestrant combination

A combination of BYL719 with fulvestrant will be investigated in post-menopausal patients with locally advanced or metastatic breast cancer whose tumors have an alteration of the PIK3CA gene. Before the MTD of BYL719 in the combination can be declared at least 12 patients must be treated in the combination dose escalation, with at least 6 evaluable patients treated at the MTD. When the MTD (or RP2D) has been established after dose escalation, a dose expansion cohort will enroll approximately 20 patients with ER+/HER2- breast cancer whose tumors have an alteration of the *PIK3CA* gene and 20 patients with ER+/HER2- breast cancer whose tumors are *PIK3CA* wild type.

The dose escalation phase will begin using BYL719 with the q.d. schedule. A b.i.d. schedule may be opened for the combination, if suggested by PK and safety data of BYL719 as single agent. The expansion of the combination will be carried out with only one of the q.d. or b.i.d. regimens, a decision which will be taken prior to initiating the expansion.

Modified formulation

As of Protocol Amendment 4, a modified formulation of BYL719 has been developed [redacted] (See Section 6.1.2)

No formal comparison between both formulations will be conducted, but a minimum of 6 patients will be enrolled in the q.d. expansion cohort using the modified formulation and followed for one cycle. If the observed PK is comparable and the overdose control criteria are met then the study will continue with the modified formulation. Otherwise dose adjustments (escalation or de-escalation) may be made in accordance with the recommendations of the BLRM until a dose level fulfilling the overdose control criteria and/or achieving comparable PK is reached. If the study continues with the modified formulation any patient receiving the previous formulation may switch over to the modified formulation after they have completed at least one cycle.

5 Population

This trial with oral BYL719 (single agent) will be conducted in adult patients with advanced solid tumors, whose tumors have an alteration (mutation or amplification) of the *PIK3CA* gene, whose disease has progressed despite standard therapy or for whom no standard therapy

[redacted]

exists. A sub-set of *PIK3CA* wild type ER+/HER2-_breast cancer patients will be treated in the single agent MTD dose expansion cohort.

The combination of BYL719 and fulvestrant will be investigated in patients eligible for fulvestrant treatment (post-menopausal, ER positive, HER2 negative locally advanced or metastatic breast cancer) whose tumors have an alteration of the *PIK3CA* gene. An additional set of ER+/HER2- breast cancer *PIK3CA* wild type patients will be treated in the BYL719 and fulvestrant MTD dose expansion cohort.

Prior to the formal screening period for this protocol, potential eligible patients will be asked to sign a "Pre-screening Informed Consent". This will allow the use of already available *PIK3CA* gene status information or to allow determination of the *PIK3CA* gene status of the tumor. This can be done while the patient is still on standard treatment or whenever possible. This will ensure that the molecular status of the tumor is known when the patient may be screened for enrollment into the study. Only once the status of the *PIK3CA* gene of the patient's tumor is determined/identified, the patient may sign the study's main Informed Consent (IC) and begin the screening/baseline visit. If the site are unable to establish the *PIK3CA* gene status, the sample can be sent to a Novartis approved laboratory.

Inclusion/exclusion criteria

The investigator or his/her designee must ensure that all patients who meet the following inclusion and exclusion criteria at screening/baseline visit are offered enrollment in the study.

5.1 Inclusion criteria

1. Patients with histologically-confirmed, advanced unresectable solid tumors who have progressed (documented as per RECIST 1.0 criteria (Novartis v2.0) on the last line of therapy before entering this trial) within three months before screening/baseline visit on (or not been able to tolerate) standard therapy or for whom no standard anticancer therapy exists.
    - The single agent expansion arm will enroll the following:
        - Patients with either head and neck cancer, or esophageal cancer carrying a molecular alteration (mutation or amplification) of the *PIK3CA* gene.
        - Patients with *PIK3CA* wild type ER+/HER2- locally advanced or metastatic breast cancer patients.
        - Patients with other solid tumors carrying a *PIK3CA* alteration
    - Patients participating in the combination arm of BYL719 and fulvestrant must be eligible for treatment with fulvestrant with post-menopausal, ER positive, HER2 negative, locally advanced or metastatic breast cancer and have had disease progression during or following anti-estrogen therapy or whose disease has relapsed following adjuvant anti-estrogen therapy. Patients with PIK3CA altered or wild type breast cancer may enter this combination expansion cohort.
2. Availability of a representative formalin fixed paraffin embedded tumor tissue sample. Archival tissue and documented *PIK3CA* gene status will be mandatory for study enrollment. If archival tumor tissue is not available, a fresh tumor biopsy must be

[redacted]

provided instead. Fresh (paired) tumor biopsies must be collected whenever feasible and accessible according to the investigator's judgment.

3. At least one measurable or non-measurable (as per RECIST 1.0 criteria) lesion
4. Age ≥ 18 years
5. World Health Organization (WHO) Performance Status ≤ 2
6. Good organ (hepatic, kidney, BM) function at screening/baseline visit as defined by:
   - Serum total Bilirubin ≤ 1.5 x ULN and AST/SGOT and ALT/SGPT ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases are present
   - Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 ml/min
   - Platelets ≥ 100 x 10^9/L, Hemoglobin (Hgb) ≥ 9 g/dL (which may be reached with transfusion), Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
7. Calcium within normal limits
8. Potassium within normal limits
9. Magnesium ≥ the lower limit of normal
10. Fasting glucose < 140 mg/dL / 7.8 mmol/L
11. Negative serum pregnancy test within 72 hours before starting study treatment in all pre-menopausal women (except those who have undergone hysterectomy, sterilization, irreversible castration) and women < 12 months after onset of menopause.
12. Able to sign informed consent and to comply with protocol requirements.

5.2 Exclusion criteria

1. Brain metastasis unless treated and free of signs/symptoms attributable to brain metastasis in the absence of corticosteroid therapy (anti-epileptic therapy is allowed). Brain scan is mandatory in case of clinical evidence of brain metastatic disease.
2. Prior treatment with PI3K, AKT or mTOR inhibitor and failure to benefit. Enrolment of patients previously treated with such agents requires approval by the Novartis Clinical Project Leader.
3. Patient with peripheral neuropathy NCI-CTC Grade ≥ 3.
4. Patient with diarrhea NCI-CTC Grade ≥ 2.
5. Patient with acute or chronic pancreatitis
6. Any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:
   1. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
   - Clinical significant heart disease such as CHF requiring treatment (NYH grade ≥ 2), LVEF < 45% as determined by MUGA scan or ECHO, or uncontrolled hypertension (please refer to WHO-ISH guidelines)
   - ST depression or elevation of ≥ 1.5 mm in 2 or more leads
   - QTcF >480 msec on screening ECG
   - Congenital long QT syndrome

[redacted]

- History or presence of clinically significant ventricular arrhythmias or atrial fibrillation
- Clinically significant resting bradycardia (< 50 beats / min)
- Complete left bundle branch block (LBBB)
- Right bundle branch block (RBBB) + left anterior hemiblock (LAHB - bifascicular block)
- Unstable angina pectoris ≤ 3 months prior to starting study drug
- Acute Myocardial Infarction (AMI) ≤ 3 months prior to starting study drug

2. Patients with clinically manifest diabetes mellitus (treated and/or clinical signs or with fasting glucose ≥ 140 mg/dL / 7.8 mmol/L), history of gestational diabetes mellitus or documented steroid-induced diabetes mellitus.
3. Patients with hepatic impairment of Child-Pugh status of B or C for those patients participating in the combination arm
4. Bleeding disorders interfering with I.M. administration for those patients participating in the combination arm
5. Other concurrent severe and/or uncontrolled concomitant medical condition (e.g. active or uncontrolled infection incl. known diagnosis of HIV) that could cause unacceptable risks or compromise compliance with the protocol guidelines.

7. Patients who are currently receiving treatment with medication that has the potential to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot either be discontinued or switched to a different medication prior to starting study drug.
8. Patients with known hypersensitivity to fulvestrant or to any components of the drug product.
9. Patients who are currently receiving treatment with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants.
10. Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BYL719 (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) or patients unable to take oral medication.
11. Patients treated with hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin is allowed for as long as it has been initiated at least 2 week prior to study enrollment.
12. Patient who have received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.
13. Patients who have received chemotherapy, targeted therapy, endocrine therapy or immunotherapy ≤ 4 weeks (6 weeks for nitrosourea and mitomycin-C) prior to starting study drug or have not recovered from side effects of such therapy.
14. Patients who have received radiotherapy ≤ 4 weeks prior to starting study drug, who have not recovered from side effects of such therapy and/or from whom ≥ 30% of the bone marrow was irradiated.
15. Patients who have undergone major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery

[redacted]

16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, are not allowed to participate in this study UNLESS they are using highly effective methods of contraception during dosing and for 5 weeks after study drugs discontinuation. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least five weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
    - Combination of the following (a+b):
        a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        b. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

    Oral contraceptives (OC), injected or implanted hormonal methods are not allowed **as** the sole method of contraception, as BYL719 has not been characterized with respect to its potential to interfere with the PK and/or the effectiveness of OCs.

    Post menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum Follicle-Stimulating Hormone (FSH) levels > 40 mIU/mL [**for US only:** and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
17. Sexually active males must use a condom during intercourse while taking the drugs and for 5 weeks after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
18. History of another malignancy within 2 years, except cured basal cell carcinoma of the skin or excised carcinoma *in situ* of the cervix.

6 Treatment

6.1 Investigational and control drugs

6.1.1 Study drug

The study drug is BYL719.

[redacted]

6.1.2 How supplied

Novartis supplies BYL719 to the investigational sites as 10 mg, 50 mg and 200 mg tablets. BYL719 will be dosed on a flat scale of mg/day and not adjusted to body weight or body surface area.

Medication labels comply with the legal requirements of each country and are printed in the local language. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

For any further information on the storage and handling of BYL719, please consult the investigators brochure.

As of Protocol Amendment 4, a modified formulation of BYL719 has been developed [redacted] Both the current and modified formulations are very similar with minor changes made to the excipients. The tablet strengths, size, shape and color are the same, with the exception of the 10mg tablets which are now changed from brown to light brown to optimize differentiation between the 50mg and 10mg tablets.

The formulation used will be captured in the CRF.

6.1.2.1 Study combination

In the combination arm, BYL719 will be administered daily together with monthly fulvestrant (for details see Section 6.6.1.4). The modified formulation of BYL719 will be used for the combination arm. Commercially available fulvestrant will be used according to the local regulations.

6.1.2.2 Active control

Not applicable.

6.1.3 Preparation and storage

6.1.3.1 Study drug

BYL719 tablets are packaged in HDPE bottles with a child resistant closure. The storage conditions for study drug will be indicated in the local language on the medication label.

The study drug will have to be stored as specified on the label and in the investigators brochure.

6.2 Treatment arms

In both the dose escalation and the dose expansion arm BYL719 will be taken orally daily, on a continuous schedule up to disease progression or unacceptable toxicity that precludes any further treatment and/or treatment is discontinued at the discretion of the investigator or by patient refusal. At first, BYL719 is tested in a once daily schedule. The starting dose and dosing schedule was selected based on pre-clinical data. For the purpose of scheduling and evaluations, a treatment cycle will consist of 28 days.

[redacted]

An additional arm will be opened to investigate the b.i.d. dosing schedule, if deemed appropriate based on PK, safety and efficacy data and in agreement between Novartis and the investigators. Then dosing will begin in new cohorts using the new dosing schedule. The statistical model will be amended to include a covariate defining the new schedule at this time using all available PK information to define the potential relationship to the continuous daily schedule. The new total dose **per** 24h must not exceed the last dose that was determined to be safe using the daily dosing schedule and must satisfy the EWOC criteria under the amended statistical model.

BYL719 in combination with fulvestrant will be investigated and enroll post-menopausal patients with ER positive, HER2 negative, metastatic breast cancer (for details see Section 4).

6.3 Patient numbering

Each patient in the study is uniquely identified by a **9 digit patient number** which is a combination of his/her **4-digit center number** and **5-digit subject number**. The center number is assigned by Novartis to the investigative site.

The procedures for subject numbering and cohort coordination between the sites involved will be provided in a separate document prior to study start. Upon signing the informed consent form, the patient is assigned a subject number by the investigator or his/her designee. Once assigned to a patient, a subject number will not be reused. If the patient fails to be started on treatment for any reason, the reason for not being started on treatment will be entered on the Screening Log eCRF, the demography page of the eCRF must also be completed. No other data will be entered into the clinical data base for screen failure patients.

Informed consent must be obtained before any protocol-specific testing to determine a patient's eligibility.

6.4 Treatment assignment

The assignment of a patient to a particular dose level or to the dose expansion arm will be coordinated by the sponsor.

No randomization will be performed in this trial.

6.5 Treatment blinding

Not applicable. This is an open-label study.

6.6 Treating the patient

6.6.1 Study drug/study treatment administration

6.6.1.1 Study drug administration

BYL719 will be taken on a continuous daily dosing schedule. BYL719 tablets should be taken as follows:

- With a glass of water and consumed over as short a time as possible. Patients should be instructed to swallow the tablets as a whole and not to chew them.

[redacted]

- 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 oranges, grapefruit or grapefruit juice, grapefruit hybrids, pummelos from 7 days prior to the first dose of study medication and during the entire study due to potential CYP3A4 interaction with the study medication. Normal oranges or orange juice are allowed. Please refer to Section 6.6.4 for more detailed information on potential drug-drug interactions.
- Missed doses should not be made up.

If the patient is following the once daily dosing then BYL719 should be taken as follows (in addition to above):

- Patients should be instructed to take the dose of BYL719 daily in the morning, at approximately the same time each day, except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic.
- BYL719 should be taken 1 hour following a light breakfast (e.g. consisting of juice, toast, and jam). Patients should continue to fast for 1 hour after the administration of each BYL719 dose. If by 12 noon the patient forgets to take the BYL719 dose, then the dose should be withheld that day. If, for any reason, a breakfast was not consumed, then the patient should still take the scheduled morning dose of BYL719 with a glass of water. If this happens on days of PK sampling, it should be documented in the eCRF.

If the patient is following the twice daily dosing then BYL719 should be taken as follows (in addition to above):

- Patients should be instructed to take the dose of BYL719 daily in the morning and in the evening, at approximately the same time each day, except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic.
- The morning dose of BYL719 should be taken at the same time each day (except on days of clinic visits) when most convenient for the patient, 1 hour following a light breakfast (e.g. consisting of juice, toast, and jam). The recommended start of administration is approximately 8am (+/- 1 hr). Patients should continue to fast for 1 hr after the administration of the morning dose. If by 12 noon the patient forgets to take the BYL719 dose, then the morning dose should be held and not taken in the afternoon.The evening dose should be taken approximately 12 hours after the morning dose, 1 hr after a light meal or snack, at approximately the same time each day. Patients should continue to fast for 1 hr after the administration of each evening dose. If, for any reason, an evening meal was not consumed, then the patient should still take the scheduled evening dose of BYL719 with a glass of water. If this happens on days of PK sampling, it should be documented in the eCRF.
- On the days which involve fasting glucose/c-peptide monitoring for pharmacodynamic purposes (i.e. Days 2 and 9 of Cycle 1 and Day 2 of Cycle 2), patients must be fasting

[redacted]

overnight for at least 8 hours prior to the blood collection for pre-dose fasting glucose and c-peptide, followed immediately by the administration of BYL719. Patients can freely drink water. Following dosing with BYL719, no breakfast or any other meal will be allowed until four (4) hours after dosing (unless medically contra-indicated). After this period, food intake is allowed.

Every effort should be made to take the morning and evening doses approximately 12 hrs apart, at the same time each day, respecting a time window of max +/- 1 hour. On the days which involve blood sampling for fasting glucose, insulin and c-peptide for safety purposes (i.e. Days 1, 8 and 15 of Cycle 1 and Days 1 and 15 of each subsequent cycle) patients must be fasting overnight for at least 8 hours prior to the blood collection for pre-dose fasting glucose, insulin and c-peptide, followed by the light breakfast and 1hour later followed by the administration of BYL719. Patients should continue to fast for 1 hour after the administration of the BYL719 dose. On the days of full pharmacokinetic blood sampling (i.e. Days 1 and 8 of Cycle 1 and Day 1 of Cycle 2), the pre-dose PK sample should be collected just prior to BYL719 administration.

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Patients participating in the combination arm should take BYL719 as instructed above. Fulvestrant should be administered as an intra-muscular injection on days 1, 15 and 29 and monthly, according to the instructions provided in the package insert.

Fulvestrant must be administered in the morning within 1 hour of the BYL719 dose.

6.6.1.2 Duration of treatment

Patients may continue treatment until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient refusal. A treatment cycle is arbitrarily defined as 28 days for the purposes of scheduling procedures and evaluations.

6.6.1.3 Definition of treatment cycle

A complete treatment cycle is defined as 28 days of daily continuous treatment with oral BYL719.

- The first dose of BYL719 defines Day 1 of the treatment cycle. The last day of a complete treatment cycle is Day 28.
- If treatment with BYL719 is interrupted on > Day 21 of a treatment cycle (i.e., on Days 22 - 28), then, when treatment is restarted, a new 28 day treatment cycle will begin.
- If treatment with BYL719 is interrupted on ≤ Day 21 of a treatment cycle, and ≤ 7 dosing days are missed, then, when treatment is restarted, treatment with BYL719 will continue until Day 28 of that treatment cycle.
- If treatment with BYL719 is interrupted on ≤ Day 21 of a treatment cycle, and > 7 days of dosing are missed, then, when treatment is restarted, a new 28-day treatment cycle will begin.

[redacted]

- If a patient requires a dose delay of BYL719 of > 21 days from the previous dose, then the patient must be discontinued from the study.

6.6.1.4 Starting dose level for cycle 1

The starting dose for BYL719, for patients enrolled in this trial, is set at 30 mg/person/day p.o. administered continuously once daily.

The starting dose in humans has been calculated on the basis of human equivalent dose (HED) as per FDA and ICH S9 guidelines. The highest Non Serious Toxic Dose (HNSTD) in the dog was 5 mg/kg/day and translates to a HED of 170 mg/person/day in man (assuming a body surface area of 1.7 m^2). Applying a 6-fold safety factor, a safe human starting dose is derived at approx. 28 mg/day. The MTD in the rat was 30 mg/kg/day and translated into a HED of 306 mg/d. Applying a 10 fold safety factor, a safe human starting dose is derived at approximately 31 mg/day.

The recommended daily dose has been adjusted to 30 mg/day in this protocol based on the availability dosage strength.

The dog and rat are considered to be equally sensitive and equally relevant species to BYL719 based on the observed parent drug exposures in preclinical safety studies. The HNSTD determined in the dog (5 mg/kg/day) corresponds to an $AUC_{0\text{-}24h}$ of 17.6/15.5 µg*h/mL (m/f) while the MTD in rats (30 mg/kg/day) occurred at an $AUC_{0\text{-}24h}$ of 133/93 µg*h/mL (m/f) while the expected exposure at the starting dose is up to 6.5 µg*h/mL.

BYL719 will be dosed on a flat scale of mg/day and not individually adjusted by weight or body surface area. Tablets at three dosage strengths of 10, 50 and 200 mg will be provided.

For the combination arm, the provisional starting dose of BYL719 will be 300mg q.d. This starting dose meets the overdose control criteria principle applied to the Bayesian Logistical Regression model presented in Section 10.4.2. Immediately before beginning the combination part, the statistical model will be run to take into consideration new data from recent cohorts. Should the predicted starting dose no longer meet the overdose control criteria, a lower starting dose will be implemented that does satisfy the overdose criteria.

The dose of fulvestrant will be 500mg/month (with one additional 500mg administration after 14 days of the first dose) as per the local label (for dose modification guidelines see Table 6-4).

6.6.1.5 Provisional BYL719 dose escalation levels

Cycle 1 doses will be administered according to the **provisional** dose escalation schedule listed in Table 6-1. Dose escalation will continue until MTD is reached or the RP2D determined (Section 6.6.1.6.1). Patients will be dosed on a flat scale of mg/day and not by weight or body surface area. The model is applicable to the dose escalation of BYL719 in each arm (single agent q.d., single agent b.i.d., and fulvestrant combination). In the combination arm there will be no escalation of the fulvestrant dose.

[redacted]

Table 6-1 Provisional dose levels for the BYL719 dose-escalation arms

Dose level	mg/day	Dose level increment from previous according to BLRM with EOC
-1	20	33% decrease
1	**30**	**Starting dose**
2	60	100%
3	120	100%
4	200	67%
5	250	25%
6	300	20%
7	350	16.7%
8	400	14.3%

At all dose levels, the adaptive Bayesian logistic regression model (with escalation with overdose control) permits alterations in the dose increments based on the observed, clinically relevant, toxicities. However, in all cases, alterations in the dose increments must adhere to the following rules:

- The maximum inter-cohort dose escalation permitted is 100%
- In general, if toxicities ≥ grade 2 are observed in at least one third of the patients in the previous cohort, then dose escalation will be limited to ≤ 50%. However, for certain toxicities such as hematologic toxicity (e.g., lymphocytopenia), and toxicities not associated with end-organ damage (e.g., alopecia, nausea, pain, headache, fever), toxicity ≥ grade 2 must be observed in at least two thirds of the patients in the previous cohort, before dose escalation will be limited to ≤ 50%
- Any dose for which the risk of overdose exceeds 25% (see Section 10.4.2 for details) will not be considered for dosing

Thus, based on the above rules, it will be possible to explore intermediate dose levels as well as dose levels > 400 mg/d based on safety, pharmacokinetics and PK-PD modeling. The clinically relevant toxicities assessed for dose escalation will have to be unrelated to disease, disease progression, inter-current illness, or concomitant medications.

6.6.1.6 Criteria for dose escalation and determination of MTD

The primary objective of the dose escalation arm of the trial is to determine the maximum tolerated dose (MTD), the highest drug dosage not causing medically unacceptable, dose-limiting toxicity (DLT) in more than 33% of the treated patients in the first cycle of treatment.

The adaptive Bayesian methodology provides an estimate of the MTD. Typically, the estimated MTD is a tested dose that has the largest posterior probability of the DLT rate lying between 16% and 33% (target toxicity). Additionally, the use of the escalation with overdose control (EWOC) principle limits the risk of exposing patients to an unsafe dose by ensuring that the 75th percentile of the estimated MTD is 33% (for further details please refer to Section 10.4.2).

The final selection of MTD will be based on the recommendation of the Bayesian model, but will also take into account further available safety and tolerability information.

[redacted]

Only patients from the dose-determining set (for a detailed definition refer to Section 10.1) will be evaluable for dose escalation-related analyses. A patient is considered to have met the minimum exposure criterion if in Cycle 1 the patient has been treated with BYL719 for ≥ 21 days (i.e. received 21 out of 28 doses in Cycle 1). Patients participating in the combination arm are eligible for the dose-determining set if, in addition to above, they have 75% of the planned dose of fulvestrant during cycle 1 (i.e. the patient must receive 500mg on day 1 and at least 250mg on day 15). In addition, patients not experiencing DLT during Cycle 1, must have been observed for ≥ 28 days following the first dose, and must have completed all safety evaluations required for dose determining decisions.

Before a drug dosage can be declared to be the MTD, at least 21 evaluable patients should have been included in the dose escalation arm. At least 12 patients must be treated in the dose escalation of the b.i.d. single agent schedule in order to declare the MTD, as well as in the combination of the selected schedule (q.d. or b.i.d.) in order to establish MTD, with at least six evaluable patients treated at the estimated MTD level for one treatment cycle.

If a decision is made to investigate b.i.d. dosing, then the statistical model will be expanded to include a covariate defining the new schedule using the DLT information to inform the potential relationship to the q.d. schedule, and new cohorts would open using the new dosing schedule. The decision will also be informed by the PK and all safety information available.

Intra-patient dose escalation is not permitted at any time within the first 4 cycles of treatment. After the 4th cycle is completed, individual patients may be considered for treatment at a dose of BYL719 higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of BYL719, he or she must have tolerated the lower dose for at least four cycles of therapy, i.e. he or she must not have experienced any BYL719-related toxicity CTCAE grade ≥ 2 at the lower dose originally assigned. Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed evaluation and has not exceeded the maximum tolerated dose (MTD). There is no limit to the number of times a patient may have his or her dose of BYL719 increased. For any further increase after the initial intra-patient dose escalation, the following rules apply: the patient must have experienced no CTCAE grade ≥ 2 BYL719-related toxicity over at least two cycles of therapy at the lower dose, and the higher dose being considered must have been fully evaluated and shown not to exceed the MTD. Consultation and agreement with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF. Data from the first cycle of treatment at the new dose level will not be formally included into the statistical model describing the relationship between dose and occurrence of DLT. However, this data will be incorporated into the clinical assessment of safety within a dose escalation teleconference (Section 6.6.1.6.1).

6.6.1.6.1 Dose escalation

At the end of each treatment cohort, Novartis will convene a teleconference with the investigators of the dose escalation arm. At the dose escalation teleconference the clinical course (safety information including both DLTs and all ≥ CTCAE Grade 2 toxicity data during Cycle 1, and PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

[redacted]

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the Bayesian logistic regression model's (with EWOC) recommendation, and a medical review of relevant clinical, PK and laboratory data. The parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohorts. Novartis will prepare minutes from these meetings and circulate them to each investigator for comment prior to finalization.

6.6.1.6.2 Dose cohort modification

In the initial stage of the dose escalation arm, at least one patient will be enrolled to each cohort to evaluate the next dose level. If this one patient has not experienced a clinically relevant ≥ CTCAE grade 2 toxicity, then one patient will be considered sufficient for decision making on the next dose level. However in case this one patient does experience a clinically relevant ≥ CTCAE grade 2 toxicity, then an additional patient must be enrolled at that dose-level. All evaluable patients in the initial dose cohort have to be assessed for decision making on dose escalation.

Once the 2nd patient experiences CTCAE grade 2 toxicity or the first CTCAE ≥ grade 3 toxicity has occurred in the study, the minimum cohort size will be 3 patients for that cohort and all subsequent cohorts. Similarly, for all dose levels for which anti-tumor efficacy has been observed in the animal setting (assumed lowest dose at which an impact on the tumor growth has been observed) at an equivalent dose (considered to be 120mg/d and onwards), at least 3 patients will be enrolled per dose level. The following rules apply at this stage:

- Due to the potential for dropouts during Cycle 1 (e.g., early disease progression), a cohort may be expanded to include an additional patient(s) if such patient(s) can be enrolled ≤ 14 days after the last cohort patient was treated (or > 14 days in case an additional patient is available with a paired fresh tumor biopsy). In this situation, the decision to dose escalate may be made based on the first 3 evaluable patients that have been treated in this cohort. If a patient withdraws during Cycle 1 due to any reason other than dose-limiting toxicity without meeting the minimum requirement for safety evaluation, leaving less than three evaluable patients who have experienced a DLT or clinically relevant toxicity ≥ CTCAE grade 2, that patient must be replaced.
- If two evaluable patients are available for assessment and those patients have not experienced DLT or clinically relevant toxicity ≥ CTCAE grade 2, then two patients will be considered sufficient for decision making on dose selection for the next cohort. Clinically relevant toxicities will be those assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications. If DLT or clinically relevant toxicity ≥ grade 2 is observed, then at least 3 evaluable patients must have been treated before dose escalation can occur.
- If a decision is made to escalate to a higher dose level, but an additional patient(s) on the lower dose level experiences a DLT in Cycle 1, then the statistical model will be updated before more patients are enrolled onto the higher dose level. Enrollment to the higher dose level may be resumed if the model continues to recommend the higher dose level after updating.

[redacted]

If at any time, two or more patients within a cohort experience DLT, the model will be updated before subsequent patients receive study drug. A decision will be made within a dose-escalation teleconference, in the same manner as described in Section 6.6.1.6.1, at which dose level dosing should continue.

If there is less than the required number of patients evaluable for the dose-determining set, replacement patients will be enrolled until at least the minimum number of evaluable patients are available for assessment. Additional patients may be enrolled to any dose to further assess safety, pharmacokinetics and pharmacodynamics, and the model will be subsequently updated. And as such, additional eligible patients from who the investigator considers it feasible to obtain paired fresh tumor biopsies, can be enrolled at any time during dose escalation in the cohort explored at that point in time.

6.6.1.7 Dose-limiting toxicity

Toxicity will be assessed using the NCI Common Toxicity Criteria for Adverse Events, version 4.0 (evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf) unless otherwise specified. A dose-limiting toxicity (DLT) is defined as an adverse event or laboratory abnormality at least possibly related to study treatment and occurs < 28 days following the first dose of BYL719 (Cycle 1), is clinically relevant and is unrelated to (underlying tumor) disease, disease progression, inter-current illness, or concomitant medications and meets any of the criteria listed in Table 6-2.

For the combination dose escalation arm, injection site reactions will not be considered as a DLT.

Table 6-2 Criteria for defining dose-limiting toxicities

TOXICITY	ANY OF THE FOLLOWING CRITERIA
Blood and lymphatic system disorders [a]	Febrile neutropenia (decrease in neutrophils associated with fever, ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)
Investigations (hematologic)	≥ CTCAE grade 3 neutropenia for > 7 consecutive days
	CTCAE grade 3 thrombocytopenia for > 7 consecutive days requiring platelet transfusion
	CTCAE grade 4 thrombocytopenia
Investigations (renal)	Serum creatinine ≥ 2.0 x ULN to ≤ 3.0 x ULN for > 7 consecutive days
	≥ CTCAE grade 3 serum creatinine
Investigations [b] (hepatic)	Total bilirubin ≥ 2.0 x ULN to < 3.0 x ULN for > 7 consecutive days
	≥ CTCAE grade 3 total bilirubin
	CTCAE grade 3 AST or ALT for > 7 consecutive days
	CTCAE grade 4 AST or ALT
	≥ CTCAE grade 3 AST or ALT with a ≥ Grade 2 bilirubin elevation of any duration
	Combination arm only: CTCAE grade 3 AST or ALT for > 7 consecutive days, or re-appearance of grade 3 for 3 consecutive days despite fulvestrant dose reduction Liver impairment Child-Pugh class C

[redacted]

TOXICITY	ANY OF THE FOLLOWING CRITERIA
Investigations (metabolic)	CTCAE grade 3 asymptomatic amylase and/or lipase, not reversible to ≤ CTCAE grade 2 for > 7 consecutive days
	CTCAE grade 4 asymptomatic amylase and/or lipase
Metabolism and nutrition disorders (not CTCAE grades, see Table 6-4)	Grade 2 hyperglycemia (confirmed with a repeat FPG within 24 hours) that does not resolve to grade 0 within 14 consecutive days (after initiation of glimepiride, glibenclamide or metformin)
	≥ Grade 3 hyperglycemia (confirmed with a repeat FPG within 24 hours)
Gastrointestinal disorders	≥ CTCAE grade 3 pancreatitis
Cardiac disorders	Cardiac toxicity ≥ CTCAE grade 3 or cardiac event that is symptomatic or requires medical intervention
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin CTCAE grade 3
Nervous system disorders	≥ 1 CTCAE grade level increase of neurotoxicity
Skin and subcutaneous tissue disorders	≥ CTCAE Grade 2 photosensitivity
	CTCAE Grade 3 rash for > 7 consecutive days despite skin toxicity treatment (as per local practice)
	CTCAE Grade 4 rash
Other adverse events[c]	≥ CTCAE grade 3 adverse events (excluding ≥ CTCAE grade 3 elevations in alkaline phosphatase)
	≥ CTCAE grade 3 vomiting despite the use of standard (as per local practice) anti-emetics
	≥ CTCAE grade 3 nausea despite use of standard (as per local practice) anti-emetics
	≥ CTCAE grade 3 diarrhea despite the use of optimal (as per local practice) anti-diarrhea treatments
	CTCAE grade 3 fatigue/asthenia for > 7 consecutive days

[a] ≥ CTCAE grade 3 anemia will not be considered DLT unless judged to be a hemolytic process secondary to study drug. ≥ CTCAE grade 3 lymphopenia will not be considered DLT unless clinically significant.

[b] For any CTCAE grade 3 or 4 hepatic toxicity that does not resolve within 7 days to ≤ grade 1 (or ≤ CTCAE grade 2 if liver infiltration with tumor present) an abdominal CT scan or an equivalent imaging procedure has to be performed to assess if it is related to disease progression or to exclude other liver disease.

[c] CTCAE grade 3 hypertension will only be considered DLT if it requires more than one drug or more intensive therapy than previously

A single patient is assumed not to tolerate the dose if he/she experiences at least one DLT.

If a lower grade AE leads to a dose interruption of more than 7 consecutive days of BYL719, this AE will be considered as DLT.

For the purposes of dose escalation and determination of the MTD, DLTs that occur during the first cycle will be necessarily considered, including those in which the event has started in cycle 1 and the confirmation of the DLT occurs in cycle 2.

Besides for hepatic investigations, the DLTs defined in this table also account for the combination of BYL719 and fulvestrant.

The investigator must notify the sponsor immediately of any unexpected ≥ CTCAE grade 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, ≥ CTCAE grade 2 adverse events will be reviewed for all patients at the current dose level.

[redacted]

Whenever a patient experiences a DLT, treatment with BYL719 will be interrupted and the toxicity will be followed up as described in the following section.

6.6.1.8 Follow-up for dose-limiting toxicities

Patients whose BYL719 treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in the Table 6-3, at least once a week during the dose interruption until the time the patient will restart BYL719 treatment or will discontinue study treatment (dose interruption > 21days) for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first.

All patients must be followed for adverse events and serious adverse events for 28 days following the last dose of BYL719.

Table 6-3 Follow-up for dose limiting toxicities

TOXICITY	FOLLOW-UP EVALUATION
Blood and lymphatic system disorders	Test twice weekly until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization.
Investigations (hematologic) Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization. Perform physical exam for check on bruising in case of major thrombocytopenia.
Investigations (renal) Serum creatinine ≥ 2 x ULN Serum creatinine > 2 x ULN AND proteinuria or hematuria > CTCAE grade 2	Test twice weekly until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization. If serum creatinine > 2.0 x ULN, +3 proteinuria or hematuria ≥ CTCAE grade 2 has been demonstrated, a 24-hour urine collection for total protein and total creatinine must be repeated at least weekly until either resolution to baseline value or until stabilization. Whenever a measured CrCl is obtained, a serum creatinine should be obtained within ≤ 72 hours of the urine collection.
Investigations (hepatic) Total bilirubin ≥ 2 x ULN OR AST/ALT ≥ CTCAE grade 3 (> 5 x ULN)	Test twice weekly until ≤ CTCAE grade 1, (or ≤ CTCAE grade 2 for ALT/AST if liver metastases are present) then restart treatment. Continue to test weekly until resolution to baseline or stabilization. Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines above, irrespective of the results of fractionation.

[redacted]

TOXICITY	FOLLOW-UP EVALUATION
Investigations (metabolic) Amylase or lipase ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 2, then restart treatment. Continue to test weekly until resolution to ≤ CTCAE grade 1 or stabilization. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver disease. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase also needs to be tested.
Metabolism and nutrition disorders	For details of the follow-up and treatment of ≥ grade 2 hyperglycemia refer to the 'Guidelines for the treatment of study drug-induced hyperglycemia' provided in [Post-text Supplement 3].
Cardiac disorders ECG abnormalities indicative of ischemic event	Twice weekly ECGs until normalization or stabilization of ECG findings, then restart treatment.
Investigations (cardiac) QTcF prolongation Troponin CTCAE grade 3	Patient who experience QTcF prolongation ≥ CTCAE grade 3 should be followed as per Table 6-4. Test twice weekly until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization.
Nervous system disorders	Patients who experience neurotoxicity should be followed as per Table 6-4.
Non-Laboratory All DLT events Rash	Evaluate once a week until resolution to baseline or stabilization, then restart treatment. Whenever a ≥ CTCAE grade 2 rash is diagnosed, the following should be obtained: A paired skin biopsy from both an affected and an unaffected skin area for local histopathology assessment. A plasma (unscheduled PK) sample to assess the concentration of BYL719 (within 10-15min after performing the biopsy). Follow-up rash by physical examination at least weekly until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization.

6.6.2 Permitted study drug adjustments

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. The following guidelines should be followed. If the patient experiences unacceptable toxicities > CTCAE grade 2, treatment with the study drug (at the same dose as in the previous cycle) must be suspended until the toxicities return to ≤ CTCAE grade 1. The criteria for interruption and re-initiation of BYL719 treatment are outlined in Table 6-4. These changes must be recorded on the Dosage Administration Record eCRF.

[redacted]

6.6.2.1 Dosing modifications

If the administration of BYL719 was not interrupted due to toxicity during a treatment cycle, then treatment with BYL719 (at the same dose as the previous cycle) may be continued on the first scheduled day of the next cycle. The same applies if the patient experienced an unacceptable toxicity, provided this toxicity resolved to ≤ CTCAE grade 1 unless otherwise specified. The criteria for interruption, dose reduction and re-initiation of BYL719 treatment are outlined in Table 6-4. Any plan to deviate from these criteria must be previously discussed and agreed upon with Novartis.

All patients considered for continued treatment cycles will be evaluated as defined in Table 7-1. Patients who must interrupt BYL719 treatment, should have at least weekly follow-up during the dose interruption until the time the patient will restart BYL719 treatment or will discontinue study treatment (dose interruption > 21days). This weekly follow up includes a physical examination, neurological examination, vital signs, weight, performance status, cardiac assessments, ophthalmologic examination as clinically indicated, and assessment of adverse events and concomitant medication in combination with regular blood draws as indicated by the observed toxicity. Following a DLT, toxicity specific requirements/tests should be performed as outlined the Section 6.6.1.8.

After the experience of DLT, patient can resume therapy (as mentioned above) but BYL719 dose will have to be reduced which means treatment at the preceding BYL719 tolerated dose level.

For each patient, a maximum of 2 BYL719 dose reductions or going down to the lowest tested BYL719 dose, will be allowed after which the patient will be discontinued from study treatment if still not tolerated. In addition, a patient must permanently discontinue treatment if, after treatment is resumed at a lower dose, the same toxicity returns with the same or higher severity. If, after interruption of treatment and resolution, treatment is resumed at the same dose following the criteria in Table 6-4, and the same toxicity recurs with the same severity, next treatment re-initiation must resume at a lower dose irrespective of duration (except for hyperglycemia; refer to [Post-text Supplement 3]. For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles except for the 2nd occurrence of grade 1 or grade 2 hyperglycemia [Post-text Supplement 3].

Dose reduction for BYL719 means treatment at the preceding BYL719 dose level. Provisional dose levels for BYL719 are listed in Table 6-1.

If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study treatment. Patients who discontinue from the study treatment for a study-related adverse event or an abnormal laboratory value must be followed as described in Section 6.6.5 and Section 6.6.6. All interruptions or changes to study drug administration must be recorded on the Dosage Administration Record eCRF.

6.6.3 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

[redacted]

who are suspected to have developed pneumonitis should stop study treatment (BYL719, and both BYL719 and fulvestrant for patients in the combination arm) immediately and undergo appropriate imaging (high resolution CT scan) and bronchoalveolar lavage for biopsy should be considered. Infectious causes of interstitial lung disease should be ruled out. Investigators should follow institutional practice for management of pneumonitis which should include treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes have not been ruled out. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment. If pneumonitis is confirmed and related to study drugs, then BYL719 (and both BYL719 and fulvestrant for patients in the combination arm) should be permanently discontinued.

Table 6-4 Criteria for interruption and re-initiation of BYL719

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE Grade [a.] unless otherwise specified (Value)	Recommended Dose Modifications any time during a cycle of therapy (including intended day of dosing)
No toxicity	Maintain dose level
Blood and lymphatic disorders	
Febrile neutropenia (decrease in neutrophils associated with fever, ANC < 1.0 x 10^9/L, fever ≥ 38.5°C (not CTCAE grade)	Omit dose until resolved, then ↓ 1 dose level
Investigations (hematologic)	
Neutropenia (ANC) Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L) Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	 Maintain dose level Maintain dose level Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level Omit dose until resolved to ≤ grade 1, then resume at ↓ 1 dose level
Thrombocytopenia Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L) Grade 3 (PLT < 50-25 x 10^9/L) Grade 4 (PLT < 25 x 10^9/L)	 Maintain dose level Maintain dose level Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Bleeding Any bleeding, related to BYL719 use, resulting in platelet transfusion	Omit dose until no further bleeding has been observed. Modify dose according to the thrombocytopenia recommended dose modifications.

[redacted]

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE Grade [a.] unless otherwise specified (Value)	Recommended Dose Modifications any time during a cycle of therapy (including intended day of dosing)
Investigations (renal)	
Serum creatinine	
< 2 x ULN	Maintain dose level
2 - 3 x ULN	Omit dose until resolved to ≤ grade 1, then • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade ≥ 3 (> 3.0 baseline; > 3.0 x ULN)	Omit dose and discontinue patient from study treatment
Investigations (hepatic)	
Bilirubin	Always have direct bilirubin assessed in case total bilirubin is elevated (> ULN).
< 2 x ULN	Maintain dose level
2 - 3 x ULN	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, ↓ dose of BYL719 by one dose level. For combination with fulvestrant: ↓ dose of BYL719 by 25% and reduce dose of fulvestrant to 250 mg
Grade 3 (> 3.0 - 10.0 x ULN)	Omit dose until resolved to ≤ grade 1, then : • If resolved in ≤ 7 days, ↓ dose of BYL719 by one dose level For combination with fulvestrant: ↓ dose of BYL719 by 25% and reduce dose of fulvestrant to 250 mg • If resolved in > 7 days discontinue patient from study treatment
Grade 4 (> 10.0 x ULN)	Omit dose and discontinue patient from study treatment Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓1 dose level and continue treatment at the discretion of the investigator. For patients with total bilirubin ≥ grade 3, a CT scan or equivalent imaging procedure to exclude disease progression or potential other liver disease should be performed.

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE Grade [a.] unless otherwise specified (Value)	Recommended Dose Modifications any time during a cycle of therapy (including intended day of dosing)
AST or ALT	
Grade 1 (> ULN - 3.0 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 in case of liver metastasis), then • If resolved in ≤ 7 days, then maintain dose level of BYL719 and for the combination reduce dose of fulvestrant to 250 mg • If resolved in > 7 days, then ↓ dose of BYL719 by 1 dose level For combination with fulvestrant: ↓ dose of BYL719 by 25% and reduce dose of fulvestrant to 250 mg
Grade 4 (> 20.0 x ULN)	Omit dose until resolved to ≤ grade 1, then • reduce dose of BYL719 by 1 dose level. • For combination with fulvestrant: ↓ dose of BYL719 by 25% and reduce dose of fulvestrant to 250 mg
Investigations (metabolic)	
Asymptomatic Amylase and/or Lipase elevation	
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 - 5.0 x ULN)	Omit dose until resolved to ≤ grade 2, then : • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓ by 1 dose level
Grade 4 (> 5.0 x ULN)	Omit dose and discontinue patient from study treatment Note: A CT scan or other imaging procedure to assess the pancreas, liver, and gallbladder is to be performed within 1 week of the first occurrence of any ≥ CTCAE grade 3 of amylase or lipase. If asymptomatic grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.

[redacted]

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE Grade [a.] unless otherwise specified (Value)	Recommended Dose Modifications any time during a cycle of therapy (including intended day of dosing)
Metabolism and nutrition disorders	
Fasting Plasma Glucose (not CTCAE grades) Grade 0 (< 140 mg/dL) [< 7.8 mmol/L] Grade 1 (140 - 199 mg/dL) [7.8 - 11.1 mmol/L] Grade 2 (200 - 249 mg/dL) [11.2 - 13.8 mmol/L] Grade 3 (250 - 399 mg/dL) [13.9 - 22.2 mmol/L] Grade 4 (≥ 400 mg/dL) [≥ 22.3 mmol/L]	Maintain dose level Please refer to the guidelines for study drug-induced hyperglycemia provided in [Post-text Supplement 3].
Investigations (cardiac) (Prolonged QTcF interval)	
During cycle 1 No QTcF change from baseline > 60 msec	Maintain dose level and ECG monitoring for subsequent cycles as in Cycle 1.
QTcF change from baseline > 60 msec (but absolute QTcF ≤ 500 msec)	Maintain dose level. ECG monitoring assessments for Cycles 2 & 3 should be performed at the same frequency as in Cycle 1. After Cycle 3, ECGs for subsequent cycles will be performed as clinically indicated by the investigator.
During any cycle ≥ Grade 3 (QTcF ≥ 501 msec as identified by the investigator on at least two separate ECGs).	Omit dose. If confirmed by the central ECG laboratory, monitor patient with hourly ECGs until the QTcF has returned to < 30 msec from baseline. Exclude other causes of QTcF prolongation such has hypokalemia, hypomagnesemia and blood oxygenation status. Once QTcF prolongation has resolved, patients may be re-treated at one dose level below, at the investigator's discretion. ECG monitoring must continue throughout the treatment period as follows: • If the ECGs obtained in the first cycle after dose reduction are without any QTcF change from baseline > 60 msec, then ECG monitoring in subsequent cycles will be continued at the same frequency for Cycle 2. • If the patient had a QTcF change from baseline > 60 msec, but the absolute QTcF ≤ 500 msec, then ECG monitoring at the same frequency as in Cycle 1 will be continued for all subsequent cycles. Patients who experience absolute QTcF ≥ 501 msec after one dose reduction will be discontinued from study. **Note:** Whenever a QTcF change from baseline > 60 msec or a new QTcF ≥ 501 msec result is observed, a plasma (unscheduled PK) sample for determination of BYL719 concentration should be obtained and the time of sample collection noted.

[redacted]

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE Grade [a.] unless otherwise specified (Value)	Recommended Dose Modifications any time during a cycle of therapy (including intended day of dosing)
Cardiac disorders	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Omit dose and discontinue patient from study treatment
Nervous system disorders	
≥ 1 CTCAE grade level increase of neurotoxicity	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
≥ Grade 3 neurotoxicity	Omit dose and discontinue patient from study
Gastrointestinal disorders	
Pancreatitis Grade 2 (enzyme elevation or radiologic finding only)	Maintain dose level
Grade ≥ 3 (severe pain; vomiting; medical intervention indicated or life threatening consequences)	Omit dose and discontinue patient from study treatment
Diarrhea Grade 1 (2-3 stools/day > pretx)	Maintain dose level
Grade 2 (4-6 stools/day > pretx)	Omit dose* until resolved to ≤ grade 1, then re-start at the current dose. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
≥ Grade 3 (≥ 7 stools/day > pretx or life-threatening consequences)	Omit dose* until resolved to ≤ grade 1, then ↓ 1 dose level Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea. * Omit dose for ≥ grade 2 diarrhea only if the diarrhea cannot be controlled with optimal antidiarrheal treatments. Please refer to the guidelines for study drug-induced diarrhea provided in [Post-text Supplement 3].
Eye Disorders	
≥ Grade 3 ocular/vision symptoms interfering with ADL (Activities of daily living) or requiring medical intervention	Omit dose and discontinue patient from study

[redacted]

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE Grade [a.] unless otherwise specified (Value)	Recommended Dose Modifications any time during a cycle of therapy (including intended day of dosing)
Skin and subcutaneous tissue disorders	
Photosensitivity	
Grade 1 - painless erythema and erythema covering <10% BSA	Maintain dose level
Grade 2 - tender erythema covering 10-30% BSA	Omit dose until resolved to ≤ grade 1 then: • If resolved in ≤ 7 days, ↓ 1 dose level • If resolved in > 7 days, discontinue patient from study
Grade ≥ 3 - erythema covering > 30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated or life-threatening consequences; urgent intervention indicated	Omit dose and discontinue patient from study
Rash	
Grade 1	Maintain dose level. Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids) *
Grade 2	Maintain dose level. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids) *
Grade 3	Omit dose until resolved to CTCAE Grade ≤ 1, then: • If resolved in ≤ 7 days, ↓ 1 dose level • If resolved in > 7 days (despite appropriate skin toxicity therapy), discontinue patient from study drug treatment. If, after having restarted BYL719 at the next lower dose level, the rash no longer meets the dose-limiting criteria, then the dose of BYL719 may be increased to the previous dose level for subsequent doses * Low-dose systemic corticosteroids need to be used with caution due to the increased hyperglycemia risk as well as the potential of drug-drug interaction; see Section 6.6.4 and [Post-text Supplement 2].
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then : • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, ↓ 1 dose level

[redacted]

Recommended Dose Modifications for BYL719	
Worst Toxicity CTCAE Grade [a.] unless otherwise specified (Value)	Recommended Dose Modifications any time during a cycle of therapy (including intended day of dosing)
Respiratory disorders	
Pneumonitis Any grade	Omit BYL719 (and both BYL719 and fulvestrant for patients in the combination arm) for any case of suspected pneumonitis. Obtain appropriate imaging (high resolution CT scan) and consider bronchoalveolar lavage for biopsy. See Section 6.6.3 for details of management of pneumonitis. Concurrent corticosteroid and antibiotic therapy is recommended if infectious causes have not been ruled out. BYL719 (and both BYL719 and fulvestrant for patients in the combination arm) should be permanently discontinued in all patients with confirmed pneumonitis related to study drugs.
Other adverse events	
Grade 1 or 2 Grade 3 Grade 4	Maintain dose level Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level Omit dose and discontinue patient from study Omit dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)
All dose modifications should be based on the worst preceding toxicity. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose of BYL719, then the patient must be discontinued from the study treatment. Patients who discontinue from the study for a study-related adverse event 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. For BYL719 dose reductions in the dose escalation are to the preceding dose level, in the dose expansion the reductions may be by 25% in the dose expansion the reductions may be by 25% or to the next lower dose level, as per investigator's judgment. [a.] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.0)	

6.6.4 Other concomitant medications

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies eCRF. In addition, all medications taken within 4 weeks prior to the administration of BYL719 will be recorded in the Concomitant medications/Significant non-drug therapies eCRF.

Patients taking medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The days of full pharmacokinetic blood sampling should be representative of the other study days with regard to the use of the

[redacted]

chronically administered concomitant medications. If a concomitant medication is used intermittently during the study, this medication should be avoided on the days of full pharmacokinetic sampling.

6.6.4.1 Drugs that are prohibited

- 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. If such agents are required for a patient then the patient must be discontinued from the study.
- Prophylactic anti-emetics will be withheld until the patient has experienced CTCAE Grade ≥ 1 nausea or vomiting. The patient may then receive (prophylactic) anti-emetics at the discretion of the treating physician.
- Prophylactic use of granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), and/ or erythropoietin are in accordance with the American Society of Clinical Oncology's (ASCO) guidelines. If a patient requires the use of a recombinant hemotopoietic growth factor, the Sponsor should be notified as soon as possible.
- Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants are not permitted. Non-fractionated heparin and LMWH are allowed.
- Patients will abstain from using herbal preparations/medications within 14 days prior to the first dose of the study drug combination and throughout the study until the final study visit. 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. The investigator should contact the Sponsor before initiating treatment with any herbal preparation.

6.6.4.2 Drugs to be used with caution

- 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 6.6.4.1.
- [redacted]

[redacted]

Patients using antiplatetet prodrugs should be carefully monitored. Note that the use of warfarin is prohibited.

- 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 glimepiride, glibenclamide or metformin. Patients receiving oral antidiabetics which are predominantly metabolized by [redacted] must be carefully monitored for hypoglycemia as BYL719 was found to be moderate reversible inhibitor of these enzymes refer to the [Post-text Supplement 2].
- If a patient requires while on BYL719 treatment, the concomitant use of any medication which may cause QT prolongation and/or torsade de pointes, then investigators, at their discretion, may co-administer such medications. Patients receiving such medications must however be carefully monitored. A list of medications that are known to prolong the QT interval can be found at www.crediblemeds.org
- [redacted]
- Contraceptives: Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. For allowed contraception methods, refer to Section 5.2. Highly effective contraception should be maintained throughout the study and for 5 weeks after study drug discontinuation.

6.6.5 Study drug discontinuation

In this protocol, **Study Treatment Completion** is defined as the time when BYL719 administration is permanently discontinued due to any reason (e.g. disease progression, adverse event, withdrawn consent, investigators decision).

If, for any patient, study treatment is permanently discontinued, the patient will be considered to have completed treatment and the (primary) reason for treatment completion will be recorded on the End of Treatment eCRF.

All patients who discontinue study treatment (or a knowledgeable informant), including those who refuse to return for the end of study treatment visit, should be contacted (either by visit, telephone or mail) for safety evaluations, antineoplastic therapies received after

[redacted]

discontinuation of study drug, and survival information during the 28 days following the last dose of study treatment. Patients lost to follow up should be recorded as such on the End of Treatment and Study Evaluation Completion eCRF.

Patients who discontinue study drug should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

6.6.6 Premature patient withdrawal

Patients may choose to discontinue the study at any time during the trial. Non-evaluable patients in the escalation arm of the study will be replaced.

6.6.6.1 End of study treatment

Patients **may** voluntarily withdraw from the study or been withdrawn from study treatment at the discretion of the investigator at any time.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the End of Treatment eCRF. Patients may be withdrawn from the study for one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol deviation (incl. introduction of any other anticancer therapy)
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Disease progression

Patients who discontinue study treatment should be scheduled for a final visit within 7 days after discontinuing study treatment, at which time all of the assessments listed for the end of study treatment visit (Table 7-1) will be performed. An End of Treatment eCRF will be completed, giving the date and reason for stopping the study treatment.

Patients whose treatment is interrupted or permanently discontinued due to a study-related adverse event or 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. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study. However, the patient will continue to be followed for toxicity as previously described (Section 6.6.1.8). All patients should be followed for adverse events and serious adverse events for 28 days following the last dose of BYL719.

[redacted]

If a patient discontinues fulvestrant for unacceptable toxicity which is unrelated to BYL719, then the patient may continue to receive BYL719 (at the discretion of the Investigator) until unacceptable toxicity or progressive disease.

6.6.7 Study evaluation completion

In this protocol, **Study Evaluation Completion (SEC)** is defined as the time when the 28 days safety follow up period is completed. The (primary) reason for study evaluation completion should be recorded in the Study Evaluation Completion eCRF. The reasons for study evaluation completion may include the following:

- Protocol deviation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- 28 Days follow up phase completed as per protocol

All cancer medications/therapies given to a patient during the 28 days following the last dose of study treatment must be recorded in the Antineoplastic therapies since discontinuation of study drug eCRF page.

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.

6.6.8 Emergency unblinding of treatment assignment

Not applicable. This is an open-label study.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an “X” the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. The table indicates which data remain in source documents only (S) or which data remain partly in the source documents and are entered partly into the database (S/D) (this is explained in the footnotes); all other data are entered into the database.

For all visits, there is a ± 3 days window on assessments to take into account scheduling over public or religious holidays **if not explicitly specified otherwise** (please refer to Table 7-4 for PK sampling windows and to Table 7-7 for biomarker sampling windows). In particular, full PK sampling and fasting plasma glucose, fasting c-peptide samplings with multiple post-dose time-points should be performed on the specified day of dosing (Day 1, Day 2, Day 8, Day 9 of Cycle 1 and Days 1 and 2 of Cycle 2) and time-point. In general, where possible, every effort must be made to follow the schedule outlined in Table 7-1.

Assessments which are indicated to be performed at screening/baseline and on cycle 1 day 1, need only to be repeated at cycle 1 day 1 if screening/baseline assessment was more than 3 days earlier.

Blood volumes taken from patients in this study are roughly estimated to be 39-58mL at screening/baseline, 162-183mL during Cycle 1, 103-116ml in cycle 2, 32-53mL per cycle (4 weeks) in subsequent cycles, and 41-51mL at end of study treatment visit depending on enrollment in dose escalation or dose expansion arm and the possible collection of fresh tumor biopsies (and corresponding non-fasting glucose metabolism blood collection) and blood for tumor markers. These volumes may further vary depending on the study sites' local laboratory procedures for clinical safety laboratory analyses.

Following local IRB/EC of protocol amendment 9, the ongoing patients will follow a reduced schedule of assessments (Table 7-2) and the assessments in Table 7-1 will no longer be applicable. Patients will follow the standard of care at the site.

[redacted]

Table 7-1 Visit evaluation schedule (Applicable until protocol amendment 9 is approved by local IRB/EC)

	Pre-screening	Screening/ Baseline	Cycle 1							Cycle 2						Subsequent cycles[26]			End of study treatment (EOT)	Safety follow-up visit / SEC [27]
Visit no.		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**777**	**778**
Day of cycle		**-14 to -1**	**1**	**2**	**8**	**9**	**15**	**22**	**28**	**1**	**2**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤7 days from last dose**	**28 days after last dose**
Informed consent (ICF prescreening) (S)[1]	X																			
PIK3CA status [1]	X																			
Informed consent (ICF general) (S)		X																		
Demography		X																		
Inclusion/ Exclusion criteria (S)		X																		
Relevant medical history/ current medical conditions		X																		
Diagnosis and extent of cancer [2]		X																		
Prior anti-neoplastic therapy		X																		
Prior/concomitant medications		X	CONTINUOUS																	
Height		X																		
Weight		X	X							X						X			X	
Vital signs [3]		X	X		X		X	X		X		X	X	X		X	X		X	
Physical examination [4] (S/D)		X	X				X			X			X			X			X	
Neurological examination (S/D) [5]		X																	X	
WHO performance status		X	X				X			X						X			X	
Chest X-ray [6]		X																		

[redacted]

	Pre-screening	Screening/ Baseline	Cycle 1							Cycle 2						Subsequent cycles[26]			End of study treatment (EOT)	Safety follow-up visit / SEC [27]
Visit no.		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**777**	**778**
Day of cycle		**-14 to -1**	**1**	**2**	**8**	**9**	**15**	**22**	**28**	**1**	**2**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤7 days from last dose**	**28 days after last dose**
Hematology [7]		X	X		X		X	X		X		X	X	X		X	X		X	
Coagulation [8]		X								X									X	
Biochemistry [9]		X	X		X		X	X		X		X	X	X		X	X		X	
Bone marker [10]		X														X			X	
Urinalysis [11]		X	X							X									X	
Serum pregnancy test [12]			X																	
Fasting plasma glucose, insulin, c-peptide (safety) [13]		X	X		X		X			X			X			X	X		X	
Hemoglobin A1c [13]		X														X			X	
Glucose metabolism markers (fasting) [14]				X		X					X									
Glucose metabolism markers (non fasting) [14]		X													X				X	
Cardiac enzymes [15]			X				X			X						X			X	
Cardiac imaging [16]		X																	X	
ECG 12-lead [17]		X	X		X		X	X		X						X			X	
Response assessment (CT or MRI) [18]		X													X			X	X	
Ophthalmologic examination [19]		X																	X	
Adverse events			CONTINUOUS																	
BYL719 dosing			CONTINUOUS daily dosing																	
Fulvestrant dosing			X				X			X						X				

[redacted]

	Pre-screening	Screening/ Baseline	Cycle 1							Cycle 2						Subsequent cycles[26]			End of study treatment (EOT)	Safety follow-up visit / SEC [27]
Visit no.		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**777**	**778**
Day of cycle		**-14 to -1**	**1**	**2**	**8**	**9**	**15**	**22**	**28**	**1**	**2**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤7 days from last dose**	**28 days after last dose**
Blood for tumor markers (as relevant for the cancer, if any) [20]		X													X			X	X	
Blood for PK [21]			X		X					X						X				
Meal record [21]			X		X					X						X				
Archival tumor sample for biomarker assessments [22]	X[23]	X																		
Fresh tumor biopsy [22]	X[23]	X													X				X	
Blood for genetic analysis [24]															X					
[redacted]		[redacted]																	[redacted]	
[redacted]		X																		
Anti-neoplastic therapies since discontinuation of study drug																				X

[1] ICF prescreening has to be signed to allow use of previously obtained *PIK3CA* gene status information or to allow determination of *PIK3CA* gene status of the tumor.

[2] Diagnosis and extent of cancer, including HER2 status and HR status for breast cancer patients.

[3] Vital signs – Sitting blood pressure (diastolic, systolic), sitting pulse (heart rate) and temperature. Vital signs must be monitored at every visit as indicated. In addition, sitting blood pressure and sitting pulse must be monitored on Day 1, Day 8 and Day 1 of Cycle 2, at predose, and at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 24h (prior to the next dose on the next day) after the administration of BYL719, in alignment with the PK time-points and partially with the ECGs.

[4] Physical examination - S/D: data will remain in the source documents except in case of abnormalities which should be entered into the database as either relevant medical history (at baseline) or adverse event (after start of study treatment).

[5] Neurological examination – at screening/baseline visit and must be repeated as clinically indicated and at the end of study treatment visit. The neurological exam should at least include tendon reflexes test, peripheral neuropathy test and Babinski sign test. S/D: data will remain in the source documents except in case of abnormalities which should be entered into the database as either relevant medical history (at baseline) or adverse event (after start of study treatment).

[redacted]

	Pre-screening	Screening/ Baseline	Cycle 1							Cycle 2						Subsequent cycles[26]			End of study treatment (EOT)	Safety follow-up visit / SEC [27]
Visit no.		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**777**	**778**
Day of cycle		**-14 to -1**	**1**	**2**	**8**	**9**	**15**	**22**	**28**	**1**	**2**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤7 days from last dose**	**28 days after last dose**

[6] If a chest CT scan is performed to assess tumor lesions, a chest X-ray is not required.

[7] Hematology – WBC plus differential (total neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts), RBC, hemoglobin, hematocrite, MCH, MCHC,MCV, reticulocyte and platelet counts. To be performed as indicated, weekly for the first 2 cycles, biweekly thereafter in cycle 3 and 4, once per cycle (Days 1, from cycle 5 and beyond) thereafter (unless contra-indicated by the preliminary findings) and at the end of study treatment visit.

[8] Coagulation – PT or INR, aPTT and fibrinogen. The coagulation profile must be performed as indicated and must be repeated as clinically indicated (and in case of bleeding, concomitant anti-coagulant therapy or major GI symptoms).

[9] Biochemistry– Potassium, sodium, calcium, magnesium, ALT, AST, total bilirubin (direct must be collected only in case total bilirubin is elevated > ULN), creatinine, amylase, lipase, alkaline phosphatase, bicarbonate, phosphorus, total cholesterol, HDL, LDL, triglycerides, urea or BUN, albumin, total protein, CRP, LDH, TSH, free T3, free T4, testosterone (for male pts only), FSH (for female pts only) and LH (for female pts only). To be performed as indicated, weekly for the first 2 cycles, biweekly thereafter in cycle 3 and 4, once per cycle (Days 1, from cycle 5 and beyond) thereafter (unless contra-indicated by the preliminary findings) and at the end of study treatment visit. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase needs to be tested as well upon receipt of the chemistry panel results. In addition, basal serum cortisol must be collected between 08:00 and 09:00 AM at screening/baseline visit, Days 1 and 8 of Cycle 1, Day 1 of Cycle 2 and at EOT.

[10] Bone marker CTX -1 (carboxyterminal cross-linked telopeptides of type I collagen) is analyzed in serum. CTX-1 must be assessed at screening/baseline visit, at C3D1 and at EOT.

[11] Urinalysis includes dipstick analysis (protein, glucose, ketones, blood, and specific gravity). A microscopic (WBC/HPF, RBC/HPF, and any additional findings) exam need only be performed if the urinalysis result is abnormal. In case a patient experiences +2 proteinuria, a 24-hour urine collection for total protein and a protein electrophoresis must be performed. The urine dipstick analysis must be repeated during study treatment as scheduled and as clinically indicated.

[12] Serum pregnancy test – must be performed within 72 hrs of dosing on C1D1 (eventually complemented within 72 h prior to C1D1 by a urine pregnancy test if serum test was performed > 72 h prior to C1D1). A urine pregnancy test should be repeated during study treatment as clinically indicated.

[13] Patients must be fasting overnight for at least 8 hours. Fasting insulin/fasting glucose/fasting c-peptide for safety assessment will be collected pre-dose prior to the light breakfast as indicated. Additional measurements may be performed as clinically indicated.

Hemoglobin A1c will be assessed at screening/baseline, Day 1 of every 3rd cycle thereafter and at EOT.

[14] Glucose metabolism markers – fasting glucose and c-peptide will be collected pre-dose, 2h and 4h post-dose at the following time-points: C1D2, C1D9 and C2D2. On these days patients must be fasting overnight for at least 8 hours before administration of BYL719 and an additional 4 hours post-dose (unless medically contra-indicated).

Glucose metabolism markers – non fasting glucose and c-peptide will be collected 4 to 6h post-dose at screening/baseline, C2D28 and End Of Treatment, i.e. at the time of the fresh tumor biopsy For further details see Section 7.10.2.1.

[redacted]

	Pre-screening	Screening/ Baseline	Cycle 1							Cycle 2						Subsequent cycles[26]			End of study treatment (EOT)	Safety follow-up visit / SEC [27]
Visit no.		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	777	778
Day of cycle		-14 to -1	1	2	8	9	15	22	28	1	2	8	15	22	28	1	15	28	≤7 days from last dose	28 days after last dose

[15] Cardiac enzymes - Troponin-I or Troponin-T. C1D1 assessments may be performed up to 72 hours before the date of that visit. Assessments must be performed as indicated and should also be performed whenever clinically indicated or the ECG or cardiac imaging demonstrates possible myocardial ischemia or infarction.

[16] Cardiac imaging (MUGA scan or echocardiogram) - A screening/baseline MUGA scan or echocardiogram to assess LVEF will be performed within 14 days prior to the first administration of BYL719, and may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity. A MUGA scan or echocardiogram will be performed at end of study treatment only if an assessment of LVEF has not been performed ≤ 14 days prior to study completion.

[17] ECG - 3 sequential 12-lead ECGs, separated by at least 5-10 minutes, must be performed prior to the first administration of BYL719 on Day 1 of Cycle 1. This is necessary to get an accurate baseline QTcF calculation. One single ECG will be performed for the other pre-dose ECGs during the trial.

On Day 1, Day 8 of Cycle 1 and Day 1 of Cycle 2, six ECGs will be done (at pre-dose and post-dose at 1h, 2h, 4h, 8h, 24h [before the next dose on the next day]). Moreover, additional pre-dose ECGs will be performed on Day 15 and Day 22 of Cycle 1, and on Day 1 of each subsequent cycle from Cycle 3, and at end of study treatment. All ECGs (except the screening/baseline ECG) will be independently reviewed by a central laboratory. ECGs will be performed per protocol schedule until all patients have potentially completed at least 6 cycles of treatment. After that, ECGs will be done at the discretion of the investigator, they will be recorded as unscheduled ECGs in the CRF and central reading of ECGs will no longer be performed.

Whenever an ECG with a QTcF change from baseline >60 msec or a new absolute QTcF ≥ 501 msec result is observed, an unscheduled PK sample should be obtained and the time of sample collection noted.

[18] Response assessment - according to RECIST Criteria. All potential sites of tumor lesions will be assessed at screening/baseline by radiologic techniques using thoracical, abdominal and pelvic CT or MRI imaging (however CT is the preferred imaging modality to be used in this study), complemented with brain scan in case of clinical evidence of brain metastatic disease. In addition, a bone scan should be performed for all patients with clinical evidence of bone metastases. Subsequent scans are done at the end of Cycle 2, and every 8 weeks thereafter (i.e. at the end of Cycles 4, 6, 8, etc), and at study treatment completion. All assessments should be performed within 7 days prior to the scheduled day of assessment. The assessment at the end of study treatment visit is only to be performed if the prior assessment occurred ≥ 21 days before.

[19] Ophthalmologic exam - a slit lamp exam must be performed as indicated and must be repeated during study treatment as clinically indicated. This examination should be performed by an ophthalmologist.

[20] Tumor markers (PSA, CEA, CA19-9 etc.) will be assessed as relevant for the respective cancer type (if any).

Blood for tumor marker assessments will be collected at screening/baseline and - only if documented to have measurable baseline levels – at the same visit the CT/MRI is performed, on Day 28 of Cycle 2 and every other cycle (or within 72 hours of that day) afterwards and at end of study treatment if this has not been evaluated ≤ 21 days prior to this day.

[21] Blood for PK - Full pharmacokinetic sampling of BYL719 will be performed on Day 1, Day 8 of Cycle 1 and Day 1 of Cycle 2 (at pre-dose and at 0.5h, 1h, 1.5h, 2h, 3h,

[redacted]

	Pre-screening	Screening/ Baseline	Cycle 1							Cycle 2						Subsequent cycles[26]			End of study treatment (EOT)	Safety follow-up visit / SEC [27]
Visit no.		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**777**	**778**
Day of cycle		**-14 to -1**	**1**	**2**	**8**	**9**	**15**	**22**	**28**	**1**	**2**	**8**	**15**	**22**	**28**	**1**	**15**	**28**	**≤7 days from last dose**	**28 days after last dose**

4h, 6h, 8h, 24h post-dose) in all patients treated on the daily dosing schedule (note that the 24h post-dose sample should be taken prior to the next BYL719 administration). Pre-dose (trough) samples will be collected on Day 1 of every cycle from Cycle 3 (i.e. Cycles 3, 4, 5, etc.) in all patients. For further details (including sampling schedule if an alternative dosing schedule is adopted) please see Section 7.9. A meal record should be completed on days of PK assessment. After all patients have potentially completed at least 6 cycles of treatment, PK samples will no longer be collected for any patient.

Whenever an ECG with a QTcF change from baseline >60 msec or a new absolute QTcF ≥ 501 msec result is observed, an unscheduled PK sample should be obtained and the time of sample collection noted. Whenever a ≥ CTCAE grade 2 rash is diagnosed, an unscheduled PK sample should be collected (within 10-15min after performing the biopsy).

[22] Fresh pre- and post-treatment tumor biopsies for biomarker analyses should be obtained whenever feasible and accessible according to the investigator's judgment at baseline, C2D28 and disease progression, The C2D28 sample should be taken within 24h of the radiological assessment, or if not feasible within 5 days before and within 24h after. The disease progression sample should be taken within 3 days post-BYL719 dose. If archival tumor tissue is not available, a fresh tumor biopsy must be provided instead before starting study drug. See Section 7.10.1.1 for further details.

[23] If an archival or fresh tumor biopsy is submitted for central *PIK3CA* gene status assessment at a Novartis designated lab during pre-screening, an additional tumor specimen is not required at screening. If during pre-screening a biopsy was performed to establish the *PIK3CA* gene status at a local laboratory then this sample may be shipped following enrollment and an additional biopsy at screening need not be performed.

[24] A blood sample for genetic analysis should be taken at end of cycle 2 and at the end of study treatment (see Section 7.10.2.2).

[25] Should be taken at screening/baseline (If this is not feasible, it can be at any time during the study) A blood sample for viral load and ELISPOT should be repeated at the first onset of grade ≥2 rash and again if grade ≥2 rash re-occurrs. (see Table 7-5)

[26] Following completion of cycle 6 patients no longer need to attend the visit on cycle day 15. However, this visit may continue at the discretion of the Investigator.

[27] All patients who discontinue study treatment, including those who refuse to return the EOT visit, should be contacted (either by visit, telephone or mail) for safety evaluations ≤ 28 days following the last dose of BYL719. Antineoplastic therapies since discontinuation of study drug and the Study Evaluation Completion (SEC) (778) eCRF pages must be completed at this visit.

[redacted]

Table 7-2 Visit evaluation schedule (Applicable upon local IRB/EC approval of protocol amendment 9)

Assessment	Treatment Phase (visit every 3 months)	End of study treatment (EOT)	Safety follow-up visit (SEC) (≤ 28 days)[1]
Adverse events	Continuous		
Concomitant medications	Continuous		
BYL719 dosing	Continuous daily dosing		
Fulvestrant dosing	Monthly[2]		
End of study treatment page		X	

Note: All other assessments are performed as per standard of care at the site and will not be captured in the CRF.

[1] All patients who discontinue study treatment, including those who refuse to return the EOT visit, should be contacted (either by visit, telephone or mail) for safety evaluations ≤ 28 days following the last dose of BYL719. Antineoplastic therapies since discontinuation of study drug and the Study Evaluation Completion (SEC) (778) eCRF pages must be completed at this visit.

[2] Patients in the fulvestrant combination arm are required to visit monthly for fulvestrant administration

[redacted]

7.1 Information to be collected on screening failures

For patients who fail screening, the only information collected on the eCRF will be the screening log and the demography page.

7.2 Patient demographics/other baseline characteristics

The data that will be collected on patient characteristics at screening/baseline should comprise all information about the diagnosis and extent of their tumor disease (including date of initial diagnosis, date at first and latest relapse (i.e. latest disease progression)), previous anticancer therapies, thorax-abdominal-pelvic CT-scan, brain CT/MRI (when clinically indicated), bone scan (when clinically indicated), vital signs, full hematology, biochemistry, coagulation, urine analysis, physical exam (including brief neurological exam), height, biomarker assessment (see Section 7.10), and cardiac functioning (ECG, ECHO/MUGA scan).

The information on the tumor should specify the histological type (including differentiation status), *PIK3CA* gene status, HER2 status (where appropriate), ER/PR status (in case of breast cancer), and the initial TNM stage/disease stage at first diagnosis.

7.3 Treatments

The study treatment will be administered until the patient experiences progressive disease or unacceptable toxicity (for details please refer to Section 6.6)

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the caregiver. Records of study medication used (taken, lost, destroyed and returned) and intervals between visits should be captured in the source document at each visit. Drug accountability will be noted by the field monitor during site visits and at the time of study treatment completion.

7.4 Efficacy

Following local IRB/EC approval of protocol amendment 9. no efficacy assessments are required to be collected by the protocol. Efficacy assessments may be performed following local standard of care.

7.4.1 Efficacy assessment

Tumor assessments will be performed for all patients in the dose-escalation arm and the MTD dose-expansion arm (Section 7.4.2).

Once the sites have received the amendment 2 approval, FDG-PET imaging should no longer

be performed on patients enrolling in the study. Patients already ongoing at this time should have follow up FDG-PET scans performed at cycle 1 day 28 and cycle 2 day 28.

Evaluation of tumor markers as potential surrogate indicators of efficacy may be done as relevant for the respective cancer type (Section 7.4.3).

[redacted]

7.4.2 Tumor response

All potential sites of tumor lesions will be assessed at screening/baseline by radiological techniques using thoracical, abdominal and pelvic CT or MRI imaging (however, CT is the preferred imaging modality to be used in this study) complemented with brain scan in case of clinical evidence of brain metastatic disease, or if appropriate, by physical examination (e.g., subcutaneous nodules). Patients with clinical evidence of bone metastases must have a bone scan with confirmatory X-rays at baseline. Repeat bone scans with confirmatory X-rays will be performed as clinically indicated and when complete response is documented. Ultrasound should not be used to measure tumor lesions.

Each lesion that is documented at screening/baseline must be measured by the same method throughout the study to ensure that a comparison between each scan can be made. Whilst the patient is enrolled in the study, follow-up CT/MRI scanning must occur at the frequency indicated in the visit assessment schedule or as clinically indicated. All tumor assessments should be performed within 7 days prior to the scheduled day of assessment, except for the bone scan which will be performed at the discretion of the investigator (see Table 7-1). In the event that a patient is discontinued from treatment for any reason other than progression, an end of study CT/MRI is recommended to be performed only if it has not been done ≤ 21 days prior to this day. Throughout the trial, the modified RECIST criteria [Post-text Supplement 1] must be applied when assessing any responses to BYL719 treatment. All complete and partial responses must be confirmed by a second assessment at least 4 weeks later.

The CT/MRI scans should be contiguous throughout the anatomical regions of interest, with the same window setting at each visit. An adequate amount of contrast agent should be consistently given, so that the tumor lesions appear with good resolution. All known lesions (measurable, non measurable) should be accounted for at baseline when assessing objective tumor status. For subsequent scans in the same patient the radiologist must account for all lesions that were present at baseline and must use the same technique as used at baseline. If possible, a single radiologist should perform all evaluations for an individual patient.

Tumor lesions assessed by physical examination must be measured on Day 1 of each cycle and at end of study treatment.

Note: any lesions that have been previously treated with radiotherapy should not be used as target lesions for tumor assessment. Exceptions may be made when these lesions are the only lesions available for evaluation and have shown definite progression since their last radiation treatment.

Whenever possible, patients discontinuing from the study for a progressive disease must have their disease progression documented by radiological evaluation.

7.4.3 Tumor markers

Tumor markers (PSA, CEA, CA 19-9, soluble mesothelin peptides, etc., as relevant for the respective cancer type, if any) may be assessed as per discretion of the investigator.

Blood for tumor marker assessments will be collected at Screening/baseline and - only if documented to have measurable baseline levels - at the same visit the CT/MRI is performed, on Day 28 of Cycle 2 and every other cycle afterwards or within 72 hours of that day and at

[redacted]

end of study treatment if this has not been evaluated ≤ 21 days prior to this day (see Table 7-1). The sampling procedure will be done as per the institutions' standards and the analysis will be performed by the institutions' local laboratories.

7.5 Safety

Safety assessments will consist of monitoring, by investigators, and recording all adverse events, serious adverse events, and the regular monitoring of laboratory evaluations, physical examination (including neurological examination), weight, vital signs, ophthalmologic examination, fasting glucose monitoring and repeat cardiac assessments including ECG, cardiac imaging, cardiac enzymes and concomitant medications.

It is important that the patient reports all concomitant medications in order to put the clinical observations in the right context.

Following the implementation of protocol amendment 9, the ongoing patients will follow a reduced schedule of assessments and the only safety collected will be adverse events, including serious adverse events. Other assessments may be performed at the Investigator's discretion following standard of care at the site.

7.5.1 Adverse events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s). Please refer to Section 6.1 for the protocol-specific definitions of study drug and study treatment.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0, unless otherwise specified (e.g. hyperglycemia, see also Table 6-4). If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, **or** grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment or Study Evaluation Completion eCRF page. Disease progression itself is not an adverse event or serious adverse event. If disease progression is the primary reason for end of study treatment it should only be reported on the End of Treatment eCRF and documented in the appropriate disease specific response eCRFs. Adverse events (i.e. undesirable signs, symptoms, or medical conditions) secondary to disease progression may be recorded as an Adverse Event or as a Serious Adverse Event if meeting the definition and occurring within 28 days of the last dose of study drug. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Adverse Events Electronic Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g.,

[redacted]

cause study interruption or discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events eCRF. SAEs occurring after signing the Informed Consent are recorded on the Adverse Event eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during 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 relationship to BYL719 (suspected/not suspected)
3. Its duration (start and end dates or if continuing at 28 days after the last dose)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined as one which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - 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
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- 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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure or will be communicated between IB updates in the form

[redacted]

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.

Adverse event monitoring should be continued for ≥ 28 days following the last dose of study drug.

7.5.2 Physical examination, neurological examination, weight, height

Physical examination, neurological examination, height (screening/baseline only) and weight must be performed as indicated in Table 7-1. These examinations will be performed according to the standards at each institution.

Physical Examinations and weight will be performed on the scheduled day, even if study medication is being withheld. More frequent examinations may be performed at the investigator's discretion and/or if medically indicated. If the screening/baseline examinations are performed ≤ 72 hours prior to the first dose of BYL719, they need not be repeated on Day 1 of Cycle 1. The physical examination comprises a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes and extremities. Special attention should be paid to possible clinical evidence of bone metastatic disease).

Neurological examination will be performed at the screening/baseline visit and must be repeated as clinically indicated and at the end of study treatment visit. The neurological exam should at least include tendon reflexes test, peripheral neuropathy test and Babinski sign test. Special attention should be paid to possible clinical evidence of brain metastatic disease.

Information about the physical and neurological examinations must be present in the source documentation at the study site by specifying the observed abnormalities. Significant findings present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions eCRF. Significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event eCRF. Body weight, and height (screening/baseline only) will be recorded on the eCRF page for vital signs.

7.5.3 Vital signs

Vital signs (monitoring assessment of temperature, sitting blood pressure, and sitting pulse) must be performed at the following times points:

- Screening/baseline
- Every study visit during the study treatment phase (except on days where only radiological assessments (C1D28, C2D28 and D28 of every other cycle) or fasting glucose metabolism assessments (C1D2, C1D9 and C2D2 are performed)).
- End of study treatment

In addition for patients sitting blood pressure and sitting pulse must be monitored on Day 1, Day 8 of Cycle 1 and Day 1 of Cycle 2 at predose, and at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 24h (prior to the next dose on the next day) after the administration of BYL719, in alignment with the PK time-points.

[redacted]

Vital signs should be assessed on the scheduled day, even if study medication is being withheld. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

7.5.4 Performance status

WHO performance status will be documented at:

- Screening/baseline
- Cycle 1: Day 1* and Day 15
- Day 1 of Cycle 2 and each subsequent treatment cycle
- End of study treatment

Assessment of WHO Performance Status will be performed on the scheduled day, even if study medication is being held.

*Note: If the screening/baseline assessment was performed ≤ 72 hours prior to the first dose of BYL719, then it does not need to be repeated on Day 1 of Cycle 1 unless the patients overall well being has changed.

Table 7-3 WHO performance status scale

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 housework, 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.

7.5.5 Laboratory evaluations

The standard clinical laboratory analyses described below are to be performed by the study site's local laboratories according to the Visit Schedule, outlined in Table 7-1. Local laboratory tests will be collected and analyzed on the scheduled day, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion if medically indicated; those results should be recorded on the Unscheduled Visit eCRFs.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded in the laboratory and/or adverse events eCRF pages. When abnormal laboratory values or test results constitute an adverse event, they must be recorded on the eCRF Adverse Events page.

Novartis will be provided with a copy of the laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept up to date on an ongoing basis. In addition, 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 for that laboratory.

[redacted]

7.5.5.1 Hematology

Hematology includes the following parameters: complete blood count consisting of red blood cells (RBCs), a total white blood cell count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, basophil counts and others), hemoglobin (Hgb), hematocrite (Hct), MCH, MCHC, MCV, reticulocyte and platelet counts.

Hematology must be performed at:

- Screening/baseline
- Day 1 of each cycle prior to the administration of BYL719 or ≤ 72 hours prior to dosing intended Day 1 of each cycle (if BYL719 is being withheld)
- Days 8, 15, 22 of Cycle 1 (on or within 24 hours)
- Days 8, 15, 22 of Cycle 2 (on or within 24 hours)
- Day 15 of Cycle 3 and Cycle 4 (on or within 24 hours)
- End of study treatment

7.5.5.2 Coagulation

The coagulation profile includes prothrombin time or INR, activated partial thromboplastin time and fibrinogen.

A coagulation profile must be performed at:

- Screening/baseline
- ≤ 72 hours prior to dosing on Day 1 of Cycle 2
- Repeat assessments as clinically indicated (and in case of bleeding, concomitant anti-coagulant therapy or major GI symptoms)
- End of study treatment

7.5.5.3 Biochemistry

Biochemistry includes the following parameters: potassium, sodium, calcium, magnesium, ALT, AST, total bilirubin (direct must be collected only in case total bilirubin is elevated > ULN), creatinine, urea or BUN, amylase, lipase, alkaline phosphatase, bicarbonate, phosphorus, total cholesterol, HDL, LDL, triglycerides, albumin, total protein, LDH, C-Reactive Protein (CRP), TSH, free T3, free T4, testosterone (for male pts only), FSH (for female pts only) and LH (for female pts only). In patients with serum triglycerides ≥ 500 mg/dL, urine amylase needs to be tested as well upon receipt of the chemistry panel results.

Biochemistry analysis must be performed at:

- Screening/baseline
- Day 1 of each cycle prior to the administration of BYL719 (or ≤ 72 hours prior to dosing) intended day 1 of each cycle (if BYL719 is being withheld)
- Days 8, 15, 22 of Cycle 1 (on or within 24 hours)
- Days 8, 15, 22 of Cycle 2 (on or within 24 hours)
- Days 15 of Cycle 3 and Cycle 4 (on or within 24 hours)
- End of study treatment

[redacted]

In addition basal serum cortisol must be collected between 08:00 and 09:00 AM at screening/ baseline visit, Days 1 and 8 of Cycle 1, Day 1 of Cycle 2 and at EOT.

7.5.5.4 Bone marker

CTX -1 (carboxyterminal cross-linked telopeptides of type I collagen) to assess bone turnover will be analyzed in serum at the following time-points:

- Screening/baseline
- Day 1 of Cycle 3
- End of study treatment

7.5.5.5 Cardiac enzymes

See Section 7.5.7 Cardiac assessment.

7.5.5.6 Glucose/insulin safety monitoring

Fasting serum insulin, fasting serum C-peptide and Fasting Plasma Glucose (FPG) for insulin and glucose safety monitoring will be assessed pre-dose prior to the light breakfast at the following time-points:

- Screening/baseline
- Pre-dose on Days 1, 8, 15 of Cycle 1
- Pre-dose on Days 1 and 15 of Cycle 2
- Pre-dose on Days 1 and 15 of each cycle from Cycle 3 onwards
- End of study treatment

Patients must be fasting overnight for at least 8 hours. Additional measurements may be performed as clinically indicated.

Hemoglobin A1c testing for hyperglycemia will be assessed at the following time-points:

- Screening/baseline
- Pre-dose Day 1 of Cycle 3 and Day 1 of every subsequent 3 cycles (i.e. Cycles 6, 9, etc.)
- End of study treatment

Fasting glucose, insulin & C-peptide for safety, as well as hemoglobin A1c will be measured at the local laboratory(s). The sample collection date and lab results must be entered on the Lab Results eCRF page.

Additional samples for both fasting and non-fasting glucose & C-peptide biomarker glucose metabolism assessment will be taken in all patients at several time-points (for further details and time-points see Section 7.10.2.1). These samples will be analyzed centrally at a designated CRO.

7.5.5.7 Urinalysis

Urinalysis includes dipstick analysis (protein, glucose, ketones, blood, and specific gravity). A microscopic (WBC/HPF, RBC/HPF, and any additional findings) exam need only be

performed if the urinalysis result is abnormal. Urinalysis must be performed at the following times unless otherwise specified:

- Screening/baseline *
- Pre-dose Day 1 of Cycle 1 and Cycle 2
- Repeat assessment during study treatment as clinically indicated.
- End of study treatment

* **Note:** If at Screening/baseline there is documentation of [+2] result or higher for protein from urinalysis, a 24-hour urine collection for total protein and measured creatinine clearance (CrCl) must be obtained at baseline. Whenever a 24-hour urine collection is performed, the total volume of urine must be recorded on the appropriate eCRF. Whenever a measured CrCl is obtained, a serum creatinine should be obtained within ≤ 72 hours of the urine collection.

During the study, if a patient experiences [+2] proteinuria or CTCAE ≥ grade 2 hematuria, or serum creatinine ≥ 2.0 x ULN, a 24-hour urine collection for total protein and total creatinine must be repeated at least weekly until resolution to baseline value to allow for re-treatment, or until stabilization (Table 6-3).

If a patient develops [+2] proteinuria, then urine protein electrophoresis must be performed during the first weekly 24-hour urine collection, and the relative % distribution of protein fractions including albumin, α1-globulin, α2- globulin, β-globulin, and γ-globulin should be recorded in the appropriate eCRF.

7.5.5.8 Pregnancy test

All females of childbearing potential (pre-menopausal or less than 12 months after the onset of menopause) should have a serum pregnancy test (β-HCG) (eventually complemented (≤ 72 h prior to cycle 1 day 1) by a urine pregnancy test if serum test > 72 h) at the following time unless otherwise specified:

- Cycle 1 Day 1 (prior to the administration of BYL719 or ≤ 72 hours prior to dosing)
- Repeat assessment (urine pregnancy test only) during study treatment as clinically indicated.

Note: Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered "of non-childbearing potential". This should be documented appropriately in the patient's medical history.

7.5.6 Radiological examinations

The following radiological examinations should be conducted as required by the protocol or clinically indicated (for specific tumor types). For each patient, if an initial radiological assessment is conducted using one imaging modality, all radiological assessments in subsequent cycles should always be conducted using the same technique.

7.5.6.1 Chest X-ray

A chest X-ray must be performed at screening/baseline and should be repeated if clinically indicated. If a chest CT is performed at screening/baseline to assess tumor lesions, then a chest X-ray is not required.

7.5.7 Cardiac assessments

7.5.7.1 Electrocardiogram (ECG)

For all patients prior to the first administration of BYL719 a minimum of 3 sequential 12-lead ECGs, separated by at least 5-10 minutes, must be performed on Day 1 of Cycle 1. This is necessary to get an accurate baseline QTcF calculation. One single ECG will be performed for the other time-points during the trial. 12-lead ECGs are to be performed at the following time-points:

- Screening/baseline
- Day 1 of Cycle 1: pre-dose (3 times), post-dose at 1h, 2h, 4h, 8h, 24h (before the next dose on the next day)
- Day 8 of Cycle 1: pre-dose, post-dose at 1h, 2h, 4h, 8h and 24h (before the next dose on the next day)
- Day 15 and Day 22 of Cycle 1: pre-dose
- Day 1 of Cycle 2: pre-dose, post-dose at 1h, 2h, 4h, 8h and 24h (before the next dose on the next day)
- Day 1 of Cycle 3 and of each subsequent cycle: pre-dose
- End of study treatment

All ECGs (except the screening/baseline ECG) will be independently reviewed by a central laboratory. Instructions for the collection and transmission of ECGs to the independent reviewer will be provided in the BYL719X2101 Lab Manual. Significant findings must be recorded either as Relevant Medical History/Current Medical Conditions (if present before treatment) or as Adverse Events (if newly occurring or worsening since starting treatment).

Whenever an ECG with a QTcF change from baseline > 60 msec or a new absolute QTcF ≥ 501 msec result is observed, an unscheduled PK sample to assess concentration of BYL719 should be obtained and the time of sample collection noted (see also Table 7-4).

ECGs will be performed per protocol schedule until all patients have potentially completed at least 6 cycles of treatment. After that, ECGs will be done at the discretion of the investigator and will be recorded as unscheduled ECGs in the CRF.

7.5.7.2 Cardiac enzymes

Cardiac troponin (troponin-I or troponin-T) will be collected:

- Day 1 of Cycle 1 (prior to the administration of BYL719 or ≤ 72 hours prior to dosing).
- Day 15 of Cycle 1
- Day 1 of Cycle 2 and every subsequent cycle.
- Whenever clinically indicated or the ECG or cardiac imaging demonstrates possible myocardial ischemia or infarction.
- End of study treatment

[redacted]

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

A baseline MUGA scan or echocardiogram to assess LVEF will be performed within 14 days prior to the first administration of BYL719, and may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity.

A MUGA scan or echocardiogram will be performed at end of study treatment only if an assessment of LVEF has not been performed ≤ 14 days prior to study completion.

7.6 Tolerability

Not applicable.

7.7 Resource utilization

Not applicable.

7.8 Patient-reported outcomes

Not applicable.

7.9 Pharmacokinetics

Following local IRB/EC approval of protocol amendment 9, no pharmacokinetic assessments are required by the protocol.

The blood sampling regimen for determining the pharmacokinetics of BYL719 after single (C1D1) and multiple oral doses (all other time-points) is given in Table 7-1. Blood for the full pharmacokinetic profiling of BYL719 will be collected on Day 1, Day 8 of cycle 1 and Day 1 of Cycle 2. Only pre-dose (trough level) samples will be collected on Day 1 of every cycle from Cycle 3 (i.e. Cycles 3, 4, 5, etc.) onwards. The sampling scheme as outlined in Table 7-4 and Table 7-5 will determine both the single dose and multiple dose (steady-state) pharmacokinetics of BYL719. As mentioned in Section 4 and Section 6.2, if the evaluation of emerging data of BYL719 indicate that it may be desirable to give BYL719 as a twice daily dosing schedule (b.i.d.) then a new cohort of patients will be enrolled and treated with a b.i.d or every other day dose that is less than the maximum tolerated single daily dose. A dosing schedule modification would be based on PK, PD and/or safety assessments and factors such as very a short half-life or a plateau in exposure with increasing doses observed with once daily dosing. In case a b.i.d. dosing schedule would be put in place, a 10 hour post-morning dose sample would be collected, instead of the 8 hour post-dose sample. This 10 hour post-morning dose sample would be the pre-evening dose sample. The PK blood collection time-points are detailed in Table 7-4 for the daily dosing schedule, and in Table 7-5 for a b.i.d. dosing schedule.

Blood samples for BYL719 plasma concentration-time profiles will be collected on all patients in the study.

The collection time of all samples must be documented in the Pharmacokinetic Blood Collection eCRF pages. The exact time of oral BYL719 dosing, date sample taken, and actual time of sampling must be entered on the eCRF. Any sampling problems (e.g., patient took

study drug before a pre-dose sample) must be noted in the comments section of the eCRF. On days and time-points when blood samples for biomarkers and pharmacokinetics are to be performed, the pharmacokinetic sample must be drawn first. A meal record should be completed on the eCRF on days of PK assessment.

On the days of full pharmacokinetic sampling (C1D1, C1D8 and C2D1), patients should take their medication at the clinic. Patients who forget to postpone their dose on these days and take their medication at home will be excluded from pharmacokinetic blood sampling for that day; they should not have blood samples collected.

On the days of full pharmacokinetic sampling, the exact time of any episodes of vomiting within the first 24 hours post-dosing on that day must be noted in a separate section of the eCRF. Similarly, in case of any increase of stool frequency (i.e. diarrhea) within the first 24 hours post-dosing on that day, this should also be documented in a separate section of the eCRF.

Drug administration guidelines for BYL719 on the days of full pharmacokinetic sampling (and any other day) are provided in Section 6.6.1.1.

The days of full pharmacokinetic blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. Therefore, patients taking medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. An intermittent concomitant medication should be avoided on the days of full pharmacokinetic sampling.

Whenever an ECG with a QTcF change from baseline > 60 ms or a new absolute QTcF ≥ 501 ms result is observed, a plasma sample to assess concentration of BYL719 should be obtained and the time of sample collection noted. Whenever a ≥ CTCAE grade 2 rash is diagnosed, an unscheduled PK sample should be collected to assess the concentration of BYL719 (within 10-15min after performing the biopsy) and the time of sample collection noted.

A detailed description of the planned pharmacokinetic analyses is given in Section 10.5.6.

After all patients have potentially completed at least 6 cycles of treatment, PK samples will no longer be collected for any patient.

7.9.1 Pharmacokinetic blood sample collection and handling

The pharmacokinetic blood sampling collection plan is presented in Table 7-4 for the daily dosing schedule, and in Table 7-5 for a b.i.d. dosing schedule. All pharmacokinetic blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

Please refer to the BYL719X2101 Lab Manual for detailed instructions for the collection, handling, and shipping of samples.

Table 7-4 PK blood collection plan daily dosing schedule

Cycle	Day	PK coll. No.	Sample. No.	Scheduled time relative to dosing
1	1	1	101	Pre-dose*
1	1	1	102	0.5 hour post-dose ± 10 min
1	1	1	103	1 hour post-dose ± 10 min
1	1	1	104	1.5 hour post-dose ± 10 min
1	1	1	105	2 hour post-dose ± 15 min
1	1	1	106	3 hour post-dose ± 30 min
1	1	1	107	4 hour post-dose ± 30 min
1	1	1	108	6 hour post-dose ± 30 min
1	1	1	109	8 hour post-dose ± 60 min
1	2	1	110	24 hour post-dose ± 120 min ***
1	8	2	111	Pre-dose*
1	8	2	112	0.5 hour post-dose ± 10 min
1	8	2	113	1 hour post-dose ± 10 min
1	8	2	114	1.5 hour post-dose ± 10 min
1	8	2	115	2 hour post-dose ± 15 min
1	8	2	116	3 hour post-dose ± 30 min
1	8	2	117	4 hour post-dose ± 30 min
1	8	2	118	6 hour post-dose ± 30 min
1	8	2	119	8 hour post-dose ± 60 min
1	9	2	120	24 hour post-dose ± 120 min ***
2	1	3	121	Pre-dose*
2	1	3	122	0.5 hour post-dose ± 10 min
2	1	3	123	1 hour post-dose ± 10 min
2	1	3	124	1.5 hour post-dose ± 10 min
2	1	3	125	2 hour post-dose ± 15 min
2	1	3	126	3 hour post-dose ± 30 min
2	1	3	127	4 hour post-dose ± 30 min
2	1	3	128	6 hour post-dose ± 30 min
2	1	3	129	8 hour post-dose ± 60 min
2	2	3	130	24 hour post-dose ± 120 min ***
3	1	4	131	Pre-dose*
4	1	5	132	Pre-dose*
5, 6, etc.	1	6, 7, etc.	133,134,etc.	Pre-dose*
NA	NA	NA	100X**	Unscheduled (i.e. QTcF change from baseline > 60 ms or a new absolute QTcF ≥ 501 ms or rash ≥ CTCAE grade 2)

[redacted]

Cycle	Day	PK coll. No.	Sample. No.	Scheduled time relative to dosing
* Take sample immediately prior to the next BYL719 administration. ** Unscheduled blood samples will be uniquely, sequentially numbered 1001, 1002, etc. *** 24 hour samples should be obtained prior to the next BYL719 administration. On days and time-points when blood for pharmacodynamic markers and for pharmacokinetics is sampled, the pharmacokinetic sample must be drawn first. No time window for full PK sampling on C1D1, C1D8 and C2D1 is allowed. These must be performed on the specific day. Blood volume total for daily BYL719 dosing schedule: Cycle 1: 60ml, Cycle 2: 30ml, from Cycle 3: every cycle 3ml per cycle.				

Table 7-5 PK blood collection plan b.i.d. dosing schedule

Cycle	Day	PK coll. No.	Sample. No.	Scheduled time relative to dosing
1	1	1	201	Pre-morning dose*
1	1	1	202	0.5 hour post-dose ± 10 min
1	1	1	203	1 hour post-dose ± 10 min
1	1	1	204	1.5 hour post-dose ± 10 min
1	1	1	205	2 hour post-dose ± 15 min
1	1	1	206	3 hour post-dose ± 30 min
1	1	1	207	4 hour post-dose ± 30 min
1	1	1	208	6 hour post-dose ± 30 min
1	1	1	209	Pre-evening dose (10 hour post-morning dose ± 120 min) ***
1	2	2	210	Pre-morning dose *
1	8	3	211	Pre-morning dose*
1	8	3	212	0.5 hour post-dose ± 10 min
1	8	3	213	1 hour post-dose ± 10 min
1	8	3	214	1.5 hour post-dose ± 10 min
1	8	3	215	2 hour post-dose ± 15 min
1	8	3	216	3 hour post-dose ± 30 min
1	8	3	217	4 hour post-dose ± 30 min
1	8	3	218	6 hour post-dose ± 30 min
1	8	3	219	Pre-evening dose (10 hour post-morning dose ± 120 min) ***
1	9	4	220	Pre-morning dose *
2	1	5	221	Pre-morning dose*
2	1	5	222	0.5 hour post-dose ± 10 min
2	1	5	223	1 hour post-dose ± 10 min
2	1	5	224	1.5 hour post-dose ± 10 min
2	1	5	225	2 hour post-dose ± 15 min
2	1	5	226	3 hour post-dose ± 30 min
2	1	5	227	4 hour post-dose ± 30 min
2	1	5	228	6 hour post-dose ± 30 min

Cycle	Day	PK coll. No.	Sample. No.	Scheduled time relative to dosing
2	1	5	229	Pre-evening dose (10 hour post-morning dose ± 120 min) ***
2	2	6	230	Pre-morning dose *
3	1	7	231	Pre-morning dose*
4	1	8	232	Pre-morning dose*
5, 6, etc.	1	9,10, etc.	233,234,etc.	Pre-morning dose*
NA	NA	NA	200X**	Unscheduled (i.e. QTcF change from baseline > 60 ms or a new absolute QTcF ≥ 501 ms or rash ≥ CTCAE grade 2)

* Take sample immediately prior to the next BYL719 administration.

** Unscheduled blood samples will be uniquely, sequentially numbered 2001, 2002, etc.

*** 10 hour post-morning dose sample should be obtained prior to evening dose (is the pre-evening dose sample).

On days and time-points when blood for pharmacodynamic markers and for pharmacokinetics is sampled, the pharmacokinetic sample must be drawn first.

No time window for full PK sampling on C1D1, C1D8 and C2D1 is allowed. These must be performed on the specific day.

Blood volume total for b.i.d. BYL719 dosing schedule: Cycle 1: 60ml, Cycle 2: 30ml, from Cycle 3: every cycle 3ml per cycle.

7.9.2 Analytical method

BYL719 concentrations in plasma will be determined by a validated bioanalytical method with an anticipated lower limit of quantification (LLOQ) of approximately 1 ng/mL and may be improved according to eventual needs for a higher sensitivity.

In addition to BYL719 analysis, exploratory BYL719 metabolite analysis on remaining plasma material may be performed using a non-validated, semi-quantitative or qualititave LC-MS/MS method, if deemed appropriate.

7.10 Biomarkers

Following local IRB/EC approval of protocol amendment 9, no biomarker assessments are required by the protocol.

Multiple biomarkers relevant to the mechanism of action of BYL719 have been incorporated into this study and are summarized in Table 7-6. These biomarkers will be evaluated for their use for assessing the effect of BYL719 as a single agent or in combination with fulvestrant at a molecular level, correlation with clinical outcome and also to possibly aid in determining optimal biological dose.

If in the course of evaluating the human pharmacodynamics of BYL719, it is determined that an alternative sampling scheme would yield more information, then that alternative sampling scheme may be implemented as long as the total number of samples or total blood volume is not increased. Likewise, the total number of samples may be decreased if the initial sampling scheme is considered unnecessarily intensive.

[redacted]

Table 7-6 Biomarker sampling and schedule

Sample	Sample type	Time-point
Tumor tissue	Archival	Screening/baseline
	Fresh tissue	Screening/baseline (pre-BYL719 dose)
		C2D28 (4 to 6h post-BYL719 dose)
		Disease progression (preferably 4-6H post last BYL719 dose) or up to 3 days following last dose
Blood	Serum for glucose metabolism markers (glucose/c-peptide)	C1D2, C1D9, C2D2 fasting
		Screening/baseline (C2D28, disease progression non-fasting
	Whole blood for genetic analysis	C2D28
	Whole blood for [redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

7.10.1 Biomarker assessments in tumor samples

Tumor tissues samples (archival or fresh biopsy) will be required for all patients prior to starting study drug. Paired pre- and post-treatment fresh tumor samples should be collected for all patients unless not feasible and/or accessible, and at least 8 analyzable pre- vs. post-treatment pairs during dose expansion will be collected in this trial. If feasible, collection of a tumor biopsy is encouraged upon patient relapse. The tumor (archival and/or fresh) material collected in this trial will be used to:

1. Determine *PIK3CA* gene status (mutations and amplifications) in patients pre-screened by a Novartis approved laboratory. Investigate BYL719 effects as single agent and in combination with fulvestrant on molecular signaling and tumor cell responses (see also Section 1.3.4.1 and Section 1.3.4.2)
2. Identify potential biomarkers predictive of efficacy (see also Section 1.3.4.3)
3. Investigate potential mechanisms of resistance to BYL719 alone or in combination with Fulvestrant.

Remaining tumor material may be used for additional analysis of other potential relevant biomarkers related to BYL719, disease and/or safety of the patients. Analysis would depend upon reagent and/or tissue availability, and on responses seen in patients.

7.10.1.1 Collection of tumor samples

During Pre-screening: If the site is unable to establish the *PIK3CA* gene status, the sample must be sent to a Novartis approved laboratory for central testing. Once the required PIK3CA

[redacted]

gene status has been documented, the patient may sign the study's main Informed Consent (IC) and can continue to be screened for enrollment. An additional tumor sample (archival or fresh) does not need to be collected during screening from patients that provide tumor material during pre-screening.

During screening/baseline: Archival formalin-fixed paraffin-embedded (FFPE) tumor samples, representing original diagnostic material and/or a prior tissue-proven recurrence, must be collected from all patients (see inclusion criterion 2). The corresponding pathology report will be sent, if available. For patients with locally documented *PIK3CA* alteration, these samples must be provided to Novartis within 4 weeks of starting study drug. If archival tumor tissue is not available, a fresh tumor biopsy must be provided instead. It is highly recommended that this material is provided as paraffin blocks. If not possible, at least 20-25 paraffin-dipped unstained slides (freshly cut) must be made available for biomarker studies.

During the study: Collection of fresh tumor samples, at screening/baseline (pre-treatment), especially during treatment (C2D28) and at disease progression (at the time of radiological tumor assessment) is critical for assessing drug effect, therefore is strongly encouraged throughout the trial, and it should be performed as described below. Paired pre- and post-treatment fresh core tumor biopsies from patients in cohorts 1 and 2 should be collected for all patients unless not feasible and/or accessible according to the investigator's judgment. Starting from the fourth cohort (potential efficacious dose) paired fresh tumor biopsies must be collected from at least 1 patients at each dose cohort and in all other patients where judged feasible by the investigator. Additional eligible patients from who the investigator consider it feasible to obtain paired fresh tumor biopsies, can be enrolled at any time during dose escalation in the cohort explored at that point in time. In the expansion arm, fresh pre- and post-treatment biopsies will be collected for all patients in single agent and combination arms, unless not feasible and/or accessible according to the investigator's judgment. A minimum of 8 analyzable matched pairs must be obtained in the expansion arm.

In addition, if the circumstances are favorable, it is encouraged to collect an additional fresh tumor biopsy at disease progression, as it will provide a unique opportunity to investigate the potential mechanisms of resistance of BYL719 in patients. This will be done using a combination of genomic, transcriptomic and proteomic technology. The tumor sample at disease progression may be obtained as a core biopsy, if feasible. Depending on the site of disease progression, if a conventional tumor biopsy is not feasible, other tumor cells, i.e., from pleural effusion or ascites, may be collected instead. The C2D28 biopsy may also be considered as the disease progression biopsy should the patient's disease progress in close proximity to the time of biopsy. Two biopsy passes should be obtained for all tumor biopsies. Details regarding the processing of each biopsy pass are provided in the BYL719X2101 Laboratory Manual.

To provide a more complete pharmacodynamic and measurement in tumor tissue all pre- and post-treatment fresh tumor biopsies should be paired with a non-fasting 2.5 ml blood sample collected at the same time to allow analysis of glucose and C-peptide levels (see Section 7.10.2.1). The sample collection date, the exact time of collection, and the time of exposure to fixative (for formalin fixed samples) must be entered on the appropriate tumor tissue collection log eCRF page(s) and/or CRO (Contract Research Organization) requisition

[redacted]

form(s). Detailed instructions for the collection, handling, and shipment of tumor samples are outlined in the BYL719X2101 Lab Manual.

Table 7-7 Tumor biopsy collection schedule

Visit		Details
Screening/baseline	Not specified	Archival tumor block
Screening/baseline	Not specified*	2 Core biopsies
C2D28	4 to 6h post-dose*	2 Core biopsies
Disease progression	Preferably 4 to 6h post dose or within 3 days post-dose	2 Core biopsies
*Pre-dose and post-dose fresh tumor biopsies should optimally be paired with serum collection for non-fasting glucose metabolism markers at all time-points		

7.10.2 Biomarker assessments in blood

Before and during treatment with BYL719, at time-points detailed in the tables below, blood samples will be collected in order to investigate drug induced changes in markers relevant to PI3K signaling and anti-cellular effect.

7.10.2.1 Blood for glucose metabolism assessments

The effect of BYL719 on PI3K signaling and, potentially, on glucose metabolism will be assessed by measuring the circulating levels of glucose and c-peptide in serum. The time-points for collecting the blood samples (2.5 mL each) are described in Table 7-8. The sample collection information must be entered on the appropriate eCRF page(s) and CRO requisition form(s). Detailed instructions for the collection, handling, and shipment of samples are outlined in the BYL719X2101 Lab Manual.

Table 7-8 Blood collection for glucose metabolism markers assessment

Visit	Time-points (BYL719 dose)	Fasting status
Screening/baseline	Pre-dose (at time of fresh tumor biopsy)	Non-fasting
C1D2	Pre-dose, 2h and 4h post-dose	Fasting
C1D9	Pre-dose, 2h and 4h post-dose	Fasting
C2D28	4 to 6h post-dose (at time of fresh tumor biopsy)	Non-fasting
C2D2	Pre-dose, 2h and 4h post-dose	Fasting
Disease Progression	Within 3 days post-dose (at time of fresh tumor biopsy)	Non-fasting

7.10.2.2 Blood for genetic analysis

An additional separate whole blood sample (~5.0 mL) will be obtained at End of Cycle 2, if compliant with local IRB requirements. This sample will be analyzed if tumor biopsies are obtained for comparing tumor-specific gene alterations in the DNA from tumor biopsies with the DNA from normal-non-tumor cells.

A whole blood sample (≈ 6 mL) will be obtained at screening/baseline, and if not obtained at that time may be taken any time during treatment, if compliant with local IRB requirements. This sample will be analyzed if tumor biopsies are obtained for comparing tumor-specific gene alterations in the DNA from tumor biopsies with the DNA from normal-non-tumor cells.

[redacted]

A second blood sample (≈ 6 mL) will be collected at screening/baseline to explore the possibility of detecting mutations retrospectively in circulating DNA.

A third whole blood sample (≈ 6 mL) will be obtained with the tumor biopsy procedure upon disease progression. [redacted] This sample may be collected within 14 days prior to the biopsy procedure. Collection of the sample immediately or shortly after the procedure is not recommended [redacted] If it is not collected prior to the procedure it may be collected anytime >48 hours after the procedure and up to 21 days afterwards.

7.10.3 Other exploratory biomarker assessments

To allow exploratory investigation for the molecular mechanisms of skin rash and other toxicities which occur during BYL719 treatment, the following tests will be performed:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

See Table 7-7 for scheduling details. Patients who have discontinued from this study may also be asked for consent to provide a blood sample for these analyses.

During the trial, in addition to the biomarkers listed above, additional exploratory biomarker research on the remaining tumor, blood (including PK samples) and tumor DNA samples will be performed when appropriate. These studies would extend the search for other potential relevant biomarkers and/or biological tests for BYL719 effect, disease and/or safety of the patient and they would be decided upon clinical outcome, reagent and sample availability.

7.10.4 Optional exploratory biomarker assessments

After the study is completed, if the patient agrees, the remaining biomarker samples (tumor, blood, tumor DNA) may be stored for up to 15 years to address further scientific questions and/or development of biological tests related to BYL719 or cancer. A decision to perform such exploratory biomarker research would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

8 Safety monitoring

8.1 Serious adverse event reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Novartis if the

[redacted]

investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) office.

The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original 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 drug, a Novartis DS&E 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 ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.2 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug 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 Novartis DS&E department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of male study participants who received study treatment. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.3 Data Monitoring Board

A Drug Safety Monitoring Board (DSMB) will not be in place for this trial. Instead, Novartis and the investigators of the dose-escalation arm will meet, during the dose-escalation arm of this study, at the end of each treatment cohort to discuss and evaluate all of the gathered safety and PK data. At these meetings, Novartis and the investigators must reach a consensus on whether to escalate the dose any further, or whether to de-escalate and/or expand recruitment into particular cohorts. The requirement to modify the inclusion/exclusion criteria or the need for any change in safety follow up will also be discussed. Novartis will prepare minutes from these meetings and circulate them to each investigator for comment prior to finalization (for details refer to Section 6.6.1.6.1).

During the expansion arm of this study, Novartis and the investigators of the dose escalation arm of this study will meet regularly (every 3 to 6 months) to review the overall safety and efficacy of the study and will determine the need for eventual inclusion/exclusion criteria changes and the need for safety follow up changes.

They will also evaluate the efficacy in each of the specific disease areas and will make recommendations on the need to extent the expansion arm number of patients to expand further with patients with a specific disease type.

9 Data review and data management

9.1 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 eCRFs 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 eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug 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 on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (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 eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are

[redacted]

performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated 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, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before transfer of data to Novartis (or designated CRO). After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

9.2.1 Electrocardiogram

Designated investigational site staff will enter the ECGs required by the protocol into the appropriate eCRFs. Field monitors will review the eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancy on the ECGs as required.

9.2.2 Biomarkers

Designated investigational site staff will enter the information required by the protocol into the appropriate Biomarker Sample Collection eCRFs and the designated CRO requisition forms that are printed on 2-part paper. One copy of the requisition form will be forwarded to the CRO laboratory with the corresponding sample(s), the other copy will be retained by the investigational site. Field monitors will review the eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancy as required.

9.2.3 Pharmacokinetics

Designated investigational site staff will enter the information required by the protocol into the appropriate Pharmacokinetic Sample Collection eCRFs and the designated CRO requisition forms that are printed on 2-part paper. One copy of the requisition form will be forwarded to the CRO laboratory with the corresponding sample(s), the other copy will be retained by the investigational site. Field monitors will review the eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancy as required.

9.2.4 Imaging

Designated investigational site staff will enter the RECIST measurements required by the protocol into the appropriate eCRFs. Field monitors will review the eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancy on the CT/MRI and PET scans as required.

9.3 Database management and quality control

Data will be entered into the study database by investigator/study coordinator for EDC studies.

[redacted]

For studies using electronic CRFs, Novartis personnel (or designated CRO) will review the eCRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Obvious errors are corrected by Novartis Data Management personnel (or designated CRO). Queries are sent to the investigational site using an electronic data query. Designated investigator site staff are required to respond to the query and make any necessary changes to the data. If the electronic query system is not used, a paper Data Query Form (DQF) will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis Data Management personnel (or designated CRO) who will make the correction to the database if required. In addition the signed original and resolved DQFs must also be sent to Novartis Data Management (or designated CRO). Copies of the resolved DQF are kept with the CRFs at the investigator site.

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

9.3.1 Electrocardiogram

ECG data (except the screening/baseline ECG) will be reviewed and processed centrally by a specialist CRO. All results will be send electronically to the designated data management CRO for validation, integration and reconciliation into the study database.

9.3.2 Biomarkers

The biomarker sampling information captured in the eCRF (the patient's PIK3CA gene status is recorded on the eCRF at screening), on CRO requisition forms, and on the bar-coded specimens will be managed by a Novartis-designated CRO that is specialized in biomarker specimen management. All information will be collated and transferred electronically to an internal Novartis sample tracking system. If any of the biomarker analyses are intended to form part of the clinical study report, they will be transferred to the data management CRO for validation, integration and reconciliation into the study database. In addition, all biomarker samples will be sent and processed centrally by a specialist CRO. All results will be sent electronically to the designated data management CRO for validation, integration and reconciliation into the study database.

9.3.3 Pharmacokinetics

Following analysis of the study PK samples, the resulting concentration data generated from these sample analyses will be stored in the Laboratory Information Management System (LIMS) database used by Novartis Bioanalytics staff. Upon the completion of the assay work, the data will be the transmitted electronically from LIMS to the data management (CRO) for validation, incorporation and reconciliation into the study database.

[redacted]

9.3.4 Imaging

9.3.4.1 CT/MRI data

CT/MRI scans will be collected, reviewed and processed centrally by an imaging specialized CRO specified by Novartis and results transferred to the Novartis Clinical Imaging Unit. All results will be send electronically to the designated data management CRO for validation, integration and reconciliation into the study database.

9.3.4.2 Primary imaging data

The diagnostic CT/MRI scans will all be transmitted (de-identified to protect patient confidentiality and identified by patient identifier and trial code) and archived by the imaging specialized CRO.

The occurrence of any protocol deviation will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Biostatistics and Statistical Reporting and the Global Therapeutic Area Head.

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic and pharmacodynamic measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

The analysis of study data for the primary CSR will be based on all patient data of the dose escalation and dose expansion parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study.

The final CSR produced for all data collected before and after the primary CSR until LPLV will only include key summaries and listings of the safety data.

10.1 Populations for analysis

The full analysis set (FAS): consists of all patients who received at least one dose of BYL719 or fulvestrant where applicable. The full analysis set will be the primary population for all analyses unrelated to safety endpoints.

The Safety set (SS): consists of all patients who received at least one dose of BYL719 or fulvestrant where applicable and had at least one post-baseline safety assessment (where the statement that a patient had no adverse events (on the Adverse Event eCRF) constitutes a

[redacted]

safety assessment). Patients who have received at least one dose of BYL719 or fulvestrant where applicable but who have no post-treatment safety data of any kind would be excluded from the safety set. The safety set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship.

The dose-determining set (DDS): consists of all patients in the safety set who have either (a) experienced DLT at any time during Cycle 1, or (b) met the minimum safety evaluation requirements without experiencing DLT within Cycle 1.

The minimum treatment and safety evaluation requirements will have been met if, in Cycle 1, the patient has been treated with the planned dose of BYL719 for ≥ 21 days, observed for ≥ 28 days following the Cycle 1 Day 1 dose, and has completed the required safety evaluations for Cycle 1. Patients enrolled in the combination arm have achieved minimum exposure if they fulfill the requirements outlined above for BYL719, and if they have received at least 75% of the planned doses of fulvestrant in the first cycle (i.e. the patient must receive 500mg on day 1 and at least 250mg on day 15). Patients who do not meet these minimum treatment and safety evaluation requirements will be regarded as ineligible for inclusion in the dose-determining set and will be replaced. The DDS will be used in the BLRM to estimate the dose-DLT relationship.

All analysis sets will be identified prior to database lock.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data characteristics will be listed individually by patient, and summarized descriptively by dose cohort. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study drug, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of BYL719 as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by means of descriptive statistics by dose cohort. The summary data will be presented for each treatment cycle individually, as well as for the whole study. The daily dose for each patient will be summarized using descriptive statistics (e.g., mean, median, and modal daily doses). Similar data will be presented for fulvestrant in the combination arm.

Doses reductions, delays (including the reasons for these) and increases will be listed and summarized.

The FAS will be used.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be listed by patient and summarized by ATC term and dose cohort by means of contingency tables. The FAS will be used.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized by treatment group.

10.4 Primary objective

The primary purpose of the phase IA dose-escalation component is to determine the maximum tolerated dose (MTD) of BYL719 when administered orally on a once or twice daily schedule as single agent or in combination with fulvestrant to adult patients with advanced solid malignancies (whose tumors have a mutation of the *PIK3CA* gene) which have progressed despite standard therapy or for whom no standard therapy exists (Section 3.1)

The corresponding primary analysis method is an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle basing on a suggestion of Babb (1998).

The information currently available about the dose-toxicity curve of BYL719 is limited to the preclinical data from 4-week GLP-toxicology studies in rats and dogs. A vague prior distribution for the model parameters is derived based on a mixture of the data from both species. This prior distribution is then updated after each cohort of patients with the DLT data from the current study. A detailed description of the used methodology can be found in Section 10.4.2.

10.4.1 Variable

Estimation of the MTD in the dose-escalation arm of the study will be based upon the estimation of the probability of DLT in Cycle 1 for patients in the dose-determining set. This probability is estimated by the model in Section 10.4.2.

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, occurring < 28 days following the first administration of BYL719 (Cycle 1) as defined in Section 6.6.1.7.

10.4.2 Statistical hypothesis, model, and method of analysis

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used in the dose-escalation. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

[redacted]

Single agent dose escalation part

A 2-parameter BLRM (Neuenschwander 2008) will be used for dose escalation of BYL719 as single agent. Standardized doses will be used such that one of the doses (d* = 290 mg) equals 1, e.g., doses are rescaled as d/d*. As a consequence α is equal to the odds of the probability of toxicity at d*. Then, the 2-parameter logistic model for these probabilities is of the form

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*)$$

where $\text{logit}(\pi_{(d)}) = \log_e(\pi_{(d)}/(1-\pi_{(d)}))$, and $\alpha, \beta > 0$. Doses are rescaled as d/d^*, and as a consequence α is equal to the odds of the probability of toxicity at d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

Once the decision to add a b.i.d. arm is taken the model will be modified by the addition of a covariate γ_1 in order to account for the change in toxicity risk that may follow the expected change in exposure due to the schedule modification.

Once the decision to add a modified formulation is taken the model will be modified by the addition of a covariate γ_2 in order to account for the change in toxicity risk that may follow due to the formulation modification.

Then, the 4-parameter expended logistic model is of the form

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*) + \gamma_1 c_1 + \gamma_2 c_2$$

where $-\infty < \gamma_1 < \infty$ and c_1 takes the value 0 for patients receiving QD dosing and 1 for patients receiving b.i.d dosing. Negative and positive values are allowed for γ_1. Indeed for any given total daily dose, the b.i.d. dosing may result in a lower rate of DLT if DLT are driven by Cmax, but may result in a higher DLT rate if toxicities are driven by AUC in comparison to the same total daily dose given as q.d.

where $-\infty < \gamma 2 < \infty$ and c2 takes the value 0 for patients receiving Initial Formulation and 1 for patients receiving Modified Formulation. Negative and positive values are allowed for γ2.

Prior specifications single agent dose escalation part

The Bayesian approach requires the specification of prior distributions for the model parameters. Data from preclinical studies showed similar toxicity and safety profile between species (rat vs. dog) in the predicted human-equivalent MTD (290 mg and 500 mg in rat and dog, respectively). For each species a vague bivariate normal prior for the model parameters (log(α),log(β)) was elicited based on prior guesses (medians) and wide confidence intervals for the probabilities of a DLT at each dose, and were obtained as follows:

- Based on the preclinical data in rat, the starting dose was determined to be 30 mg and the MTD was predicted to be 290 mg. Median prior probabilities of DLT were set to be approximately 1% and 33% at the starting dose and the predicted MTD, respectively
- Based on the preclinical data in dogs, the starting dose was determined to be 30 mg and the MTD was predicted to be 500 mg. Median prior probabilities of DLT were set to be approximately 0.1% and 33% at the starting dose and the predicted MTD, respectively.
- In each case, the prior medians of probability of DLT for the remaining doses were assumed linear in log-dose on the logit-scale.

[redacted]

- Based on the above medians for the probability of DLT at each dose and wide prior credible intervals, obtained from minimally informative Beta distributions, (Neuenschwander 2008), the optimal parameters of the individual bivariate normal distributions were obtained.

In order for the model to estimate the dose-toxicity curve accurately in the instance that one of either the rat or dog data is most predictive for human toxicity, a mixture of these two priors is then obtained by assigning a weight to each. These weights are based on the prior belief in the estimates from each species being more or less related to human. Since we believe that the dog and rat data have the same ability to predict the toxicity in humans (see Section 1.3.2 and Section 6.6.1.4), we assign then equal weight to the rat (40%) and dog (40%). In addition, a third and fourth component are introduced to allow for the case that humans are more/less tolerant than the most/least tolerant pre-clinical species. The prior for the "low toxicity" component (or "flat" prior) assumes that the increase in toxicity as dose increases is close to 0, and is derived as follows:

- The mean and standard deviation of log(α) are derived such that the prior median and 97.5% quantile for the P(DLT) at the reference dose are 0.01 and 0.10, respectively.
- The mean for log(β) is set equal to -5 and the standard deviation is set equal to 0.01, In essence, fixing the shape of the prior to be almost flat.

The prior for the "High toxicity" component assumes that the increase in probability of DLT as dose increases is high, and is derived as follows:

- Median prior probabilities of DLT were set to be approximately 0.5% and 33% at dose 10mg/person/day and 100mg/person/day, respectively
- For the remaining doses, the prior medians of probability of DLT were assumed linear in log-dose on the logit-scale
- Based on the above medians for the probability of DLT at each dose and wide prior credible intervals, obtained from minimally informative Beta distributions, (Neuenschwander 2008), the optimal parameters of the individual bivariate normal distributions belonging to the "high toxicity" component were obtained.

In the derivation of the mixture prior, 15% weight is assigned to the "high toxicity" component of the prior, with 5% weight assigned to the "low toxicity" component. The 20% assigned to these prior relationships is small in comparison to the total weight assigned to the priors derived from pre-clinical data (80%). These weights are updated directly in the model according to the observed toxicity data. For example, if there are no DLTs observed at doses up to and surpassing the rat predicted MTD, the rat and "high toxicity" components of the prior are down-weighted, whilst the weight on the other two components increases since they are more likely to be true. Alternatively, if DLT is seen early in the trial, weight moves from the dog and low toxicity components to the more sensitive rat and "high toxicity" components as a direct result of the posterior updating procedure.

Specification of γ_1 prior

From information on BYL719 exposure, mean AUC with the b.i.d schedule is expected to have the same level than with qd, with less than 20% chance of being more than 2 fold higher (80%tile no larger than 2). Based on the assumption that exposure is linearly related to dose

[redacted]

and using the logistic model above and the mean prior of log(β), the log-odds-ratio γ_1 between b.i.d and qd schedule is assumed to be normally distributed with mean 0 and standard deviation 1.010.

Specification of γ_2 prior

For the covariate parameter, the prior distribution for the log-odds-ratio γ_2 for covariate c_2 is obtained by the specification of two prior quantiles (97.5th percentile and median). From pre-clinical information, BYL719 Modified Formulation exposure is expected to have the same level than with Initial Formulation. Based on the assumption γ_2 was assumed normally distributed with median = 0 and 97.5th percentile = 1.61. Thus the 95% prior Odds Ratio interval for c_2 is (0.2,5).

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]1	

[redacted]

Table 10-2 [redacted]

Daily Dose (mg)	Prior probabilities that Pr(DLT) is in interval:			Mean	Sd	Quantile		
q.d. dosing – Initial Formulation								
	0-0.16	0.16-0.33	0.33-1.0			2.5%	50%	97.5%
30	0.802	0.072	0.126	0.112	0.217	0.000	0.009	0.834
60	0.735	0.091	0.175	0.151	0.248	0.000	0.022	0.889
120	**0.633**	**0.113**	**0.255**	**0.213**	**0.285**	**0.000**	**0.061**	**0.935**
200	**0.528**	**0.129**	**0.343**	**0.284**	**0.315**	**0.000**	**0.134**	**0.963**
250	**0.473**	**0.137**	**0.391**	**0.323**	**0.327**	**0.001**	**0.188**	**0.975**
350	**0.366**	**0.150**	**0.484**	**0.397**	**0.337**	**0.004**	**0.308**	**0.989**
400	**0.317**	**0.153**	**0.530**	**0.433**	**0.339**	**0.005**	**0.372**	**0.993**
BID dosing – Initial Formulation								
	0-0.16	0.16-0.33	0.33-1.0			2.5%	50%	97.5%
30	0.795	0.069	0.135	0.119	0.230	0.000	0.008	0.873
60	0.731	0.085	0.184	0.159	0.260	0.000	0.021	0.918
120	**0.631**	**0.108**	**0.261**	**0.221**	**0.297**	**0.000**	**0.060**	**0.955**
200	**0.531**	**0.123**	**0.346**	**0.290**	**0.325**	**0.000**	**0.132**	**0.975**
250	**0.476**	**0.130**	**0.394**	**0.329**	**0.336**	**0.001**	**0.185**	**0.983**
350	**0.374**	**0.141**	**0.485**	**0.402**	**0.347**	**0.003**	**0.308**	**0.992**
400	**0.330**	**0.141**	**0.529**	**0.436**	**0.349**	**0.004**	**0.373**	**0.995**
q.d. dosing – Modified Formulation								
	0-0.16	0.16-0.33	0.33-1.0			2.5%	50%	97.5%
30	0.799	0.070	0.131	0.116	0.224	0.000	0.008	0.857
60	0.731	0.089	0.179	0.155	0.255	0.000	0.021	0.906
120	**0.631**	**0.111**	**0.258**	0.218	0.292	0.000	0.060	0.947
200	**0.530**	**0.125**	**0.346**	0.288	0.322	0.000	0.132	0.971
250	**0.475**	**0.131**	**0.393**	0.327	0.333	0.001	0.186	0.980
270	**0.454**	**0.135**	**0.411**	0.342	0.336	0.001	0.208	0.983
350	**0.372**	**0.143**	**0.485**	0.400	0.344	0.003	0.308	0.991
400	**0.326**	**0.143**	**0.530**	0.435	0.346	0.004	0.374	0.994
b.i.d. dosing – Modified Formulation								
	0-0.16	0.16-0.33	0.33-1.0			2.5%	50%	97.5%
30	0.792	0.069	0.139	0.123	0.237	0.000	0.008	0.893
60	0.725	0.085	0.189	0.164	0.268	0.000	0.021	0.933
120	**0.629**	**0.104**	**0.267**	0.226	0.304	0.000	0.058	0.963
200	**0.530**	**0.120**	**0.350**	0.295	0.332	0.000	0.131	0.98
250	**0.477**	**0.126**	**0.397**	0.334	0.343	0.001	0.186	0.986
270	**0.457**	**0.127**	**0.416**	0.348	0.346	0.001	0.208	0.988
350	**0.382**	**0.132**	**0.486**	0.405	0.353	0.002	0.308	0.994
400	**0.340**	**0.132**	**0.529**	0.439	0.356	0.003	0.375	0.996
Note: bold values indicate doses not meeting overdose (safety) criteria based on prior distribution of DLT rates.								

[redacted]

Combination dose escalation part

In amendment 4, the addition of BYL719 in combination with fulvestrant required the development of a new model and the computation of a new prior. The Bayesian combination model was applied to allow for testing of BYL719 QD or BID in combination with fulvestrant.

A 6-parameter BLRM for combination treatment will be fitted on the Cycle 1 dose-limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose escalation to model the dose-toxicity relationship of BYL719 QD or BID and fulvestrant when given in combination. A prior distribution will be used for an interaction parameter describing the change in toxicity that may result from an interaction between the BYL719 QD and fulvestrant.

Pre-clinical data and historical data from the ongoing study BYL719X2101 QD single agent were used in order to derive an informative prior of the model parameters.

The 6-parameter BLRM is formulated in the following way: Let $\pi_1(d_1)$ be the probability of a DLT if BYL719 is given as a single agent QD at dose d_1, where c_1 takes the value 1 if BYL719 BID is being administered and zero otherwise. Similarly, let $\pi_2(d_2)$ the probability of a DLT if fulvestrant is given as a single agent at dose d_2. The dose-response relationship is then modeled as:

$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*) + \gamma_1 c_1$

$\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$

$\text{Odds}(\pi_{12}(d_1,d_2))) = \pi_{12}(d_1,d_2)/(1-\pi_{12}(d_1,d_2)) = \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1)+\pi_2(d_2)-\pi_1(d_1)\pi_2(d_2))/((1-\pi_1(d_1))(1-\pi_2(d_2)))$,

Where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1-\pi.(d.)\}]$, $d_1^* = 290$mg (QD) and d2*= 500mg are the reference doses of BYL719 and fulvestrant respectively, $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2 > 0$, $-\infty < \gamma_1 < \infty$ and $-\infty < \eta < \infty$ is a scalar.

Prior specifications combination dose escalation part

BYL719 QD

An informative bivariate normal prior for the model parameters ($\log(\alpha_1)$, $\log(\beta_1)$) are obtained as follows:

- Based on preclinical data, the starting dose for BYL719 was determined to be 30 mg, and the MTD dose was estimated to be 290 mg, which was taken as the reference dose for the single agent prior. A mixture prior consisting of components for the rat, the dog, a low toxicity and a high toxicity component was used in order to take the preclinical information into account. More details on the exact derivation of the prior can be found in prior specifications for single agent dose escalation part.
- Data from the 36 patients considered eligible for the dose-determining set of the ongoing study were added into a 2-parameter BLRM model for single agent (see Table 10-3).
- An assumption about heterogeneity single escalation part and combination escalation part was captured in the prior distributions of the standard deviation of ($\log(\alpha_1)$,$\log(\beta_1)$), denoted by τ_1 and τ_2. Both τ_1 and τ_2 were assumed to follow a log-normal distribution with

[redacted]

mean log(0.25) and standard deviation 0.01, assuming moderate between-trial heterogeneity.

- The updated distribution for the model parameters were obtained via simulation. This distribution is then used as the prior distribution for the parameters ($\log(\alpha_1)$,$\log(\beta_1)$).

Table 10-3 Data from BYL719X2101 (as of Feb 8th 2012)

Dose of BYL719 (mg, QD)	No of DLTs / No of evaluable patients
30	0/1
60	0/3
90	0/6
180	0/6
270	0/4
400	0/7
450	4/9

Specification of γ_1 prior (BYL719 BID)

More details on the exact derivation of the prior can be found in prior specifications for single agent dose escalation part for γ_1.

Fulvestrant

A non-informative bivariate normal prior for the model parameters ($\log(\alpha_2)$,$\log(\beta_2)$) is obtained as follows:

The risk of DLT associated to fulvestrant treatment for patients previously treated with fulvestrant without experiencing DLT is considered to be very low. Hence, a conservative estimate of the rate was assumed to be 5% for the 500mg/month dose level. [redacted]

A non-informative prior reflecting the current uncertainty about the toxicity of the combination treatment is used for η. Since there not expected to be an interaction between BYL719 and fulvestrant, the parameter η follows a normal distribution with median=0 (no increase on odds of DLT) and 97.5th percentile = 1.1 (~3 fold increase on odds of DLT) allowing for the potential of both synergy and antagonism of the safety profiles.

[redacted]

Should additional data become available prior to the initiation of the testing of the combination part of the study then these prior distributions may be updated to incorporate that additional data.

[redacted]

Table 10-5 Summary of prior distribution of DLT rates

BYL719 Daily Dose (mg)	Prior probabilities that Pr(DLT) is in interval:			Mean	Sd	Quantile		
q.d. dosing in combination with fulvestrant 500mg								
	0-0.16	0.16-0.33	0.33-1.0			2.5%	50%	97.5%
30	0.984	0.011	0.004	0.057	0.036	0.041	0.051	0.115
60	0.974	0.019	0.007	0.062	0.047	0.038	0.052	0.165
120	0.948	0.035	0.016	0.072	0.065	0.033	0.056	0.259
200	0.893	0.075	0.031	0.092	0.09	0.027	0.065	0.368
250	0.828	0.122	0.049	0.111	0.107	0.025	0.077	0.440
270	0.793	0.148	0.060	0.121	0.114	0.025	0.084	0.473
350	0.537	0.292	0.171	0.200	0.165	0.029	0.147	0.655
400	**0.373**	**0.303**	**0.324**	**0.286**	**0.225**	**0.033**	**0.217**	**0.885**
BID dosing in combination with fulvestrant 500mg								
	0-0.16	0.16-0.33	0.33-1.0			2.5%	50%	97.5%
30	0.981	0.012	0.007	0.059	0.046	0.041	0.051	0.13
60	0.967	0.021	0.012	0.064	0.060	0.038	0.052	0.194
120	0.934	0.043	0.023	0.077	0.082	0.033	0.056	0.314
200	0.869	0.082	0.049	0.102	0.112	0.027	0.066	0.462
250	0.799	0.128	0.073	0.124	0.133	0.025	0.077	0.556
270	0.763	0.150	0.087	0.136	0.143	0.024	0.085	0.591
350	0.528	0.252	0.220	0.221	0.199	0.026	0.150	0.779
400	**0.386**	**0.259**	**0.355**	**0.306**	**0.252**	**0.029**	**0.222**	**0.922**
Note: bold values indicate doses not meeting overdose (safety) criteria based on prior distribution of DLT rates.								

Dose recommendation

Once updated, the distribution summarizes the probability that the true rate of DLT for each dose lies in the following categories:

1. [0,16%) under-dosing
2. [16%,33%) targeted toxicity

3. [33%,100%] excessive toxicity

The escalation with overdose control principle (Babb 1998, Neuenschwander 2008) mandates that any dose of BYL719 as single agent or in combination with fulvestrant that has more than a 25% chance of being in the excessive toxicity category is not considered for the next dose cohort. A clinical synthesis of the available toxicity information (including adverse events that are not DLTs), PK, PD, and efficacy information as well as the recommendations from the Bayesian model by the investigators and Novartis trial personnel will be used to determine the dose schedule for the next cohort at a dose-escalation teleconference.

The frequency of DLTs will be tabulated by dose for patients in the dose escalation arm and information about the DLTs will be listed by dose.

10.4.3 Handling of missing values/censoring/discontinuations

Patients in the dose-escalation arm who are ineligible for the dose-determining set will be replaced. Patients in the dose-expansion arm who are ineligible for the safety set will be replaced. Patients in the dose-expansion arm who are of unknown clinical response will be treated as failures.

Patients continuing to receive study drug at the time of the core or extension reports will have time-to-event data (e.g., progression-free survival, duration of response, etc.) censored at the time of last measurement prior to the data cut-off point used in the report. Continuing events (e.g., adverse events, concomitant medication, etc) will be summarized using the data cut-off date as the date of completion, with an indication within listings that the event is continuing.

For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above paragraph.

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug, duration of exposure to study drug and date of discontinuation for each patient, by dose cohort.

Other missing data will simply be noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

Additional exploratory and supportive analyses will be conducted if appropriate.

10.5 Secondary objectives

Additional analyses studying the association between endpoints of PK, PD, cellular response, molecular status of predictive biomarkers, proteomic, and/or clinical nature will be conducted as appropriate toward the achievement of secondary objectives. Refer to Section 3.2 for secondary objectives of both the dose-escalation and dose-expansion arms.

10.5.1 Efficacy analysis

The analysis of efficacy will be descriptive.

Efficacy will be assessed overall for the

[redacted]

- 22 head and neck or esophageal cancer PIK3CA altered patients treated at the single agent MTD/RP2D level
- 20 PIK3CA wild type ER+/HER2- metastatic breast cancer patients at the single agent MTD/RP2D level
- 20 PIK3CA altered ER+/HER2- metastatic breast cancer patients treated at the MTD/RP2D level of BYL719 in combination with fulvestrant
- 20 PIK3CA wild type ER+/HER2- metastatic breast cancer patients treated at the MTD/RP2D level of BYL719 in combination with fulvestrant

The patients in the study with ER+/HER2+ breast cancer will be analysed separately for efficacy and only listed.

In addition, for exploratory purpose, if a significant number (approximately 10) of the all comers patients have the same cancer type, descriptive statistics for efficacy may be presented for this cancer type.

CT/MRI: Assessment of preliminary efficacy will be based on best overall tumor response as defined by the RECIST criteria: progressive disease (PD), stable disease (SD), partial response (PR) and complete response (CR). Further details can be found in [Post-text Supplement 1]. The number and proportion of PD, SD, PR and CR will be presented by dose cohort. The ORR will be summarized in terms of percentage rates and credible interval when more than 10 patients are available

The sum of the longest diameters (SLD) across lesions will be listed, summarized and analyzed by dose cohort and any relevant variable (e.g. disease indication, relevant biomarkers). The relevant combination of exploratory graphics and modeling that may be used will be described in the Reporting and Analysis Preparation (RAP) documents.

PFS will be presented descriptively using a Kaplan-Meier curve for the MTD/RP2D only. Summary statistics from the Kaplan-Meier distribution will be determined, including the median and estimates at 4 and 6 months. These statistics will be provided as point estimates with 95% confidence intervals.

Population and grouping for the analyses

For all safety analyses, the safety set will be used. All other secondary analyses will use the population specified in the relevant section below. All listings and tables will be presented by dose cohort in the clinical study report, with patients classified to dose cohorts as describe in Section 10.1.

Safety parameters and analyses

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

[redacted]

10.5.2 Adverse events (AE)

10.5.2.1 Adverse events (AE)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, severity based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, type of adverse event, relationship to the study drug by dose cohort. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by primary system organ class, type of adverse event and dose cohort. DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.0, type of adverse event, and by dose cohort. The dose-determining set will be used for these summaries.

Any other information collected (e.g., start/end dates and duration of adverse event, severity or relatedness to study medication) will be listed as appropriate.

10.5.2.2 Laboratory abnormalities

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.0. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

For each laboratory test (e.g., hematology, biochemistry etc.), a listing of laboratory values will be provided by laboratory parameter, patient, and dose cohort. The frequency of all laboratory abnormalities will be displayed by parameter, worst CTCAE version 4.0 grade experienced and dose cohort. A separate listing will display laboratory abnormalities (i.e., newly occurring CTC grade 3 or 4 laboratory toxicities while on study treatment). Laboratory data will be summarized by presenting grade shift tables for those parameters for which CTCAE version 4.0 allows classification. All remaining data will be summarized by presenting shift tables based on normal ranges.

Laboratory data will also be displayed by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges).

10.5.2.3 Other safety data

Data from other tests (e.g., electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.5.3 Tolerability

Tolerability of study drug will be assessed by summarizing the number of dose interruptions and dose reductions by treatment group. Reasons for dose interruption and dose reductions will be listed by patient and treatment group and summarized by treatment group. Cumulative dose, dose intensity and relative dose intensity of BYL719 will be listed separately by patient and treatment group and summarized separately by treatment group.

[redacted]

Categories for relative dose intensity of BYL719 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented by treatment group.

10.5.4 Resource utilization

Not applicable.

10.5.5 Patient-reported outcomes

Not applicable.

10.5.6 Pharmacokinetics

A secondary objective of this study is to determine the single and multiple dose pharmacokinetics of oral BYL719 as single agent or in combination with fulvestrant.

The plasma samples from all patients will be assayed for BYL719 concentrations by Novartis using methods described in the Laboratory manual. Values below the assay LLOQ will be reported as 0.00 ng/mL. Missing values will be labeled accordingly. 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. Calculation of PK parameters will include up to the last measurable concentration t_{last}, as outlined in the Novartis Internal Guidance Standardization of pharmacokinetic parameters.

Pharmacokinetic parameters will be determined for all patients using non-compartmental method(s) using WinNonlin® Pro (Version 5.2 - Pharsight, Mountain View, CA). PK parameters listed in Table 10-6 will be estimated and reported, when feasible. Exploratory PK analysis will be conducted using compartmental modeling when necessary. In addition, in case drug accumulation is observed upon multiple dosing, additional PK parameters describing drug accumulation will be added to the analysis (i.e., accumulation ratio, effective half-life)

Descriptive graphical plots of individual and mean plasma concentration (per treatment) along with its time course will be generated. Further graphical exploratory analyses will be carried out if deemed appropriate. Pharmacokinetic parameters for each dose cohort will be analyzed by descriptive statistics, including the mean, SD, CV% or median (range). Since t_{max} is generally evaluated by a non-parametric method, median values and ranges will be given for this parameter.

Assessment of dose-proportionality, inter- and intra-individual variability and steady-state attainment will be conducted. If appropriate, an analysis of variance (ANOVA) will be performed on log-transformed AUCs and C_{max} using a linear mixed effect model to assess day effect.

Exploratory metabolite analysis on remaining plasma material from samples collected during the study will be performed, if deemed appropriate. Non compartmental parameters, including but not limited to AUC (AUC0-tlast and/or AUC0-inf), T1/2, Cmax and Tmax will be reported.

[redacted]

Table 10-6 Non-compartmental PK parameters

$AUC_{0\ -tlast}$	The area under the plasma concentration-time curve from time zero to the last measurable concentration (T_{last}) (mass x time x volume-1)
AUC_{0-inf}	The area under the plasma concentration-time curve from time zero to infinity (mass x time x volume-1)
AUC_{0-24}	The area under the plasma concentration-time curve from time zero to 24 hours (mass x time x volume^{-1})
AUCex[1]	Area under the plasma concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC (%)
C_{av}	The average drug concentration in plasma during the dosing interval (mass x volume-1)
C_{last}	Last measurable plasma concentration
C_{max}	The maximum (peak) observed plasma drug concentration after oral dose administration (mass x volume-1)
T_{last}	Time to reach the last measurable plasma concentration
T_{max}	The time to reach maximum (C_{max}) plasma drug concentration after oral dose administration (time)
$t_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic *concentration-time curve (time)*
CL/F	Apparent total body clearance of drug from the plasma after oral administration (volume x time-1)
Vz/F	The apparent volume of distribution during terminal phase after a (single) oral administration (associated with λz) (volume)
Rsqadj[1]	Square of the correlation coefficient associated with λz
[1] AUCex and Rsqadj will be used in the interpretation of the primary PK parameters and therefore will be included in the listings only.	

10.5.7 Biomarkers

Since this clinical trial was not designed to address specific biomarkers-related hypotheses, the analyses of this data should be viewed as hypotheses generating. Additional data from subsequent clinical trials will be required to confirm any findings. No adjustment for multiple comparisons is planned.

There may be circumstances when a decision is made to stop a collection, or not perform or discontinue the analysis of blood/tumor samples due to either practical or strategic reasons (e.g. inadequate sample number, issues related to the quality of the samples, or issues related to the assay that preclude the analysis of samples). Under such circumstances, the sample size number may be too small (e.g. limited number of fresh tumor biopsies) to perform any data analysis and the available data will be only listed. Alternatively, the data may be combined, as appropriate, with those from other studies as appropriate to enlarge the data set for analysis.

Data transformations may be applied in order to summarize and analyze the data adequately.

Complementary analyses may be performed following the review of the analyses described herein. For instance, the influence baseline characteristics on change from baseline in biomarkers may be estimated through statistical modeling.

[redacted]

10.5.7.1 Tumor biomarker analyses

10.5.7.1.1 Potential predictive markers

Baseline protein expression levels of PTEN and mutational status for selected genes (*PIK3CA*, PTEN, KRas, and BRaf) will be listed by patient and summarized by means of descriptive statistics. Correlation between markers at baseline may be explored graphically. In addition the association between these markers and clinical outcomes of interest (e.g. OR, PFS, occurrence of specific AEs) may be investigated to explore their role as potential predictors of efficacy.

10.5.7.1.2 Potential PD markers

Change from baseline for markers measured pre and post baseline to assess the effect on PI3K signaling (e.g. p-Akt, p-S6) will be listed by patient and may be summarized by means of descriptive statistics. If sufficient data are available, longitudinal plots displaying patients and mean profiles (along with corresponding 90% confidence intervals) may be produced.

Additional analyses may be provided as well: shift tables (from baseline) based on normal ranges, proportions of patients with significantly increased (activation of pathway) and/or decreased (inhibition of pathway) biomarker levels from baseline. Thresholds for significant increase/decrease or the method used to derive these thresholds will be defined in the RAP.

Correlation between changes from baseline for all or a subset of these markers may be explored graphically. Finally, the association between changes from baseline in these markers and clinical efficacy (OR) and/or exposure to BYL719 may also be investigated.

10.5.7.2 Blood biomarker analyses

To assess the effect on the PI3K signaling (glucose metabolism markers), changes from baseline for these markers will be listed, summarized and analyzed as per the PD markers measured in the tumor (see above). In addition, baseline levels and changes from baseline for these markers may be used to explore their role as potential predictors of efficacy.

During the trial, in addition to the biomarkers mentioned above, additional exploratory biomarker research on the remaining tumor, blood and tumor DNA samples will be performed when appropriate. These studies would extend the search for other potential relevant biomarkers for BYL719 effect, disease and/or safety of the patient and they would be decided upon clinical outcome, reagent and sample availability. After the study is completed, if the patient agrees, the remaining biomarker samples (tumor, blood, tumor DNA) may be stored for up to 15 years to address further scientific questions related to BYL719 or cancer. A decision to perform such exploratory biomarker research would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

10.6 Interim analysis

No formal interim analyses are planned. However, the dose-escalation design in the dose-escalation arm of the study foresees that decisions based on the current data are taken before

the end of the study. More precisely, after each cohort in the dose-escalation arm, the next dose will be chosen depending on the observed data.

10.7 Sample size calculation

10.7.1 Dose-escalation arm

Cohorts of at least one to three MTD-evaluable patients per dose level will be enrolled in the dose-escalation arm including at least six patients at the MTD level (see Section 6.6.1.6 for further details). Due to the potential for dropouts during the first treatment cycle (e.g., early disease progression), a cohort may be expanded to include additional patient(s) if the additional patient(s) can be enrolled ≤ 14 days after the last cohort patient received their first dose. Cohorts may be expanded at any dose level below the MTD (or RP2D) for further elaboration of safety, pharmacokinetic and/or pharmacodynamic parameters as required. And as such, additional eligible patients from who the investigator considers it feasible to obtain paired fresh tumor biopsies, can be enrolled at any time during dose escalation in the cohort explored at that point in time. At least 21 patients should be enrolled for the model to have reasonable operating characteristics relating to its MTD recommendation (A summary of the operating characteristics of the Bayesian logistic regression model can be found in [Post-text Supplement 4] Section 4). For the same reason, at least 12 patients must be enrolled in the dose escalation of the b.i.d. single agent schedule in order to declare the MTD as well as in the combination escalation of the selected schedule (q.d. or b.i.d.) in order to establish MTD, with at least 6 patients treated at the MTD.

10.7.2 Dose-expansion arm

The RP2D or MTD of BYL719 single agent will be expanded by enrolling additional patients to a total of at least 65 patients eligible for the safety set (including those treated at the RP2D or MTD in the dose-escalation arm of the study who are eligible for the safety set).

With a sample of size 65 there is a 86% probability of detecting an AE with a true incidence rate of 3% (see Table 10-7).

The RP2D or MTD of BYL719 in combination with fulvestrant will be expanded by enrolling additional patients to a total of at least 40 patients eligible for the safety set (including those treated at the RP2D or MTD in the dose-escalation arm of the study who are eligible for the safety set). With a sample of size 40 there is a 87% probability of detecting an AE with a true incidence rate of 5% (see Table 10-7).

[redacted]

Table 10-7 Probability of detecting adverse events with a specified incidence in the MTD cohort as a function of the cohort sample size

AE incidence rate	Number of Patients						
	10	20	22	30	40	45	65
0.01	0.10	0.18	0.20	0.26	0.33	0.36	0.48
0.03	0.26	0.46	0.49	0.60	0.70	0.75	0.86
0.05	0.40	0.64	0.68	0.79	0.87	0.90	0.96
0.10	0.65	0.88	0.90	0.96	0.99	0.99	1.00
0.15	0.80	0.96	0.97	0.99	1.00	1.00	1.00
0.20	0.89	0.99	0.99	1.00	1.00	1.00	1.00
0.25	0.94	1.00	1.00	1.00	1.00	1.00	1.00

Assessment of efficacy in head and neck patients (N=22) and breast cancer (N=20) patients

The sample size of the expansion part is primarily calculated for continued safety evaluation. However, the sample size in each patient group will also allow us to provide statements about the observed efficacy of the BYL719 as single agent or given in combination with fulvestrant. Table 10-8 and Table 10-9 below show the 95% credible interval for N=22 and N=20 for different response rates using a minimally informative beta distribution as prior distribution with parameters a=1/19 and b=1. This assumes a pessimistic a priori response rate of 5% (Neuenschwander 2008). Note that the final interval will depend on the final sample size.

Table 10-8 95% credible interval for different responses (N=22)

Observed response	Observed response rate	Posterior mean	Posterior (95% credible interval)
0	0.00	0.002	**0.000 - 0.026**
1	0.05	0.046	**0.001 – 0.158**
2	0.09	0.089	**0.012 – 0.231**
3	0.14	0.132	**0.030 0.294**
4	0.18	0.176	**0.053 0.351**
5	0.23	0.219	**0.079 0.405**
6	0.27	0.262	**0.109 0.455**
10	0.45	0.436	**0.245 0.637**

Table 10-9 95% credible interval for different responses (N=20)

Observed response	Observed response rate	Posterior mean	Posterior (95% credible interval)
0	0.00	0.002	**0.000 - 0.029**
1	0.05	0.050	**0.002 – 0.173**
2	0.10	0.098	**0.013 – 0.252**
3	0.15	0.145	**0.033 – 0.320**
4	0.20	0.192	**0.059 – 0.381**
5	0.25	0.240	**0.088 – 0.439**
6	0.30	0.288	**0.120 – 0.493**
10	0.50	0.572	**0.273 – 0.686**

[redacted]

10.8 Power for analysis of critical secondary variables

No formal power analysis is performed for the secondary variables.

11 Administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, 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.

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. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. 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.

Informed consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form 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.

Exploratory Biomarker consent form

This study includes optional Exploratory Biomarker components which require separate signatures if the patient agrees to participate. The optional Exploratory Biomarker informed consent questions are integrated in the main informed consent form of the Study. If a subject opts not to participate in the optional Exploratory Biomarker assessments, this in no way affects the subject's ability to participate in the main research Study.

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/REB at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Study drug supply and resupply, storage, and tracking/drug accountability

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, BYL719 should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

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

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

At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of

the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

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 trial 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.

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NOVARTIS

Clinical Development

BYL719 (Alpelisib)

Protocol CBYL719X2101

A phase IA, multicenter, open-label dose escalation study of oral BYL719, in adult patients with advanced solid malignancies, whose tumors have an alteration of the PIK3CA gene

RAP Module 3 – Detailed Statistical Methodology

Author: [redacted] Trial Statistician

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Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes

1 Introduction

This document provides the detailed statistical methodology for the analysis of data from study BYL719X2101. The table, figure and listing shells of the statistical analysis plan can be found in Module 7.

A core Clinical Study Report (CSR) will be prepared based on all data collected from patients enrolled in the study, up to the data cutoff date (when all such patients have potentially completed at least 6 cycles of study treatment or have discontinued from the study).

The additional data for any patients continuing to receive study drug past this time, as allowed by the protocol, will be further summarized in a short, closeout CSR once these patients have either completed or discontinued the study.

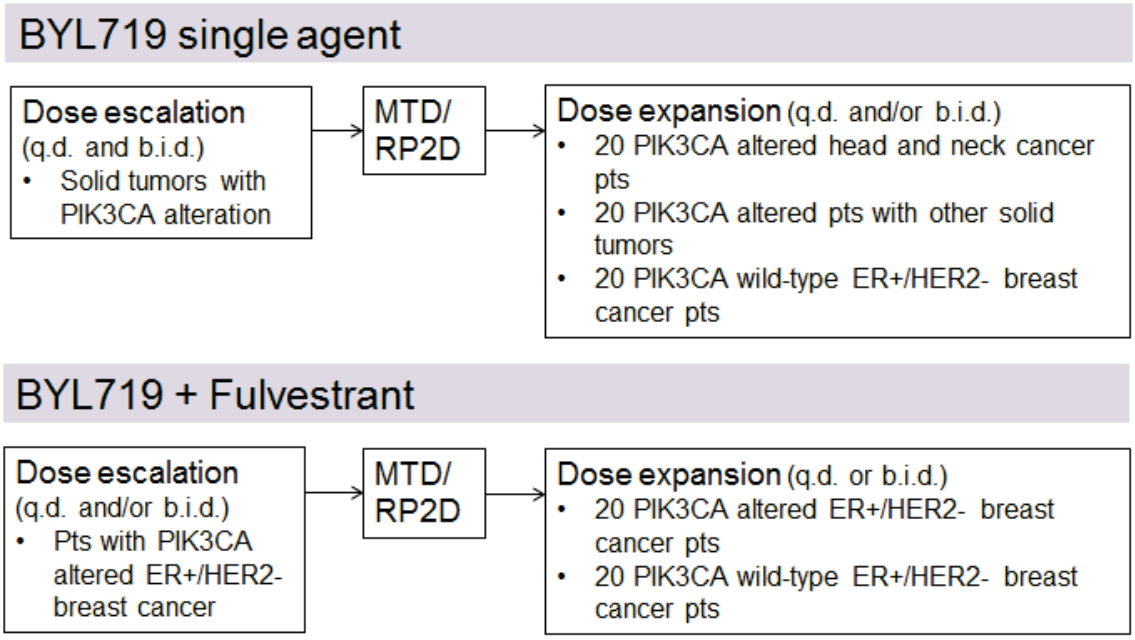
The purpose of the core CSR is to report the observed dose limiting toxicities (DLT), preliminary safety profile and preliminary efficacy of BYL719 in patients with selected advanced solid tumors.

All changes to the planned analysis described in Modules 3, 7 and 8 required before or after database lock will be made through an amendment or an addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in RAP module 7 without the need to amend this module.

1.1 Study design

This study has been designed as a multi-center, open-label phase IA study with dose escalation arms for q.d. or b.i.d. dosing.

Figure 1-1 Study design



Once daily (q.d.) single agent BYL719

At first, dose escalation will be conducted investigating a once daily (q.d.) administration of BYL719. An adaptive Bayesian logistic regression model (BLRM) for dose escalation with overdose control (EWOC), will guide the dose escalation arm to determine the MTD. Before a drug dosage can be declared to be the MTD, at least 21 evaluable patients should have been treated, with at least six evaluable patients treated at the MTD.

Once the MTD is determined, for the purpose of evaluating safety with sufficient accuracy, the MTD (or RP2D) cohort will be expanded to at least 65 patients (for example, if 6 patients are enrolled to establish the MTD (or RP2D), an additional approximately 60 patients will be added). Approximately 20 of these patients will have head and neck, or esophageal, cancer carrying molecular alteration (mutation or amplification) of *PIK3CA*. Approximately 20 of these will be *PIK3CA* wild type ER+, HER2- breast cancer patients, and the remaining patients will have other solid tumors carrying a molecular alteration of *PIK3CA* (including, for example, metastatic breast, ovarian, colorectal, or gastric cancer).

Twice daily (b.i.d.) single agent BYL719

Once the MTD of BYL719 using a q.d. schedule is determined, a b.i.d. dosing schedule will be investigated in parallel by the addition of a new arm. Before the b.i.d. MTD can be declared at least 12 patients must be treated in the b.i.d. dose escalation, with at least 6 evaluable patients treated at the MTD. It is possible that two MTDs (for each q.d. and b.i.d.) will be established.

Once the MTD is determined for the b.i.d. schedule, a safety expansion arm may be opened. PK and safety data will be analyzed to determine whether any of the expansion arms may be discontinued.

BYL719 and fulvestrant combination

A combination of BYL719 with fulvestrant will be investigated in post-menopausal patients with locally advanced or metastatic breast cancer whose tumors have an alteration of the PIK3CA gene. Before the MTD of BYL719 in the combination can be declared at least 12 patients must be treated in the combination dose escalation, with at least 6 evaluable patients treated at the MTD. When the MTD (or RP2D) has been established after dose escalation, a dose expansion cohort will enroll approximately 20 patients with ER+/HER2- breast cancer whose tumors have an alteration of the *PIK3CA* gene and 20 patients with ER+/HER2- breast cancer whose tumors are *PIK3CA* wild type.

The dose escalation phase will begin using BYL719 with the q.d. schedule. A b.i.d. schedule may be opened for the combination, if suggested by PK and safety data of BYL719 as single agent. The expansion of the combination will be carried out with only one of the q.d. or b.i.d. regimens, a decision which will be taken prior to initiating the expansion.

Modified formulation

As of [Protocol Amendment 4], a modified formulation of BYL719 has been developed to improve the stability of the product.

No formal comparison between both formulations will be conducted, but a minimum of 6 patients will be enrolled in the q.d. expansion cohort using the modified formulation and followed for one cycle. If the observed PK is comparable and the overdose control criteria are met then the study will continue with the modified formulation. Otherwise dose adjustments (escalation or de-escalation) may be made in accordance with the recommendations of the BLRM until a dose level fulfilling the overdose control criteria and/or achieving comparable PK is reached. If the study continues with the modified formulation any patient receiving the previous formulation may switch over to the modified formulation after they have completed at least one cycle.

1.2 Objectives

1.2.1 Primary objective

To determine the MTD (or RP2D) of oral BYL719 as single agent in adult patients with advanced solid malignancies whose tumors have an alteration (mutation or amplification) of the *PIK3CA* gene, and in combination with fulvestrant in post-menopausal patients with ER positive locally advanced or metastatic breast cancer whose tumors have an alteration of the *PIK3CA* gene

1.2.2 Secondary objectives

1. To assess the overall safety and tolerability of BYL719 treatment both as single agent and in combination with fulvestrant

2. To characterize the full pharmacokinetic profile of oral BYL719 after single (Cycle 1 Day 1) and multiple administrations (Cycle 1 Day 8 and Cycle 2 Day 1) of oral BYL719 both as single agent and in combination with fulvestrant
3. To assess the preliminary efficacy of oral BYL719 as single agent in patients with relapsing/refractory *PIK3CA* mutant solid malignancies and in combination with fulvestrant in ER+ breast cancer patients
4. To assess the preliminary anti-tumor activity of oral BYL719 as single agent and with fulvestrant in patients with locally advanced or metastatic *PIK3CA* wild type ER+, HER2- breast cancer

1.2.3 Exploratory objectives

1. To assess downstream effects of PI3K pathway inhibition
2. To assess markers that may correlate with prediction of response and/or resistance: altered molecular status (e.g. gene mutation, amplification, deletion and/or protein over-expression or activation)
3. To assess pre- and post-treatment changes in circulating tumor markers (as relevant for the respective cancer types), if applicable, as potential surrogate for indication of efficacy
4. To perform additional analysis on remaining material from samples collected during the study (blood and tumor) that could help in the understanding of BYL719 drug action and/or identify potential biomarkers that may correlate with efficacy and safety

1.3 Endpoints

1.3.1 End-point for primary objective

Incidence rate of dose limiting toxicities (DLT) (in the first cycle (of 28 days) of each investigated dose level).

1.3.2 End-points for secondary objectives

1. Safety and tolerability: type, intensity, severity and seriousness of adverse events (AE) according to NCI CTCAE v. 4.0.
2. Pharmacokinetics of BYL719 as single agent or in combination with fulvestrant: plasma concentration-time profiles and derived basic PK parameters of BYL719, including but not limited to $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, CL/F, Vz/F and the terminal half-life ($t_{1/2}$) and other PK parameters if deemed appropriate.
3. Objective tumor response rate (ORR), defined as the sum of complete response and partial response as best reported response by RECIST 1.0 criteria [redacted]
4. Progression Free Survival (at MTD/RP2D only)

1.3.3 End-points for exploratory objectives

1. Inhibition of the PI3K pathway assessed by:
    - Pre- and post-treatment changes in glucose metabolism (i.e. of fasting glucose, fasting c-peptide in blood)
    - Levels of pS6 and pAkt in tumor tissue.

2. Pre- and post-treatment changes in circulating tumor markers (as relevant for the respective cancer types, if any) as a measure of tumor response
3. Additional analysis on remaining material from samples collected during the study (blood, and tumor) that could help in the understanding of BYL719 drug action.
4. Whole exome sequencing, RNA and proteomic profiling of tumor tissue in order to detect changes in molecular (e.g. acquired mutations), RNA and proteomic (e.g. upregulation of tyrosine kinase) profiles from patients at baseline, on-treatment and at disease progression. If potential tumor-specific findings are detected, these might warrant a comparison with non-tumorous normal tissue (blood sample). Molecular mechanisms of drug susceptibility (e.g. HLA, MDR1, ELISPOT or viral load testing) from blood samples

1.4 Data Analysis

The statistical analysis of this study will be performed by Novartis personnel. SAS® version 9.4 will be used in all analyses other than Bayesian analyses for the MTD. The Bayesian modeling of the dose-toxicity relationship used for dose escalation decision making and inference for the MTD is performed using internal Novartis R functions created by Novartis's Methodology group and are run using R version 2 in MODESIM/GPSII environment.

All data captured in the clinical database and derived values of each patient are listed, by treatment and patient unique identifier and are available in Sections 14 and 16 of the CSR.

2 Definitions and general methodology

2.1 General definitions

2.1.1 Study drug and study treatment

2.1.1.1 Naming conventions

Study drug refers to BYL719 or fulvestrant.

Study treatment refers to BYL719 + fulvestrant for combination part or BYL719 for single agent part.

Other naming conventions

- "Cohort" or "Dose Cohort": group of typically 3 to 6 patients enrolled sequentially at once during the dose escalation and intended to receive the same dose of study drug/treatment.
- "Treatment group": group of patient intended to receive the same study treatment, for instance same dose level of study drug/treatment. A treatment group can include several cohorts of patients who have received the same dose level but were recruited at different point in the study.
- "Study arm": refer to separate groups of patient to be displayed separately according to study design even if receiving the same treatment.
- "Study parts": refers to the sequential parts of the study: dose-escalation, dose expansion.

2.1.1.2 Planned/received treatment

Intended/planned treatment is the first planned treatment reported [redacted] For combination trial it is the combination of the first planned treatment reported [redacted] of each component of the combination.

Treatment received is equivalent to intended/planned treatment. No distinction will be made between several dose levels accidentally administered to different patients.

The treatment received is defined as (i) the treatment assigned if it was received at least once, or (ii) the first treatment received when starting study drug. Each patient will be classified into and analyzed consistently within one (and only one) treatment group.

2.1.2 Time Units

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

2.1.3 Data included in the analyses

The following sets of data will be used for the production of all or subsets of the planned analyses:

- Final analysis for core CSR at the end of the dose expansion part: cut-off = when all patients have completed at least 6 cycles of study treatment and as agreed with the CTT and EPT
- IB updates and internal data review and external publications: cut-off as agreed with the CTT and EPT

2.1.4 Subgroup analyses

Summary tables and listings are presented by treatment group. There are an “All patients” category present in summary tables where all patients are grouped into a single column, except where such a summary is not appropriate, e.g. PK parameters. Each summary table is produced by any specific indicator (‘by group’) variable in order to assess potential difference in study outcome by that variable. This is done by disease group (e.g. primary site of cancer), PIK3CA alteration status (Section 2.1.6), or other variables of interest.

2.1.5 Assessment windows, baseline and post baseline definitions, missing data handling

2.1.5.1 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a nonzero dose of study drug is administered [redacted] For the sake of simplicity, the date of first administration of study drug will also be referred as start of study drug.

2.1.5.2 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered [redacted]

2.1.5.3 Date of first administration of study treatment

The date of first administration of study treatment is the same as the date of first administration of study drug for the single agent part

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment (BYL719 or fulvestrant) is administered [redacted] for the combination agent part.

For the sake of simplicity, the date of first administration of study treatment will also be referred as start of study treatment.

2.1.5.4 Date of last administration of study treatment

The date of last administration of study treatment is the same as the date of last administration of study drug for the single agent part.

The date of last administration of study treatment is derived as the last date when a non-zero dose of any component of the study treatment (BYL719 or fulvestrant) is administered.

2.1.5.5 Last date of exposure to study drug/treatment

The study schedule is organized in cycles of 28 days.

BYL719 is administered daily on a continuous once daily dosing schedule. Hence, the last date of exposure to BYL719 is the date of last administration of BYL719.

Fulvestrant is administered on

- Cycle 1 day 1
- Cycle 1 day 15 and on the first day of every cycle thereafter (e.g. cycle 2 day 1, cycle 3 day 1 etc.).

Due to the 14 day treatment period and irregularly spaced fulvestrant dose administration, the last date of exposure to fulvestrant is calculated using two different methods depending on the cycle at which fulvestrant was discontinued:

1. If the patient discontinues fulvestrant on or after cycle 2 day1, then:
    - The last date of exposure to fulvestrant is calculated as (last date of administration of fulvestrant) + (length of time interval - 1) i.e. [last date of fulvestrant administration+ (28-1)].
    - If the patient died or was lost to follow-up within last date of administration of fulvestrant + 27 days, the last date of exposure to fulvestrant is the date of death or the date of last contact, respectively.
2. If the patient discontinues fulvestrant between cycle 1 day 15 and cycle 2 day1, then:

- the last date of exposure to fulvestrant is calculated as (last date of administration of fulvestrant) + (length of time interval - 1) i.e. [last date of fulvestrant administration+ (14-1)].
- If the patient died or was lost to follow-up within last date of administration of fulvestrant + 13 days, the last date of exposure to fulvestrant is the date of death or the date of last contact, respectively.

The last date of exposure to study treatment is derived to be the latest date of the last date of exposure to BYL719 and fulvestrant.

2.1.5.6 Study day

The study day for all assessments post-treatment is calculated as the difference between the date of the event (e.g., visit date, onset date of an event, assessment date, disease progression, etc.) and the start of study treatment, plus one day. The first day of study treatment administration is therefore Study Day 1.

The study day for assessments pre-treatment is calculated as the difference between the date of the event (e.g., visit date, onset date of an event, assessment date, disease progression, etc.) and the start of study treatment. The day before start of study treatment administration is therefore Study Day -1. For the particular case of pre-treatment assessments performed on the day of first administration study day will be set to Day 1.

The study day for all assessments after start of cycle 1 is calculated as the difference between the date of the event (e.g., visit date, onset date of an event, assessment date, disease progression, etc.) and the start of study treatment on C1D1, plus one day. The first day of study treatment administration is therefore Study Day 1.

Unless specified otherwise, the study day is displayed in the data listings.

Cycle definition

The cycle number and day within cycle attributed to a visits or assessment will be derived according to the following rules:

- C1D1 coincides with the start date of drug/treatment
- All pre-treatment assessments are displayed as Cycle 0 with a negative day (e.g., Day -1 for the day before the patient started treatment) or with day 1.
- Day 1 of a cycle corresponds to the day reported by investigator on the start of cycle log form.
- For all cycles but the last, the end date of a cycle is defined as the day before Day 1 of the following cycle as recorded on the cycle log form.
- The end date of the last cycle is when treatment administration is permanently discontinued at the latest of the following days:
  - Date of last administration
  - 28 days after the first day of the last cycle where 28 is the duration of the cycle or day of patient’s death if earlier when date of last administration is not known

- All post-cycles assessments are displayed as follow-up and with, by analogy, Day 1 representing the first day after the end of the last cycle.

The duration (in days) of a cycle is defined as the cycle end date – cycle start date + 1.

Cycle number and day within cycle are computed to be displayed in listings only.

2.1.5.7 Baseline

Baseline is the last available and valid assessment performed or value measured within 14 days before the first administration of study treatment, unless otherwise stated under the related assessment section. Baseline can be the day before first treatment administration or the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, PK samples, samples for biomarkers).

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times.

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

Computation of the baseline for ECG and biomarker are described in each specific section.

2.1.5.8 On-treatment assessment/event

An on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the date of first administration of study treatment until the date of last administration of study treatment (i.e., including combination partner) + 28 days inclusive.

2.1.5.9 Imputation rule of partial or missing dates/data

Imputation rule of partial or missing dates

The following rule will be applied to handle partial dates. When the day if missing, it is imputed to the 15th of the month (e.g., DEC2007 imputed to 15DEC2007). When both the day and month are both missing then the date is imputed to July 1st of that year (e.g., 2007 imputed to 01JUL2007). All imputed data are flagged in the listings.

Standard Tables and Listings (STL*)* standard imputation rules for adverse events (AEs) and concomitant medications partial or missing dates will be used. In order to be conservative, these rules tend to maximize the duration of AEs under treatment and are equivalent to the rule above otherwise.

For other partial dates, the general STL standard imputation rules will be used.

For computation of time intervals (e.g. elapse time between initial diagnosis to first recurrence/relapse), time interval should be set to missing when the imputation rule leads to a negative value.

As of the date of data cutoff for the purposes of reporting, continuing events (e.g. adverse events, concomitant medication, etc.) will be summarized using the cut-off date as the date of completion, with an indication within listings that the event is continuing.

For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event with the appropriate censoring as described in the above paragraph.

Handling of missing data

Unless otherwise specified missing data will not be imputed. Handling of missing data will depend on the nature of the data:

- Baseline characteristics: number of patient with missing data will be reported and descriptive statistics will be computed on patients with non-missing data.
- RECIST best overall response (BOR): patients with missing or unknown BOR will be considered as failure in the overall response rate computation (see Section 3.5)
- Time-to-event endpoints: appropriate statistical methods will be used to account for censored patients (see Section 3.5)
- PK and biomarker data, laboratory data, ECG data, vital signs: number of patient with missing data will be reported and descriptive statistics will be computed on patients with non-missing data.

2.1.6 PIK3CA alteration status

PIK3CA alteration status will be based on molecular alteration (mutation or amplification) as per clinical data base (from local assessment and from 3rd party data - [redacted]). The following 3 groups of patients will be derived:

- PIK3CA altered: PIK3CA mutation or amplification reported by investigator or by central [redacted] analysis
- PIK3CA not altered: no PIK3CA mutation and no amplification or missing reported by investigator or by central [redacted] analysis
- PIK3CA Missing/Unknown: unknown PIK3CA mutation reported by investigator or by central [redacted] analysis or no PIK3CA analysis

2.2 Analysis sets

For inclusion in any analysis set it is required that a patient has correctly consented and has received at least one dose of study treatment.

The following analysis sets which will be derived prior to database lock will be used.

2.2.1.1 Full analysis set

The full analysis set (FAS) consists of all patients who received at least one dose of BYL719 or fulvestrant where applicable. The full analysis set will be the primary population for all analyses unrelated to safety endpoints.

2.2.1.2 Safety set

The Safety set (SS) consists of all patients who received at least one dose of BYL719 or fulvestrant where applicable and had at least one post-baseline safety assessment (where the

statement that a patient had no adverse events (on the Adverse Event eCRF) constitutes a safety assessment). Patients who have received at least one dose of BYL719 or fulvestrant where applicable but who have no post-treatment safety data of any kind would be excluded from the safety set. The safety set will be the primary population for all safety related endpoints except determination of the dose-DLT relationship.

2.2.1.3 Dose-determining set

The dose-determining set (DDS): consists of all patients in the safety set who have either (a) experienced DLT at any time during Cycle 1, or (b) met the minimum safety evaluation requirements without experiencing DLT within Cycle 1.

The minimum treatment and safety evaluation requirements will have been met if, in Cycle 1, the patient has been treated with the planned dose of BYL719 for ≥ 21 days, observed for ≥ 28 days following the Cycle 1 Day 1 dose, and has completed the required safety evaluations for Cycle 1. Patients enrolled in the combination arm have achieved minimum exposure if they fulfill the requirements outlined above for BYL719, and if they have received at least 75% of the planned doses of fulvestrant in the first cycle (i.e. the patient must receive 500mg on day 1 and at least 250mg on day 15). Patients who do not meet these minimum treatment and safety evaluation requirements will be regarded as ineligible for inclusion in the dose-determining set and will be replaced. The DDS will be used in the BLRM to estimate the dose-DLT relationship.

Protocol deviations

Table 2-1 is a summary of protocol deviations leading to exclusion from analysis sets. Patients were excluded from the analysis sets defined above based on the protocol deviations entered in the database.

Table 2-1 Protocol deviations leading to exclusion from analysis sets

Analysis set	Protocol deviations [severity codes leading to exclusion]
Full analysis set	Patient not correctly consented [8]
Safety analysis set	Patient not correctly consented [8] Patient has no adverse event record (including no record that no event occurred) [5]
Dose determining analysis set	Patient not correctly consented [8] Patient did not have sufficient safety evaluations for the investigator to be able to complete the end of cycle 1 DLT assessment [18] Minimum exposure requirements not met [18]

[8] (exclude from all analysis) / [5] (exclude from all safety analyses) / [18] (exclude from dose-determining analysis set)

2.3 Sample size and power considerations

2.3.1 Dose-escalation arm

Cohorts of at least one to three MTD-evaluable patients per dose level will be enrolled in the dose-escalation arm including at least six patients at the MTD level. Due to the potential for dropouts during the first treatment cycle (e.g., early disease progression), a cohort may be expanded to include additional patient(s) if the additional patient(s) can be enrolled ≤ 14 days after the last cohort patient received their first dose. Cohorts may be expanded at any dose level below the MTD (or RP2D) for further elaboration of safety, pharmacokinetic and/or pharmacodynamic parameters as required. And as such, additional eligible patients from who the investigator considers it feasible to obtain paired fresh tumor biopsies, can be enrolled at any time during dose escalation in the cohort explored at that point in time. At least 21 patients should be enrolled for the model to have reasonable operating characteristics relating to its MTD recommendation (A summary of the operating characteristics of the Bayesian logistic regression model can be found in [Post-text Supplement 4 of study protocol] Section 4). For the same reason, at least 12 patients must be enrolled in the dose escalation of the b.i.d. single agent schedule in order to declare the MTD as well as in the combination escalation of the selected schedule (q.d. or b.i.d.) in order to establish MTD, with at least 6 patients treated at the MTD.

2.3.2 Dose-expansion arm

The RP2D or MTD of BYL719 single agent will be expanded by enrolling additional patients to a total of at least 65 patients eligible for the safety set (including those treated at the RP2D or MTD in the dose-escalation arm of the study who are eligible for the safety set).

With a sample of size 65 there is a 86% probability of detecting an AE with a true incidence rate of 3% (see Table 2-2).

The RP2D or MTD of BYL719 in combination with fulvestrant will be expanded by enrolling additional patients to a total of at least 40 patients eligible for the safety set (including those treated at the RP2D or MTD in the dose-escalation arm of the study who are eligible for the safety set). With a sample of size 40 there is a 87% probability of detecting an AE with a true incidence rate of 5% (see Table 2-2).

Table 2-2 Probability of detecting adverse events with a specified incidence in the MTD cohort as a function of the cohort sample size

AE incidence rate	Number of Patients						
	10	20	22	30	40	45	65
0.01	0.10	0.18	0.20	0.26	0.33	0.36	0.48
0.03	0.26	0.46	0.49	0.60	0.70	0.75	0.86
0.05	0.40	0.64	0.68	0.79	0.87	0.90	0.96
0.10	0.65	0.88	0.90	0.96	0.99	0.99	1.00
0.15	0.80	0.96	0.97	0.99	1.00	1.00	1.00
0.20	0.89	0.99	0.99	1.00	1.00	1.00	1.00
0.25	0.94	1.00	1.00	1.00	1.00	1.00	1.00

Assessment of efficacy in head and neck patients (N=22) and breast cancer (N=20) patients

The sample size of the expansion part is primarily calculated for continued safety evaluation. However, the sample size in each patient group will also allow us to provide statements about the observed efficacy of the BYL719 as single agent or given in combination with fulvestrant. Table 2-3 and Table 2-4 below show the 95% credible interval for N=22 and N=20 for different response rates using a minimally informative beta distribution as prior distribution with parameters a=1/19 and b=1. This assumes a pessimistic a priori response rate of 5% (Neuenschwander 2008). Note that the final interval will depend on the final sample size.

Table 2-3 95% credible interval for different responses (N=22)

Observed response	Observed response rate	Posterior mean	Posterior (95% credible interval)
0	0.00	0.002	**0.000 - 0.026**
1	0.05	0.046	**0.001 – 0.158**
2	0.09	0.089	**0.012 – 0.231**
3	0.14	0.132	**0.030 0.294**
4	0.18	0.176	**0.053 0.351**
5	0.23	0.219	**0.079 0.405**
6	0.27	0.262	**0.109 0.455**
10	0.45	0.436	**0.245 0.637**

Table 2-4 95% credible interval for different responses (N=20)

Observed response	Observed response rate	Posterior mean	Posterior (95% credible interval)
0	0.00	0.002	**0.000 - 0.029**
1	0.05	0.050	**0.002 – 0.173**
2	0.10	0.098	**0.013 – 0.252**
3	0.15	0.145	**0.033 – 0.320**
4	0.20	0.192	**0.059 – 0.381**
5	0.25	0.240	**0.088 – 0.439**
6	0.30	0.288	**0.120 – 0.493**
10	0.50	0.572	**0.273 – 0.686**

2.4 Interim analyses

No formal interim analyses are planned. However, the dose-escalation design in the dose-escalation part of the study implies that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose-escalation phase, the dose given to a new cohort of patients will be chosen depending on the observed data.

3 Statistical methods used in reporting

The data will be summarized by treatment group and overall (when appropriate) with respect to demographic and baseline characteristics, preliminary efficacy and safety observations and measurements, and all relevant pharmacokinetic and pharmacodynamic measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

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

Data from participating centers will be combined so that an adequate number of patients will be available for analysis. Unless otherwise specified, patients of the escalation and expansion parts treated at the same dose levels will be pooled into a single treatment group.

Listings of all raw data will be produced and ordered by treatment group, center, country and patient. Missing data will simply be noted as missing on appropriate tables/listings.

Unless otherwise specified FAS will be used for all listings, summaries and analyses.

3.1 Patient disposition, background and demographic characteristics

3.1.1 Patient disposition

The number of patients who were enrolled, and treated as well as those who completed or discontinued the study (along with their reasons for premature discontinuation) or were still ongoing at the time of the analysis will be summarized. A listing of study completion by treatment will be produced. Patients are considered to be ongoing if they have not discontinued due to any reason (e.g., disease progression, AE, withdrawn consent).

Patients who were screened but never started treatment will be listed. Since screening failures are not part of any analysis sets, they will not be included in any of the summary tables.

3.1.2 Protocol deviations

All protocol deviations will be finalized before database lock. Protocol deviations and reasons for exclusion from populations will be tabulated. The number and percentage of patients in the FAS with any protocol deviations will be tabulated by the deviation category [redacted] All protocol deviations are listed.

3.1.3 Background and demographic characteristics

Background and demographic characteristics including age, gender, race, ethnicity, height, weight, WHO performance status, tumor type, medical conditions, etc. will be listed and summarized using descriptive statistics. The summaries will be based on the assessments from the screening visit (baseline).

In addition, the following derived variables derived from the demographic (e)CRF will be described:

- age groups summarized as class (<65, ≥65years)

- weight summarized as class (<55, 55-75, ≥75kg)
- Body mass index (BMI) calculated as weight/(height**2) (kg/m^2) where weight is measured in kg and height in m. BMI will be summarized as class (<30, ≥30 kg/m2)
- The body surface area (BSA) is calculated using Gehan and George formulae:
  BSA [m^2] = 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000

3.1.4 Medical History

Past and current medical history and will be summarized and listed. Separate summaries will be presented for current and past historical medical conditions; these summaries will be presented by primary system organ class and preferred term. (Medical history/current medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

3.1.5 Prior antineoplastic therapy

Prior anti-neoplastic therapies will be listed and the latest therapy summarized in three separate tables for surgery, radiotherapy and medications.

The summary of prior anti-neoplastic surgery included a summary of procedure at last surgery and the residual disease for non-biopsy procedure. Last surgery (non-biopsy procedure) is based on the end date of surgery.

The summary of prior anti-neoplastic radiotherapy included a summary of radiotherapy locations, including all locations recorded for each patient. Setting and best response at last radiotherapy is summarized. Last radiotherapy is derived based on end date.

The summary of prior anti-neoplastic medication included a summary statistics of the number of regimens, the setting at last medication, and also the best response at last medication and the reason for discontinuation. In addition, the time between end of last medication to start of treatment, will be described. Last treatment is derived based on the last end date of any of the components of the regimen.

Prior chemotherapy, anti-estrogen (Tamoxifen, Fulvestrant), aromatase inhibitors (Anastrozole, Exemestane, Letrozole), targeted therapy (anti-HER2, mTOR), GnRH-analogues for the combination arm will be also summarized in the metastatic setting (which is based on the palliative or therapeutic settings) and in the neoadjuvant/adjuvant setting. Summary statistics of the number of regimens in the metastatic setting will be provided.

The summary of prior anti-neoplastic radiotherapy/surgery included the time since last radiotherapy/surgery (non-biopsy procedure) and categorized as <1, 1-<6, 6-<12, or ≥12 months.

A summary of prior anti-neoplastic medications will be presented by ATC and preferred term.

3.1.6 Diagnosis and extent of cancer

Diagnosis and extent of cancer will be listed and the summarized by number (%) of patients in each of the categories for the following variables: primary site of cancer (group and details), details of tumor histology/cytology, histological grade, stage at initial diagnosis, current

extent of disease (metastatic sites), number of metastatic sites, types of lesions at baseline, estrogen and progesterone and HER2 receptor status, PIK3CA alteration (molecular and amplification) status based on local and central Quest analysis (Section 2.1.6).

In addition the following continuous and categorized time intervals will be computed and summarized:

- Time since initial diagnosis to first dose of study drug, calculated as (date of study treatment start – date of initial diagnosis of primary site + 1)/30.4375. The following categories will be used: <6 months, ≥6 to <12 months, ≥12 to <24 months, ≥24 months
- Time since initial diagnosis to first relapse, calculated as (date of first relapse – date of initial diagnosis of primary site + 1)/30.4375. The following categories will be used: <6 months, ≥6 to <12 months, ≥12 to <24 months, ≥24 months
- Time since initial diagnosis to most recent recurrence/relapse, calculated as (date of most recent recurrence/relapse – date of initial diagnosis of primary site + 1)/30.4375. The following categories will be used: <6 months, ≥6 to <12 months, ≥12 to <24 months, ≥24
- Time since most recent recurrence/relapse to first dose of drug, calculated as (date of study treatment start - date of most recent recurrence/relapse + 1)/30.4375.The following categories will be used: <1 month, ≥1 to <2 months, ≥2 to <3 months, ≥3 months

Due to the imputation method for partially missing dates (see Section 2.1.5.9), the four time intervals indicated above could be computed as negative. In such situation, they must be handled as missing dates.

3.1.7 Other baseline characteristics

All data collected during the baseline evaluation, including child bearing potential, pregnancy test results will be listed.

3.2 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

3.2.1 Study medication

Exposure will be summarized in terms of:

- The duration of study drug/treatment exposure,
- The cumulative dose,
- The dose intensity (DI) and/or relative dose intensity (RDI)
- The percentage of actual days dosed during the treatment period for daily dosed compounds
- The percentage of days received planned doses during the treatment period for daily dosed compounds

Exposure will be summarized on the Full analysis set.

3.2.1.1 Duration of study drug/treatment exposure

The following algorithm will be used to compute the duration of study drug/treatment exposure for patients who took at least 1 dose of any of the components of the study treatment/study drug:

Duration of exposure to study drug (for BYL719 and fulvestrant) is defined according to dosing regimen for each study drug as outlined in Section 2.1.5.5.

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

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

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

The duration includes the periods of temporary interruption. 'Date of first administration of study drug/treatment' and 'last date of exposure to study drug/treatment' are defined in Sections 2.1.5.1, 2.1.5.3 and 2.1.5.5.

Duration of exposure to study drug/treatment will be categorized into time intervals (<4 weeks, 4-<8 weeks, 8-<12 weeks etc.). In addition, summary statistics will be displayed.

For patients who did not take any drug the duration of drug exposure is by definition equal to zero.

3.2.1.2 Cumulative dose

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

For patients who do not receive any drug the cumulative dose will be set to zero.

The cumulative dose is defined according to the type of dosing schedule and is calculated from the DAR eCRF pages. It is expressed in mg for BYL719 and fulvestrant.

BYL719

The cumulative dose for BYL719 administered at daily dosing (qd or bid) is:

Cumulative dose (mg) = Sum of doses of the study drug administered to the patient from the start date to the last date of study drug.

Fulvestrant

The cumulative dose for fulvestrant with cyclic administration is based on the entire duration of exposure for the cycle.

The sum of 'dose administered' (mg) during the exposure to fulvestrant.

Average daily dose = [Cumulative dose (mg) / Number of dosing days]

3.2.1.3 Dose intensity and relative dose intensity

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

DI (dosing unit / unit of time) = Cumulative dose (dosing unit) / Duration of exposure (unit of time).

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

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

For BYL719:

- DI (mg/day) = Cumulative dose (mg) / duration of exposure (days)
- PDI (mg/day) = planned cumulative dose (mg) / duration of exposure (days).
- RDI (%) = DI (mg/day) / PDI (mg/day) *100

For Fulvestrant:

- DI (mg/day) = Cumulative dose (mg) / duration of exposure (days)

The categorical summaries of RDI (<0.75, 0.75-0.9, 0.9-1.1, >=1.1) and the continuous summaries of RDI (i.e. mean, standard deviation etc.) will be presented.

3.2.2 Dose interruption and reduction

The number (%) of patients with dose reductions or interruptions and associated reasons, will be summarized separately for each study drug (BYL719 and fulvestrant).

3.2.2.1 Dose interruption

For BYL719, a temporary dose interruption is defined as a zero dose on one or more days between two non-zero dosing periods.

For fulvestrant, an interruption is defined as a zero dose administered on the scheduled day of administration on one or more days between two non-zero doses.

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

3.2.2.2 Dose reduction

For BYL719 and fulvestrant, a dose reduction is defined as a decrease in dose from the planned dose (actual dose less than planned dose and different from 0).

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

3.2.3 Concomitant medication

The Safety Set will be used for all below mentioned concomitant medication tables.

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that were administered to a subject preceding or coinciding with the study assessment period.

Concomitant medications entered into the database will be coded using the NovDTD (Novartis Drug/Therapy Dictionary) to allow for categorization by preferred term and by Anatomical Therapeutic Chemical (ATC) class (note that a medication/therapy can appear with more than one ATC class). Concomitant medications and significant non-drug therapies taken concurrently with the study treatment will be listed and summarized by ATC class, preferred term. 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 and summarized by ATC class, preferred term.

Anti-neoplastic therapies since discontinuation of study drug will be listed and tabulated by ATC class and preferred term.

3.3 Analysis of the primary variable(s)

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used in the dose-escalation. The use of Bayesian response adaptive models for Phase I studies has been advocated by the EMEA guideline on small populations (2006) and by Rogatko (2007) and is one of the key elements of the FDA's Critical Path Initiative.

Single agent dose escalation part

A 2-parameter BLRM (Neuenschwander 2008) will be used for dose escalation of BYL719 as single agent. Standardized doses will be used such that one of the doses (d* = 290 mg) equals 1, e.g., doses are rescaled as d/d*. As a consequence α is equal to the odds of the probability of toxicity at d*. Then, the 2-parameter logistic model for these probabilities is of the form

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*)$$

where $\text{logit}(\pi_{(d)}) = \log_e(\pi_{(d)}/(1-\pi_{(d)}))$, and α, $\beta>0$. Doses are rescaled as d/d^*, and as a consequence α is equal to the odds of the probability of toxicity at d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

Once the decision to add a b.i.d. arm is taken the model will be modified by the addition of a covariate γ_1 in order to account for the change in toxicity risk that may follow the expected change in exposure due to the schedule modification.

Once the decision to add a modified formulation is taken the model will be modified by the addition of a covariate γ_2 in order to account for the change in toxicity risk that may follow due to the formulation modification.

Then, the 4-parameter expended logistic model is of the form

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*) + \gamma_1 c_1 + \gamma_2 c_2$$

where $-\infty < \gamma_1 < \infty$ and c_1 takes the value 0 for patients receiving QD dosing and 1 for patients receiving b.i.d dosing. Negative and positive values are allowed for γ_1. Indeed for any given total daily dose, the b.i.d. dosing may result in a lower rate of DLT if DLT are driven by

Cmax, but may result in a higher DLT rate if toxicities are driven by AUC in comparison to the same total daily dose given as q.d.

where $-\infty < \gamma 2 < \infty$ and c2 takes the value 0 for patients receiving Initial Formulation and 1 for patients receiving Modified Formulation. Negative and positive values are allowed for $\gamma 2$.

Combination dose escalation part

In amendment 4, the addition of BYL719 in combination with fulvestrant required the development of a new model and the computation of a new prior. The Bayesian combination model was applied to allow for testing of BYL719 QD or BID in combination with fulvestrant.

A 6-parameter BLRM for combination treatment will be fitted on the Cycle 1 dose-limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose escalation to model the dose-toxicity relationship of BYL719 QD or BID and fulvestrant when given in combination. A prior distribution will be used for an interaction parameter describing the change in toxicity that may result from an interaction between the BYL719 QD and fulvestrant.

Pre-clinical data and historical data from the ongoing study BYL719X2101 QD single agent were used in order to derive an informative prior of the model parameters.

The 6-parameter BLRM is formulated in the following way: Let $\pi_1(d_1)$ be the probability of a DLT if BYL719 is given as a single agent QD at dose d_1, where c_1 takes the value 1 if BYL719 BID is being administered and zero otherwise. Similarly, let $\pi_2(d_2)$ the probability of a DLT if fulvestrant is given as a single agent at dose d_2. The dose-response relationship is then modeled as:

$$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*) + \gamma_1 c_1$$

$$\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

$$\text{Odds}(\pi_{12}(d_1,d_2))) = \pi_{12}(d_1,d_2)/(1-\pi_{12}(d_1,d_2)) = \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1)+\pi_2(d_2) - \pi_1(d_1)\pi_2(d_2))/((1-\pi_1(d_1))(1-\pi_2(d_2))),$$

Where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1-\pi.(d.)\}]$, $d_1^* = 290$mg (QD) and d2*= 500mg are the reference doses of BYL719 and fulvestrant respectively, $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2 > 0$, $-\infty < \gamma_1 < \infty$ and $-\infty < \eta < \infty$ is a scalar.

Summaries of the posterior distribution of DLT rates based on the DLT data from all patients enrolled in the dose escalation arm and included in the dose determining set will be produced.

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 4.0 unless otherwise specified (e.g. hyperglycemia), type of adverse event, and by treatment group. The dose-determining set will be used for these summaries.

3.4 Efficacy evaluation

Preliminary anti-tumor activity will be assessed using Investigator read CT/MRI assessments evaluated under RECIST 1.0. All data including Best overall response (BOR), Overall

response rate (ORR), disease control rate (DCR), PFS will be listed. ORR, DCR and PFS will also be produced for selected indications and PIK3CA alteration (head and neck or esophageal, ER+/HER2- metastatic breast cancer) where at least 10 patients were enrolled at the MTD(s) and/or RP2D.

The patients in the study with ER+/HER2+ breast cancer will be analyzed separately for efficacy and only listed.

Patients who discontinue the study and are lost to follow-up without a known date of progression or death due to any cause or before the cut-off date will be censored in the analysis at the date of their last available CT scan. Other missing data will simply be noted as missing on appropriate tables/listings.

3.4.1 RECIST related endpoints

Response and progression evaluation will be performed according to the RECIST guideline version 1.0 (as described in detail in [Post-text Supplement 1 of the study protocol]) whenever it applies.

3.4.1.1 Best overall response and other binary endpoints

Best overall response

Only overall tumor assessments reported by investigator and performed before the start of any further anti-neoplastic therapies (i.e., any additional secondary anti-neoplastic therapy or surgery) will be considered in the assessment of best overall response.

Confirmation of complete and partial responses (CR and PR, respectively) must be made 4 weeks apart.

Patients who are of unknown clinical response will be treated as non-responders.

3.4.1.2 Computation of time to event endpoints

Progression free survival

Progression-free survival (PFS) is defined as the time from the date of first study treatment intake to the date of the first radiologically documented disease progression or death due to any cause or initiation of new antineoplastic therapy.

By default, if disease progression, death or initiated new antineoplastic therapy is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last tumor evaluation with overall lesion response of CR, PR or SD.

3.4.1.3 Handling of missing data and special cases

No measurable lesion at baseline

Evaluation using RECIST criteria implies that patients have measurable lesion at baseline. However, patient without measurable lesion may be enrolled in the study.

According to RECIST guidelines, the overall Response should be UNK or PD. In Phase I studies when the presence of target lesions is not mandatory for enrollment, in order to avoid the presence of too many "UNK" the overall response will be derived based on non-target lesions only when no target lesion is available. CR and SD will be assigned if the non-target lesion responses are respectively CR, non CR-non PD, respectively, without the appearance of a new lesion.

Analysis of other progression screening methods

In the efficacy analysis, additional screening methods (e.g., bone scans) are handled differently than the regular tumor assessments. The general rule is that they are only impacting the overall lesion response of a given assessment when they are documenting an unequivocal progression/new lesion.

In addition, if the screening method is not available at a given assessment this does not automatically make the overall lesion response "Unknown" at that assessment.

Change in imaging modality

As per RECIST, the same imaging method used at baseline should also be used at all subsequent assessments. However, for various reasons such as site error (e.g., switch from MRI to CT) or renal dysfunction (making contrast a risk), this is not always done. The strict implementation of RECIST would mean that any change in the imaging method apart from that used at baseline would lead to an overall response of "unknown" at that assessment.

However, the presence or absence of contrast does not necessarily change the precision of the image. To cover that possibility, the following imaging modalities listed under the same bullet point below were considered the same for the calculation of change from baseline of the sum of longest diameters of target lesions (SLD):

- 'CT with contrast' and 'CT without contrast'
- 'Spiral CT with contrast' and 'Spiral CT without contrast'
- 'MRI with contrast', 'MRI without contrast', 'Dynamic contrast – enhanced MRI' and 'Gadolinium-MRI'.

For other efficacy endpoints, investigator judgment only is considered even if overruling the computed response.

3.4.2 Models and method of analysis

3.4.2.1 Analyses of time-to-event data

The following section presents the general methodology used to analyze time-to-event variables (e.g., PFS)

Kaplan-Meier curve and related estimates of PFS will be provided displaying patients at and above 270mg for selected indications (Breast ER+, HER2-) and at and above MTD/RP2D PIK3CA alteration when more than 10 patients have been treated in each category. In addition, the PFS distribution will be summarized by presenting the estimates of median PFS as well as estimate PFS rates at 2, 4 and 6 months. These statistics will be provided as point estimates with 95% confidence intervals as appropriate.

Details on Kaplan-Meier estimates

An estimate of the survival function can be constructed using the Kaplan-Meier (product-limit) method [redacted]

Median survival was obtained along with 95% confidence intervals [redacted]. The confidence interval was constructed using Greenwood's formula for the standard error of the Kaplan-Meier estimate.

Kaplan-Meier estimates with 95% confidence intervals will be also summarized at specific time (2, 4 and 6 months) points.

Hypotheses and test statistics

Hazard ratio

In order to estimate Hazard ratios and their confidence interval, Cox proportional hazards model will be implemented using PHREG procedure with option TIES=EXACT. It assumes that there is a true but unknown ordering for the tied event times as contrasted to option TIES=DISCRETE which assumes that the events in fact occurred at exactly the same time.

3.4.2.2 Analysis of Overall response rate, disease control rate and clinical benefit rate

Best overall response will be summarized using the Objective Response Rate and the Disease Control Rate which are the proportion of patients having respectively a best overall response of PR or CR, or SD, PR or CR. Clinical benefit rate is defined as the proportion of patients with an overall response of complete response (CR) or partial response (PR) or stable disease (SD) lasting more than 24 weeks based on local investigator's assessment according to RECIST 1.0

Statistical hypothesis, model, and method of analysis

Response rate, disease control rate and clinical benefit rate will be summarized as percentages with 95% confidence intervals. As a standard, an exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper & Pearson, 1934).

[redacted]

A Bayesian design will be used to estimate the ORR at or greater than 270mg for selected indications/PIK3CA alteration status (head and neck, ER+/HER2- metastatic breast cancer for single agent) and at or greater than MTD/RP2D for ER+/HER2- metastatic breast cancer PIK3CA altered or WT for combination agent.

Vague prior beliefs about the ORR distribution reflecting the current uncertainty about the efficacy in the study will be summarized in prior distributions. Minimally informative Beta distribution priors (Neuenschwander 2008) with prior means equal to the clinical threshold for futility (5%) will be utilized. The parameter values of the prior distribution for ORR are summarized in Table 3-1 and Table 3-2 summarizes the corresponding prior distribution that ORR falls within the pre-specified efficacy intervals.

Table 3-1 Prior parameters for minimally informative Beta distribution of ORR

Prior parameters	
α	β
1/19	1

Table 3-2 Summary of prior distribution of ORRs

Efficacy intervals Prior probabilities that ORR is in interval:			Mean	SD	Quantiles		
No/weak	Limited	Clinically relevant			2.5%	50%	97.5%
[0, 10%]	(10%, 20%]	(20%, 100%]					
0.716	0.093	0.076	0.15	0.242	0	0.02	0.866

The posterior distribution of the ORR is upon completion of the study following the update of the prior distribution with all the available data from the FAS. The posterior distribution will be used to derive the probability that the true ORR lies in the pre-specified efficacy intervals.

3.4.2.3 Construction of waterfall graphs

The waterfall graph is used to depict anti-tumor activity. This plot displays both BOR and the best percentage change from baseline in the sum of the longest diameter of all target lesions for each patient

The best overall response will be shown above each of the displayed bars in the graph.

Patient with missing/unknown best percentage change from baseline will be excluded in the waterfall graph.

Patients will be ordered in the graph using the following display (from left to right):

1. Bars above the horizontal axis representing tumor growth
2. Bars under the horizontal axis representing tumor shrinkage

Waterfall plots will show the cut-off limits for target lesions for PR (-30%) as dotted lines.

On the top of the waterfall plot a heatmap will be added in order to display per patient (matching with the bar on the waterfall plot) the information regarding prior medication for

the combination part or selected indication (CRC, Breast, Ovarian, Head and Neck and others) for single agent part.

3.5 Safety evaluation

The assessment of safety is based on the type and frequency of AES as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria [CTC] version 4.0 grading limits or normal ranges as appropriate). Other safety data includes electrocardiogram, vital signs, visual test, and special tests.

The SS will be used for summaries and listings of all safety data in Section 14 of the CSR with the exception of dose limiting toxicities (DLT) for which the DDS will be used. Safety analyses will be performed per treatment received (see Section 2.2.1.2). The FAS will be used for Section 16 of the CSR, including for safety listings. These listings will be displayed per intended treatment as per all analyses performed on the FAS (see Section 2.2.1.1). Differences between treatment received and intended treatment, if any, will be provided in a listing.

The safety summary tables will include only assessments collected no later than 28 days after study treatment discontinuation. All safety assessments will be listed, and those collected later than 28 days after study treatment discontinuation will be flagged.

3.5.1 Adverse event

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology and will be reported by primary system organ class (SOC) and preferred term (PT) by Standardized MedDRA Queries (SMQs) and Novartis MedDRA Queries (NMQs) (for safety topics of interest). Although CTCAE version 4.0 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening and death, CTCAE grade 5 (death) was not used since this information was collected on the "End of Treatment" or "Survival Information" CRF pages.

Separate listing for adverse events, serious AEs (SAEs) and death recorded during the study will be provided. Adverse events (All), Grade ¾ AEs, SAEs and deaths will be tabulated by primary system organ class, preferred term and treatment. Additional summaries based on the relationship to study drug by treatment, study drug discontinuation, requiring dose adjustment or delay will be produced.

Listing and summaries will be produced according to the following rules:

- Patients reporting and experiencing multiple occurrences of a specific AE will have occurrences listed but will be counted only once in the appropriate event category/class and according to the worst observed grade within summary tables.
- AEs will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each primary system organ class and for each preferred. AE will be sorted by descending frequency or alphabetically (system organ class [SOC] and preferred term [PT]).

Specific Safety Event Categories (SEC) consist of adverse events for which there is a specific clinical interest in connection with BYL719 treatment (i.e. where BYL719 may influence a

common mechanism of action responsible for triggering them) or adverse events which are similar in nature (although not identical).

General considerations for adverse events described in Section 3.6.1 is applicable for SEC. Each of these SECs uses MedDRA terms (SMQ, NMQ, HLGT etc.) to group preferred terms for which there is a specific clinical interest. One SEC can be defined by one or several MedDRA terms. The MedDRA terms used to define the SECs are defined in the program Case Retrieval Strategy (CRS) document and will be listed.

The following SECs will be:

- Hyperglycemia
- Hypersensitivity, Rash
- Nausea, Vomiting, Diarrhea
- Pneumonitis

Additional SECs may be reported if there are any updates to the CRS at the time of the analyses.

3.5.2 Laboratory data

All laboratory values will be converted into SI units when applicable and the severity grade calculated using the National Cancer Institutes Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) unless otherwise indicated (see glucose monitoring section). A severity grade of 0 will be assigned when the value is within normal limits. In the case when a local laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value will still be considered within normal limits and assigned a CTC grade of zero. If the CTC grading is based both on laboratory values and clinical observations, only boundaries of laboratory values will be used for grading. If the same boundaries were used for 2 different grades but with different associated clinical manifestation, then the lower grade was reported (see Table 3-3).

Table 3-3 Boundaries example

	Grade 1	Grade 2	Grade 3
Hyperuricemia	]ULN - 10 mg/dL] without physiologic consequences		]ULN - 10 mg/dL] with physiologic consequences

Uric acid level between ULN and 10mg/dL was displayed in laboratory data analysis as Grade 1 and should be reported as Grade 3 AE if associated with physiologic consequences.

In case of the WBC differentials both relative and absolute values could be obtained. If only relative values were available they were transformed into absolute values based on total WBC. If both were reported, absolute values were left unchanged. Grading was applied to absolute values.

Because the rules above were deviating from the strict application of NCI-CTCAE, Version 4.0, the grading used for laboratory values was referred to as “Adapted CTC grade”.

The following summaries will be produced for the laboratory data by laboratory parameter:

- Shift tables to the worst post-baseline value from baseline value (both expressed in CTC grades) will be produced.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

The following listings will be produced for the laboratory data:

- Listing of patients with laboratory abnormalities of CTC grade 3 and 4
- Listing of laboratory normal ranges by laboratory identification number and laboratory group
- Listing of all laboratory data with values flagged to show corresponding CTC grades and/or the classifications relative to the laboratory reference ranges (i.e., High (H) or Low (L))

3.5.2.1 Hematology and coagulation

Hematology includes the following parameters: complete blood count consisting of red blood cells (RBCs), a total white blood cell count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin, and platelet count, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), reticulocytes.

Differential counts will be converted to absolute values for CTC grade classification. For all the differential counts, % will be converted to absolute values, if necessary:

e.g. Absolute WBCdiff (Wunit) = Absolute WBC (Wunit)*Relative WBCdiff(%)/100

Coagulation profile includes prothrombin time or International Normalized Ratio (INR), activated partial thromboplastin time and fibrinogen.

3.5.2.2 Biochemistry

Biochemistry includes the following parameters: urea or Blood Urea Nitrogen (BUN), creatinine, sodium, potassium, calcium, albumin, total protein, total bilirubin (direct and indirect), amylase and urine amylase, lipase, alkaline phosphatase, AST, ALT, phosphorus, magnesium, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, and c-reactive protein (CRP), testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), LDH, bicarbonate.

3.5.2.3 Urinalysis

Urinalysis included dipstick analysis (protein, glucose, ketones, blood, and specific gravity). A microscopic (WBC/High Power Field (HPF), RBC/HPF, and any additional findings) exam need only be performed if the urinalysis result was abnormal. 24-hour urine collection and distribution of protein fractions (albumins, α1-globulins, α2-globulins, β-globulins, and γ-globulins) will only be listed.

3.5.2.4 Other assessments

Basal cortisol and bone marker CTX -1 (carboxyterminal cross-linked telopeptides of type I collagen) will be listed.

Cardiac enzymes since cardiac troponin-I or troponin-T will be listed and summarized.

Thyroid (Free T3, Free T4 and Thyroid stimulating hormone (TSH)) will be listed and summarized.

Glucose monitoring

The following tables will be produced for Fasting Plasma Glucose (FPG) for patients under fasting conditions:

- Shift tables from worst post-baseline value will be produced using protocol reference ranges
- Shift tables from worst post-baseline value will be produced using laboratory reference ranges
- Shift tables from worst post-baseline value will be produced using CTC grading

The following listings will be produced for the FPG:

- Listing of all FPG data with values flagged to show corresponding classifications relative to the CTC grading
- Listing of all FPG data with values flagged to show corresponding classifications relative to the laboratory reference ranges (i.e. High (H) or Low (L)) and protocol ranges

The protocol defined special ranges for fasting plasma glucose as follows:

Normal: < 140 mg/dL [< 7.8 mmol/L]

Grade 1: >= 140 - 200 mg/dL [>=7.8 – 11.2 mmol/L]

Grade 2: >=200- 250 mg/dL [>=11.2 – 13.9 mmol/L]

Grade 3: >=250 - 400 mg/dL [>=13.9 - 22.3 mmol/L]

Grade 4: >= 400 mg/dL [>=22.3 mmol/L]

The following tables will be produced for insulin, C-peptide for patients under fasting conditions:

- Shift tables from worst post-baseline value will be produced using laboratory reference ranges

The following tables will be produced for Hemoglobin A1C data:

- Shift tables from worst post-baseline value were produced using laboratory reference ranges

The following listings will be produced for the Hemoglobin A1C data:

- Listing of all Hemoglobin A1C data with values flagged to show corresponding classifications relative to the laboratory reference ranges (i.e. High (H) or Low (L))

Association between FPG, insulin, c-peptide and treatment will be explored using boxplot of the maximum fold change during the first 28 days of treatment and will be summarized by treatment with n, mean, standard deviation, %CV mean, geomean, %CV geomean, median, minimum, and maximum for baseline level, at time of maximum change and for fold change.

3.5.3 Vital signs, weight and physical examinations

All vital signs measures (e.g., oral temperature, respiratory rate, sitting blood pressure, and sitting pulse) and weight will be listed by parameter, treatment, patient and timepoint (cycle). Vital sign abnormalities as defined in the Table 3-4 will be derived and displayed in the listings.

The number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e., both clinically notable high and low values) will be tabulated.

Table 3-4 Notable vital signs ranges

Vital sign	Criteria for clinically notable ranges
Systolic blood pressure [mmHg]	≥180 mmHg/≤90 mmHg with increase/decrease from baseline of ≥20 mmHg
Diastolic blood pressure [mmHg]	≥105 mmHg/≤50 mmHg with increase/decrease from baseline of ≥15 mmHg
Pulse rate [bpm]	≥120 bpm/≤50 bpm with increase/decrease from baseline of ≥15 bpm
Oral body Temperature [°C]	Body temperature: ≤ 35, ≥ 39
Weight [kg]	≥10% decrease/increase from baseline

3.5.4 WHO/ECOG performance status

Frequencies and percentages for the categories of the WHO performance scale will be summarized at baseline. Data will be listed.

3.5.5 Electrocardiograms

3.5.5.1 ECG data descriptive statistics

For central ECG, baseline is the mean of the last triplicate at pre-dose. In the case when there are no available pre-dose on the same day as first treatment administration, baseline is the mean of pre-dose records on the last day before start date of treatment. For local ECG, baseline is the last available and valid assessment performed before the start of treatment.

Data from electrocardiogram will be listed, notable values will be flagged, and any other information collected will be listed. The frequency and percentage of patients with notable ECGs and newly occurring qualitative ECG abnormalities will be tabulated for central and investigator reading.

Post-baseline values will also be categorized and tabulated to flag notable values according to the following rules:

Table 3-5 Notable ECG values

Parameters	Criteria for ECG notable values

Parameters	Criteria for ECG notable values
QTcF (msec), QTcB (msec) and QT (msec)	New: > 450, >480, >500 msec
	Increase from baseline >30
	Increase from baseline >60
VR (bpm) for central ECG	RR decrease >25% to a VR >100
	RR increase >25% to a VR <50
HR (bpm) for local ECG	RR decrease >25% to a HR >100
	RR increase >25% to a HR <50
PR (msec)	Increase >25% to a value >200
QRS (msec)	Increase >25% to a value >110

In addition, in the listing QT or QTc values were also considered notable when >450 msec, >480 msec and > 500msec and will be flagged as such. For local ECG the RR is calculated with the formulae: RR=60/HR where HR is the heart rate.

3.5.6 Other safety analyses

Cardiac imaging scan or echocardiogram, chest X-ray will be listed and ophthalmic examination data will be listed and summarized by treatment group.

3.6 Pharmacokinetic data

3.6.1 Descriptive statistics

PK concentration data for BYL719 will be listed and summarized. BYL719 metabolites ([redacted] only) will be listed. In addition to descriptive statistics, graphical presentation of geometric mean plasma concentrations for BYL719 at each scheduled timepoint (Cycle 1 Days 1, 8 and Cycle 2 Day 1) will be provided for each dose. The plasma through concentration of BYL719 will be summarized and a graphical representation of arithmetic mean (SD) through concentration-time profiles for BYL719 will be provided. Further graphical exploratory analyses will be carried out if deemed appropriate (striplots for AUC0-24 and Cmax at C1D8 by treatment group for single agent vs. combination administration part).

Plasma concentrations that were excluded for the derivation of PK parameters and labeled as such in the listings will also excluded from the graphical presentations and summary statistics. For graphical representation, modeling and descriptive statistics, values below the lower limit of quantification (LLOQ) will be treated as zero in summary statistics.

PK parameters determined by a non-compartmental method from concentration data will be divided into primary PK parameters and secondary PK parameters. The primary PK variables are AUC0-t (t=12h for b.i.d. and t=24h for o.d./q.d.), AUCinf, Cmax, and Tmax, T1/2 and Racc. Other PK parameters (AUClast, Tlast, CL/F_obs, CLss/F, Vz/F_obs, Vz/F) are secondary. The primary and secondary parameters will be listed and summarized using relevant statistics (example table 3-6 below) separately.

Table 3-6 PK parameters – descriptive statistics

Parameters	Descriptive statistics

AUC[(1)] , C_{max}, $C_{min,}$, C_{av}, CL/F, Vz/F, accumulation ratio RA, $t_{½}$	Mean standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum.
T_{max}, T_{last}	Median, minimum, and maximum.
[(1)] any AUC: AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-tz}, AUC_{τ} , etc., With : CV% = coefficient of variation (%) = sd/mean*100 CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100	

3.6.2 Modeling of PK data

Selected primary PK parameters (AUC0-t and Cmax at steady state) will be analyzed using mixed model to assess the dose proportionality.

Dose proportionality

Dose proportionality for BYL719 in the single agent q.d. and bid part will be assessed for AUC0-t and Cmax at steady state. An analysis of variance is performed on log-transformed parameters by using a mixed-effect model with patient as random effect, regimen (qd vs bid) as covariate and log(dose) as continuous fixed effect.

Only profile days assumed to be at steady state will be included in the model, i.e. C1D8 and C2D1. Note that this model makes the assumption that the dose exposure relationship is the same at C1D8 and C2D1.

3.7 Biomarkers

3.7.1 Biomarker data

Since the study was not adequately powered to assess specific biomarker–related hypotheses, the statistical analyses of these data should be considered exploratory in nature. Analytical results from such analyses may be used to generate additional hypotheses that may then be verified with data derived from subsequent clinical trials.

All biomarker sample results obtained will be listed by patient and summarized by means of descriptive statistics. Distinct listings and summaries will be produced for each group of biomarkers define by type (i.e. IHC, ELISA) and sample (i.e. archival tumor sample, fresh tumors sample, blood). Furthermore, additional exploratory analyses described below are expected be performed if appropriate. However, 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 samples). Under such circumstances, the number of samples may be inadequate to generate summaries or perform data analyses planned below and the available data will only be listed.

3.7.1.1 Variable derivation

Limit of quantification

Values below the lower limit of quantitation (which may be reported with the label "LLOQ" or have a numerical value below the assays lower limit of quantification) will be imputed as 0.5*LLOQ, which will be specified by the performing lab and is assay specific. For values above the upper limit of quantification (either reported as "ULOQ" or a numerical value greater than the assays upper limit of quantification), the values will be set to the ULOQ threshold of the assay.

PIK3CA Mutational status at baseline

PIK3CA alteration (molecular and amplification) status based on local and central [redacted] (from SMU2 and FISH panels) analysis will be derived as outlined in Section 2.1.6

If PIK3CA alteration (molecular and amplification) are analyzed in multiple samples from a patient (e.g. biopsy) or/and fresh/frozen sample, the patient will be considered having a PIK3CA mutation if a mutation is observed in at least one of the samples.

If PIK3CA alteration (molecular and amplification) are analyzed in multiple samples from a patient (e.g. biopsy) or/and fresh/frozen sample, the patient will be considered having no PIK3CA mutation if a WT is observed in at least one of the samples and the other are all unknown.

Computation of H scores

Immunohistochemistry (IHC) data reported from the lab will include quantitative data such as percent tumor and percent positive cells or a semi quantitative measure of protein expression cellular compartments (i.e. cytoplasm, nucleus, membrane). The pathologist determines

whether the staining in a cellular compartment is absent (0+), slight (1+), moderate (2+), or strong (3+). The histoscore (i.e. H-Score) for each cellular compartment is then calculated as the sum of (the percentages of stained cells * their intensity), or (%1+) + (2 * %2+) + (3 * %3+), and ranges between 0 and 300. H-score from IHC2 panel for pS6(235), pS6(240), P4EPB1 and pAKT will be listed and summarized by cellular compartment. All other markers (PTEN) will be listed.

Definition of baseline for IHC

Unless otherwise specified the definition in Section 2.1.5.7 will be used. For assessments performed in tumor biopsies, fresh biopsy results will be used for baseline when both archived and fresh tumor samples are available.

% change from baseline for IHC

Change from baseline, percent change or fold change from baseline will be calculated.

Percent change from baseline is calculated as (biomarker value at visit i - baseline biomarker value) / baseline biomarker value*100.

If both the baseline and post baseline values are below LLOQ, absolute change, percent change will not be imputed and reported as missing.

3.7.2 Reporting

Tables

Standard contingency tables with counts and percent will be reported at each time point for categorical biomarker data (includes those categorized from continuous data).

Continuous biomarker data will be reported as follows:

- Mean, standard deviation, CV%, median, minimum, and maximum, as well as absolute change from baseline and relative change from baseline for biomarkers measured during treatment.

3.7.3 PD and PD/efficacy analyses

3.7.3.1 Exploratory imaging markers with [^{18}F]-FDG-PET

Descriptive statistics will be generated for each timepoint with the sSUVmax level, percentage changes from baseline, overall metabolic response by treatment group. The association between the [^{18}F]-FDG PET assessments (metabolic response) and clinical response (best overall response as defined by RECIST) will be assessed (at the patient level).

3.7.3.2 Circulating tumor markers

Baseline and post baseline levels for these markers (PSA, CEA, CA19-9, CA15-3, CA125, NSE, CYFRA21-1, SCC, CA72-4, AFP, HCG, Calcitonin, SMRP, HTG, thyroglobulin) measured will be listed.

3.7.3.3 Glucose metabolism markers

Descriptive statistics and mean (SD) profile plots will be generated for each timepoint (C1D2, C1D9 and C2D2) for the glucose metabolism markers. Only patients under fasting condition will be used for the summary statistics and figures. All data will be listed.

3.7.4 Next Generation Sequencing (NGS) data / efficacy

The NGS data will be summarized and listed according to the type of variant, type of mutation for each gene. Only sample with reported result will be summarized. Only somatic or unknown mutation origin and effects on phenotypic or tumorigenic (i.e. known or likely) will be included in the descriptive summary and listing. There are 3 types of variants: Short variant or sequence variant, copy number variant and re-arrangement.

Short variant mutations

Small-scale mutations or short variants are those affecting a small gene in one or a few nucleotides, including:

- Point mutations which include silent, nonsense and missense mutations. A point mutation is declared when the reference and alternate (observed) sequences (ref>alt) consist of identical length
- Insertions which consist on an addition of one or more extra nucleotides from DNA
- Deletion which consist on an removal of one or more extra nucleotides from DNA

Large scale mutations

Large scale mutations are those affecting a large chromosomal region, including:

- Amplification (or gene duplications) leading to multiple copies of the genes (copies >2)
- Deletion leading to loss of the genes (copies <2)

Re-arrangements

Re-arrangements include chromosomal mutations:

The number of patients (and percentages) with at least one genetic alteration will be summarized by genes and type of alteration. Post baseline (at time of EOT or PD) will only be listed.

The relationship between radiological (RECIST) response and NGS will be evaluated based on:

- Waterfall plots as per investigator assessment (see Section 3.5.2.3) and heatmap with most frequent (>=5%) genetic alteration by selected indication.

4 References

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[Smith BP, Vandenhende FR, DeSante KA, et al (2000)] Confidence interval criteria for assessment of dose proportionality. Pharm. Res; 17(10):1278-83.