New Mexico Cancer Care Alliance	**New Mexico Cancer Care Alliance**

INST UNM 1601: Compassionate Use of BYL 719 Alpelisib

TABLE OF CONTENTS:

Ian Rabinowitz, MD

Principal Investigator Date 01/19/2017

1.0 **RATIONALE**

This is a compassionate use protocol of BYL719 (alpelisib) treatment for a single patient with locally advanced lymphangioma positive PI3K alpha H1047R mutation.

2.0 **OBJECTIVES**

2.1 To provide off-label use of alpelisib to this patient with locally advanced lymphangioma.

2.2 To record outcomes of this patient while he is on alpelisib.

3.0 **BACKGROUND**

3.1 Drug Chemistry:

Alpelisib is provided as 50-mg and 200-mg film coated tablets as individual patient supply, packaged in bottles. Alpelisib will be administered at a starting dose of 350mg orally once daily on a continuous dosing schedule and can be adjusted for toxicity.

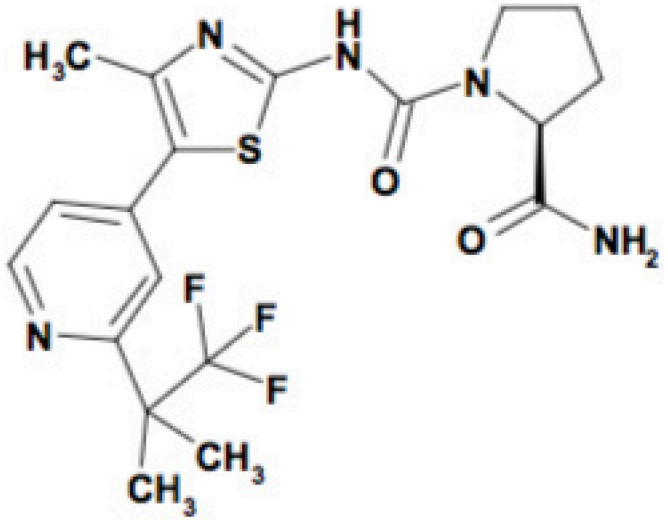
Alpelisib is currently prepared as film-coated tablets, which are intended for oral administration. The tablets in early phases are supplied at dosage strengths 10 mg, 50 mg, and 200 mg. 50 mg, 150 mg, and 200 mg are planned to be used as commercial strengths.

Different formulations of the drug product have been used in early trials. The tablets that were developed initially contained the following excipients: Microcrystalline cellulose / cellulose microcrystalline, Lactose monohydrate, Croscarmellose sodium, Hypromellose / hydroxypropylmethylcellulose, Poloxamer, Colloidal silicon dioxide / colloidal anhydrous silica, and Magnesium stearate. The tablet film coat contains the following excipients: Hypromellose / Hydroxypropylmethylcellulose, Titanium dioxide, Macrogol / Polyethylene glycol (PEG), Talc, Iron oxide yellow, Iron oxide red, and Iron oxide black.

An optimized tablet was developed to replace the initial tablet formulation. In addition to the active substance, the tablets contain the following excipients: Microcrystalline cellulose / cellulose microcrystalline, Mannitol, Sodium starch glycolate (Type A) / Sodium starch glycolate, Hypromellose / hydroxypropylmethylcellulose, and Magnesium stearate. The tablet film coat contains the following excipients: Hypromellose / Hydroxypropylmethylcellulose, Titanium dioxide, Macrogol / Polyethylene glycol (PEG), Talc, Iron oxide red, and Iron oxide black.

Alpelisib is (2S)-1-N-{4-Methyl-5- [2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl} pyrrolidine-1,2-dicarboxamide. Its molecular formula is $C_{19}H_{22}F_3N_5O_2S$. Its relative molecular mass is 441.47.

Its structural formula is:



Alpelisib exists as white to practically white powder.

Alpelisib, being a base drug substance, shows pH dependent solubility, is soluble in low (acidic) pHs, and remains insoluble in high (alkaline) pHs. The following table shows its solubility in various media.

Table 3-1 Solubility of alpelisib at 25 degree Celsius

Solvent	Solubility (mg/mL)
Buffer pH 1.0	>5
Buffer pH 3.0	0.08
Buffer pH 5.0	0.03
Buffer pH 6.8	0.02
SGF[1], pH 2.0	0.30
FaSSIF[2], pH 6.5	0.05
FeSSIF[3], pH 5.0	0.32
[1] Simulated gastric fluid [2] Fasted state simulated intestinal fluid [3] Fed state simulated intestinal fluid	

3.2 **Reported adverse Events**

Summary and incidence of adverse events is mentioned here and detailed management algorithms will be mentioned later in the protocol.

1) Hyperglycemia

Hyperglycemia is an on-target effect of alpelisib, and it has been observed both in preclinical and clinical studies. In studies of alpelisib, at the maximum tolerated dose (MTD) of 400 mg, the frequency of hyperglycemia (all grades) ranged between 51.4 and 66.2%; being the frequency of grade 3/4 events from 21.4 to 40.0%. When alpelisib is administered at 300 mg QD as a single agent in study CBYL719X2101, the frequency of grade 3/4 hyperglycemia is 12.5%.

2) Rash

Skin toxicity, mainly in the form of maculopapular rash or generalized rash, has been observed in clinical trials with alpelisib. In studies of alpelisib, at the MTD of 400 mg, the frequency of rash (all grades) ranged between 43.1-60%; and the frequency of grade 3/4 events from 0-21.4%. When alpelisib is administered at 300 mg daily (QD) as a single agent in study CBYL719X2101, the frequency of grade 3/4 rash is 0%.

3) Gastrointestinal (GI) toxicity

In preclinical toxicology studies, animals treated at the MTD of alpelisib experienced gastrointestinal (GI) toxicity, mainly consisting of vomiting and diarrhea. Clinical experience shows that nausea, vomiting and diarrhea are common AEs when alpelisib is administered either as a single agent or in combination; however grade 3/4 events are infrequent. In BYL719 studies (including combination studies with other agents) at the MTD of 400 mg the frequency of nausea, vomiting, diarrhea ranged between 40-83.1%; and the frequency of grade 3/4 events from 0-13.8%. When alpelisib is administered at 300 mg QD as a single agent in study CBYL719X2101, the frequency of grade 3/4 nausea, vomiting, diarrhea is 0%.

4) Cardiovascular toxicity

Preclinical studies indicate a minimal risk of an electrophysiological effect of alpelisib . In the single agent arm of the study CBYL719X2101, when BYL719 was administered above 270 mg QD, three cases of QT prolongation were observed. Two of them when alpelisib at 300 mg QD (n=6), and one case was observed at 400 mg QD (n=65). None of these events were grade 3/4 nor had a clinically-significant associated signs and/or symptoms. Alpelisib did not cause any clinically significant arrhythmia.

In the single agent arm of the study CBYL719X2101, at the MTD (i.e. 400 mg QD cohort, n=65) one patient (1.5%) experienced drug-related hypertension. Single measurements of increased blood pressure were observed at various dose levels, which were all transient without clinical significance. No other clinically significant hypertension was reported at lower dose, further selected for clinical development (i.e. 300 mg QD or 350 mg QD).

In the single agent arm of the study CBYL719X2101, at the MTD (i.e. 400 mg QD cohort, n=65) one episode of ST segment depression [0.7%] was reported. This event was not grade 3/4 and had not clinically significant associated signs and/or symptoms, such as cardiac arrhythmias or cardiac ischemia events. No clinically evident arrhythmias have been reported with alpelisib as a single-agent.

5) Hematological toxicity

In animal toxicology studies, BYL719 showed effects on the erythropoietic (decrease in hemoglobin, red blood cells, and reticulocytes) and lymphopoietic (decrease in lymphocytes) systems. In the study CBYL719X2101, at 400 mg QD of alpelisib (n=65) given as a single agent, there were 18 events (27.7%) of hematopoietic cytopenias, of which 3 (4.6%) were grade 3/4. One event (1.5%) of grade 3/4 febrile neutropenia was observed. Current protocols mandate for an adequate bone marrow function at study entry. In addition, in order to ensure patients' safety, hematological assessments are conducted at regular intervals, at least once per treatment cycle, in all alpelisib clinical studies.

6) Pneumonitis, interstitial lung disease

Based on the most recent review of both the clinical and pharmacovigilance databases, Novartis concludes that as of 20 May 2015, there were nine serious cases of pneumonitis reported with alpelisib (regardless of relationship to drug) including three with fatal outcome. Of the nine serious cases, one case was reported with BYL719 single agent and eight with alpelisib in combination with agents including cetuximab, fulvestrant, MEK162, AMG479, LGX818, LJM716 and LEE011. On 12th December 2014, Novartis issued an Investigator Notification for a patient from the CLJM716X2103 trial (alpelisib in combination with the anti-HER3 monoclonal antibody LJM716) with a serious, unexpected, possibly related adverse event of fatal pneumonitis.

3.3 Mechanism of action

The phosphatidylinositol 3-kinase (PI3K) signaling pathway regulates diverse cellular functions, including cell proliferation, survival translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso 2001) PI3K signaling also serves a central role in the pathogenesis of numerous forms of neoplasia. At the structural level, the enzyme PI3K is composed of a 110-kDa catalytic subunit and an 85-kDa adaptor subunit. PI3K signaling is modulated by multiple regulators, including growth factors (such as EGF, IGF-1, and FGF), hormones (such as estrogen and thyroid hormone), integrins, intracellular calcium levels, and RAS signaling. PI3K signaling is negatively regulated at the level of PIP3 clearance by phospholipid phosphatases, such as the phosphatase and tensin homologue (PTEN) protein and the inositol 5-phosphatase-2 (SHIP2) protein.

Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors which contribute to the onset and growth of many solid tumors as well as tumors of the hematopoietic system (Liu 2009). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal

therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006). Moreover, preliminary data suggest that activation of the PI3K pathway might be a predictor of poor prognostic outcome in many cancers.

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

PI3K alpha signaling in malignant cells

Somatic PIK3CA missense mutations have received a great deal of attention since the discovery that these missense mutations occur at high frequency in many human cancer types. Sequencing of the entire gene revealed that PIK3CA, is somatically mutated in 32% of CRCs (Samuels 2004), 27% of glioblastomas (Samuels 2004, Hartmann 2005), 25% of gastric cancers (Samuels 2004a Samuels 2004b, Li 2005), 36% of hepatocellular carcinomas (Lee 2005), 18 to 40% of breast cancers (Bachman 2004, Levine 2005, Wu 2005), 4-12% of ovarian cancers (Levine 2005, Wu 2005), and 4% of lung cancers (Samuels 2004).

From these mutation frequencies, PIK3CA, the gene encoding p110α is one of the most commonly mutated genes identified in human cancers, suggesting that p110α is the main PI3K isoform which drives tumor growth. In particular, high frequencies of “hot spot” mutations have been observed in colorectal, gastric, brain, breast and lung cancers (Samuels 2004, Liu 2006, Isakoff 2005, Ikenoue 2005). 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 and H1047R, which represents about 80% of the mutations observed, suggesting that they confer a selective advantage to the cell carrying the mutation.

In addition to the hot-spot mutations, numerous rare cancer specific mutations are widely distributed over the entire 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).

Together these observations suggest that the catalytic subunit p110α of the PI3K pathway could be a critical therapeutic target for the treatment of patients with advanced PIK3CA-driven malignancies who often have limited therapeutic options beyond the standard of care.

Hence, the α-selective-PI3K inhibitor alpelisib may potentially address an unmet medical need in such patients.

Alpelisib (NVP-BYL719) is an oral class I α-specific phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2-aminothiazole class of compounds. Alpelisib is best described as PI3Kα inhibitor in that it inhibits p110α (and p110α mutations) but less strongly the β, δ, and γ

isoforms. It is inactive against the majority of other kinases. Alpelisib has been studied extensively in non-clinical models and is currently being evaluated in clinical trials.

3.4 Distribution

Alpelisib had a low clearance (CL), a moderate volume of distribution at steady state (V_{SS}) 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 binding is independent of the concentration. Alpelisib showed a rapid distribution to almost all rat tissues, except the brain (radiolabeled ^{14}C-BYL719 study). Alpelisib was found to be preferentially present in melanin containing tissues such as the choroid and ciliary body of the eye but declined with time. The highest tissue exposures after dosing were found in the liver, bile, harderian gland, hair follicles, tactile hair and in the preputial gland.

The overall metabolic turnover was very low in dog and human hepatocytes followed by the rat. Cytochrome P450 (CYP)3A4 was found to be the major P450 enzyme involved in hepatic oxidative metabolism in vitro with small contribution by other enzymes. While UGT phenotyping showed that UGT1A9 enzyme could be involved in the glucuronidation of alpelisib in human liver microsomes, the turnover rate of phase II metabolism in vitro was low. The main biotransformation pathway that was observed consistently in vitro and in vivo across species was amide hydrolysis to BZG791. No covalent drug protein adduct formation was noted in human microsomes or hepatocytes.

Alpelisib is a substrate of breast cancer resistance protein (BCRP) and multidrug resistance (MDR)-1 (low affinity). It also showed very weak inhibition of MDR-1. No inhibition could be observed on BCRP- or MRP2-mediated transport. Uptake of alpelisib in human hepatocytes was found to be concentration-independent and was not influenced by inhibitors of the major transporter families OCT, OAT, OATP and NTCP. Assessment of the hepatobiliary disposition mechanisms of alpelisib in sandwich-cultured rat and human hepatocytes showed that it is actively transported into bile pockets. Alpelisib is not considered a human pregnane X receptor (PXR) or aryl hydrocarbon receptor (AhR) activator. Reversible weak inhibition of CYP2C8, CYP2C9 and CYP2C19 was observed. The compound is also a strong time-dependent inhibitor of CYP3A4. Alpelisib may possibly inhibit acetaminophen sulfation but is not expected to inhibit acetaminophen glucuronidation.

Results from 4-week Good Laboratory Practice (GLP)-toxicology studies in dogs 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. Increase in exposure up to doses of 50 mg/kg in rat was observed in a different non-GLP rat toxicology study. The toxicology studies provided no clear evidence of increased exposures following multiple dosing (<2-3-fold). No gender differences were observed in rat or dog.

The overall biotransformation of alpelisib in hepatocytes was low in all species tested (i.e. low in the rat, lower in dog and lowest in human hepatocytes). The main biotransformation pathway that was observed consistently across species was hydrolysis of proline amide moiety

(this is the only metabolite that was detected in human and dog hepatocyte incubations). No covalent drug protein adduct formation was noted in human microsomes or hepatocytes.

3.5 Metabolism

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

Median terminal elimination half-life ($T_{1/2}$) after a 400 mg oral dose was 7 to 8 hours and generally appeared to be independent of dose and time. Steady-state alpelisib plasma levels can be expected to be reached at 2 to 3 days following onset of therapy in most patients. At the MTD dose, median C_{max} and drug exposure within a dosing interval (AUC_{0-24h}) after one month of daily dosing was ~3810 ng/mL and ~46600 ng·h/mL, respectively. The median accumulation ratio (R_{acc}) of alpelisib across all dose levels was calculated to be about 1.3 which is in agreement with the short half-life of alpelisib. An apparent higher drug accumulation than expected based on the drug half-life was observed in some patients, with no clear relationship with dose. Also, an approximate dose proportional increase in both C_{max} and AUC was found, indicating no relevant deviation from linear pharmacokinetics. Dosing at 400 mg once daily produced a low mean oral plasma clearance (CL_{ss}/F) of 9.6 L/h. CL_{ss}/F appeared to be independent of dose. Moreover, the estimate of oral plasma clearance obtained from AUC_{inf} after a single 400 mg dose was comparable to the values obtained at steady-state (11.5 L/h), suggesting that clearance is not expected to change with dose or time. The oral clearance was about 10 to 15% of liver blood flow, and therefore a relatively minor contribution of hepatic first pass metabolism to the overall clearance of the drug is expected.

3.6 Excretion

Results from the rat ADME study showed that [^{14}C]BYL719- derived radioactivity was mainly excreted into feces with ~75-85% of the dose recovered by day 7, regardless of dose route (DMPK R0900368). Renal excretion was minor at 11-15% of the dose in urine in intact animals. In bile duct-cannulated rats, ~40% of BYL719 related radioactivity was recovered in bile, with an additional 25% being excreted in feces indicating potential intestinal secretion in rats Distribution data in rats following i.v. dosing indicate that radioactivity was present in the intestinal mucosa, which supports this conclusion. In total, about 20% of the dose was excreted unchanged in rat as BYL719 following i.v. and p.o. dosing. Unchanged BYL719 was found at 8.66% and 10.9% of dose in bile and feces after i.v. dosing to bile cannulated rats. Renal excretion of parent BYL719 was a minor component and accounted for less than 2% of the dose. Recovery of radiolabeled material was nearly complete for both dose routes with values of 92-100% indicating BYL719 related substance(s) is not retained in the body.

The potential active hepatobiliary disposition of apelisib was studied in sandwich-cultured rat (DMPK R1200423) and human hepatocytes (DMPK R1300212), which exhibit the formation of canalicular networks as well as polarized excretory function. Apelisib was found to be actively transported into the bile pockets of both the sandwich cultured rat and human hepatocytes.

3.7 Drug Interactions

In vitro studies demonstrate that alpelisib was found to be a time dependent inhibitor of CYP3A4 (Ki 5.6 µM, Kinact 0.011 min-1). Alpelisib may therefore increase exposure to drugs metabolized by CYP3A4. Reversible inhibition of CYP2C8 (Ki 32 µM = 14 µg/mL), CYP2C9 (Ki 22 µM = ~10 µg/mL) and CYP2C19 (IC50 75 µM) was also observed. Alpelisib may inhibit metabolic clearance of co-medications metabolized by CYP3A4, CYP2C8, CYP2C9 and CYP2C19, if sufficiently high concentrations are achieved in vivo (C_{max} ~3 µg/mL see 1.2.1.3). Clinically significant pregnane X receptor-mediated induction of CYP3A4 or aromatic hydrocarbon receptor-mediated induction of CYP1A2 by alpelisib is not expected.

Alpelisib is also a substrate of Breast Cancer Resistance protein (BCRP) and has low affinity for Pglycoprotein (P-gp/MDR1). Alpelisib does not inhibit BCRP or Multi-drug resistance protein-2 (MRP2), but showed very weak inhibition of P-gp (IC50 = 97 µM). As the maximal inhibition of P-gp was only about 32% with respect to positive control, the overall interaction potential is expected to be low.

Treating Physicians, at their discretion, may administer concomitant medications known to be metabolized by CYP3A4/5, CYP2C8, CYP2C9 and CYP2C19. Patients receiving such medications must be carefully monitored for potential toxicity due to any individual concomitant medications. Particularly, caution is advised when alpelisib is co- administered with drugs that are sensitive substrates for CYP3A4, CYP2C8, CYP2C9 or CYP2C19 and which have a narrow therapeutic index

3.8 How supplied

Alpelisib will be supplied as 50-mg and 200-mg film coated tablets, packaged in bottles, and will be given orally with a flat daily dose based. The tablets are packaged in HDPE bottles with a plastic child resistant closure.

The storage conditions for alpelisib will be described on the medication label. Indication labels will provide no information about the patient.

Treatment with Alpelisib

Packaging and labeling:

Treatment	Packaging	Labeling	Dosing Frequency
Alpelisib	Tablets in bottle 50 MG and 200 MG	Labeled as BYL719	Once Daily Dosing

4.0 PATIENT ELIGIBILITY

4.1 Inclusion criteria

Patient eligible for inclusion in this Treatment Plan have to meet all of the following criteria:

1) Patient has signed the Informed Consent (ICF) prior to any eligibility evaluations being performed and is able to comply with protocol requirements

2) Patient is an adult and $\geqslant$ 18 years old at the time of informed consent

3) Patient has locally advanced or metastatic cancer resistant or refractory to available standard of care treatment options and has no other available comparable or satisfactory alternative treatment options

4) PIK3CA mutation, or other molecular alteration known to activate PI3K, in tumor tissue as determined by a standard Laboratory

5) Patient is not eligible for participation in any ongoing clinical trials with alpelisib, or has recently completed a clinical trial with alpelisib that has been terminated, and after considering other options (e.g. trial extensions, amendments, etc.), the treating physician has determined that treatment is necessary and there are no other feasible alternatives for the patient

6) Patient is not being transferred from an ongoing clinical trial for which they are still eligible

7) Patient has adequate bone marrow and organ function as defined by the following laboratory values:

    a. Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L

    b. Platelets ≥ 100 x 10^9/L (For patients with hematologic malignancies involving the bone marrow, platelet count $>$ 75 x 10^9/L may be acceptable)

    c. Hemoglobin $\geqslant$ 9.0 g/dL

    d. INR $\leqslant$ 1.5

    e. Potassium, magnesium and calcium (corrected for albumin), within normal limits for the institution, or ≤ Grade 1 severity according to NCI-

CTCAE version 4.03 if judged clinically not significant by the investigator

f. Serum creatinine ≤ 1.5 x ULN and/or creatinine clearance > 50% LLN (Lower Limit of Normal)

g. Total serum bilirubin < ULN (or ≤ 1.5 x ULN if liver metastases are present; or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal range in patients with well documented Gilbert's Syndrome, (defined as presence of several episodes of unconjugated hyperbilirubinemia with normal CBC results including normal reticulocyte count and peripheral blood smear, normal liver function test results, and absence of other contributing disease processes at the time of diagnosis)

h. Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) ≤ 2.5 ULN (or < 5.0 x ULN if liver metastases are present)

8) Patient is deemed by the Treating Physician to have the initiative and means to be compliant with the treatment plan (treatment and follow-up requested by the Treating Physician)

4.2 Exclusion criteria

Patients eligible for this Treatment Plan must not meet any of the following criteria:

1) Patient has history of hypersensitivity to any drugs or metabolites of similar chemical classes as alpelisib

2) Patient has not recovered to grade 1 or better (except alopecia) from related side effects of any prior antineoplastic therapy

3) Patient has had major surgery within 4 weks prior to starting treatment with alpelisib or has not recovered from major side effects

4) Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting treatment with alpelisib, or has not fully recovered from side effects of such treatment

5) Patient with clinically manifest diabetes mellitus, or documented steroid induced diabetes mellitus

6) Patient is being treated at start of treatment with alpelisib with any of the following drugs:

Drugs known to be strong inhibitors or inducers of isoenzyme CYP3A4 including

herbal medications, or drugs with a known risk to induce Torsades de Pointes (See Appendix 1, Table 2 for a full list of prohibited medications).

Note: The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the treatment with alpelisib is initiated. Switching to a different medication prior to starting treatment with alpelisib is allowed.

7) Patient is currently receiving warfarin or other coumarin derived anti-coagulant for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.

8) Patients who have other concurrent severe and/or uncontrolled medical conditions that would, in the Treating Physician's judgment, contraindicate patient participation in the individual patient program (eg. active or uncontrolled severe infection, chronic active hepatitis, immuno-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.)

9) Patient has a known history of HIV infection (testing not mandatory) infection

10) Patient has any of the following cardiac abnormalities:

    a. Symptomatic congestive heart failure

        i. History of documented congestive heart failure (New York Heart Association functional classification III-IV), documented cardiomyopathy

        ii. Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)

    b. Myocardial infarction ≤ 6 months prior to enrolment

    c. Unstable angina pectoris

    Acute coronary angioplasty, or stenting), < 3 months prior to screening coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass graft (CABG).

    d. Serious uncontrolled cardiac arrhythmia

    History or current evidence of clinically significant cardiac arrhythmias, atrial fibrillation and/or conduction abnormality, e.g. congenital long QT syndrome, high-grade/complete AV-blockage: per guidelines.

e. Symptomatic pericarditis

f. QTcF > 480 msec on the screening ECG (using the QTcF formula) currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to starting treatment with alpelisib.

11) Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of alpelisib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)

12) Patient has other prior or concurrent malignancy (except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, early gastric or GI cancer resected completely by endoscopy procedures or any other cancer from which the patient has been disease free for $\geqslant 3$ years)

13) Patient has a history of non-compliance to medical regimen or inability to grant consent

14) Patient who does not apply highly effective contraception during the treatment with alpelisib and through the duration as defined below after the final dose of alpelisib:

a. Sexually active males should use a condom during intercourse while taking drug and for 4 weeks* after the final dose of alpelisib and should not father a child in this period, but may be recommended to seek advice on conservation of sperm. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
b. Women of child-bearing potential, defined as all female physiologically capable of becoming pregnant, must use highly effective contraception during the IPP and through at least 4 weeks* after the final dose of alpelisib
c. Highly effective contraception is defined as either:
    i. Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception].
    ii. Female sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before starting treatment with alpelisib. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    iii. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female patients participating to this IPP, the vasectomized male partner should be the sole partner for that patient]

iv. Use a combination of the following (both 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.

Note: Hormonal contraception methods (e.g. oral, injected, and implanted) are not allowed as alpelisibBYL719 may decrease the effectiveness of hormonal contraceptives.

* Please consult your local product labels should any concomitant medications be used, as this period may be longer for other potentially genotoxic compounds.

A female is 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 have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago before the treatment start. For females with therapy-induced amenorrhea, oophorectomy or serial measurements of Follicle-Stimulating Hormone (FSH) and/or estradiol are needed to ensure postmenopausal status.

NOTE: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LHRH) agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression.

5.0 **TREATMENT PLAN**

Informed consent must be obtained before conducting any treatment-specific procedures. Alpelisib is provided as 50-mg and 200-mg film coated tablets as individual patient supply, packaged in bottles. Alpelisib will be dosed on a flat scale of mg/day and not be adjusted to body weight or body surface area.

As a single agent, alpelisib will be administered at a starting dose of 350 mg orally once daily on a continuous dosing schedule and can be adjusted for toxicity per the recommendations in this protocol. No pretreatment will be given prior to the medication.

We plan on treating this individual patient for a tentative period of 12 weeks at which time treating physician will reevaluate the patient's clinical and radiological response and further duration of treatment will be contingent on that assessment.

The following general guidelines must be followed for alpelisib administration:

1) Patients should be instructed to take the dose of alpelisib once daily in the morning, at approximately the same time each day

2) Alpelisib must be taken within 1 hour after a light breakfast (e.g., consisting juice, toast and jam). A light breakfast is defined as approximately 500 calories, with approximately

75% from carbohydrates and approximately 25% from protein and/or fat.

3) Alpelisib should be taken with a glass of water. Patients should swallow the tablets as a whole and not chew them, however for patients with swallowing dysfunction without G tube, BYL719 film-coated tablets can be administered as drinkable suspension by crushing the tablets and suspending them in water. The drinkable suspension prepared from the film-coated crushed tablets is not permitted for administration into feeding tubes.

4) To limit the potential impact of H_2 antagonists, alpelisib should be administered at least one hour before or 10 hours after H_2 antagonists (or proton pump inhibitor, antacid, etc.) administration

5) If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose

6) If the patient forgets to take her dose before 18:00 (6:00 PM), then the dose should be withheld that day and alpelisib should be restarted the following day

7) Patients must avoid concomitant intake of strong CYP3A inhibitors and inducers.

6.0 PRETREATMENT EVALUATION

6.1 A complete history and physical examination to include performance status, weight, vital signs and concurrent non-malignant disease and therapy will be done before starting treatment. Prior surgery, chemotherapy, and radiotherapy details will be noted.

6.2 Laboratory studies should include a CBC with differential cell count, platelet count, electrolytes, liver function tests, fasting plasma glucose, and coagulation parameters.

6.3 A pregnancy test in women of childbearing potential.

6.4 ECG, ECHO cardiogram.

7.0 EVALUATION DURING STUDY

1) Physical examination, performance status and toxicity recording will be done every 4 weeks.

2) During the study, patients will be followed every 4 weeks with a ($\pm$7 days) CBC, differential and platelet counts, electrolytes, liver function tests

3) Measurable and evaluable disease will be evaluated by appropriate studies at least every 12 weeks to evaluate response.

4) All female patients of childbearing potential will use barrier contraception during treatment.

5) Monitoring will continue for at least 8 weeks after the end of drug treatment, or until

any adverse events are resolved (whichever is longest).

8.0 CRITERIA FOR RESPONSE AND TOXICITY

1) Toxicity will be evaluated at each course of therapy. The following dose modifications will be used for toxicity:

Starting Dose Level 0	350 MG
Dose Level -1	300 MG
Dose Level -2	250 MG

2) All toxicities encountered during the study will be evaluated according to the grading system (0-4) NCI CTCAE version 3 and recorded prior to each course of therapy. Duration of side effects and ancillary treatment will be recorded. The management of individual toxicities and grading will be as below

Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib/placebo**
Investigations (Fasting Plasma Glucose)	
Hyperglycemia	
Grade 1 (> ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For patients with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this apply only for values > 140 mg/dL (7.7 mmol/L)	Maintain dose level and re-check within 24 hours: if grade worsens, follow specific recommendations*; if grading is confirmed continue alpelisib/placebo dosing. • Initiate oral anti-hyperglycemic therapy (e.g. metformin or thiazolidinediones) or intensify medication with appropriate anti- diabetic treatment • Check FPG as clinically indicated and at least weekly for 8 weeks, then continue checking at least every 2 weeks until FPG resolves to < Grade 1
Asymptomatic Grade 2 (>160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	Maintain dose level and re-check within 24 hours: if grade worsens or improves, follow specific recommendations; if grading is confirmed continue alpelisib/placebo dosing. • Initiate oral anti-hyperglycemic therapy (e.g. metformin orthiazolidinediones) or intensify medication with appropriate anti- diabetic treatment, consider adding a second oral agent if no improvement after several days • Monitor FPG as clinically indicated and at least weekly until FPG resolves to ≤ Grade 1 • If FPG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib/placebo by 1 dose level

	• Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks
Asymptomatic Grade 3 (> 250 - 500 mg/dL) [> 13.9 - 27.8 mmol/L] Or Grade 2 with signs or symptoms of hyperglycemia (e.g., mental status changes, excessive thirst, polyuria)	Omit alpelisib/placebo and re-check within 24 hours: if grade worsens or improves, follow specific recommendations. If grading is confirmed omit alpelisib/placebo dosing. • Consider administering intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate • Initiate or intensify medication with appropriate anti-diabetic treatment (consider adding insulin) as per investigator's discretion. • Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1 • If FPG resolves to ≤ Grade1 within 21 days, then re-start alpelisib/placebo and reduce 1 dose level • Continue with anti-diabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks • If FPG doesn't resolve to Grade1 within 21 days, then discontinue patient from alpelisib/placebo
Grade 4 (> 500 mg/dL) [≥ 27.8 mmol/L] Or Grade 3 with signs or symptoms of hyperglycemia (for ex., mental status changes, excessive thirst, polyuria)	Immediately omit alpelisib/placebo, initiate or intensify medication with appropriate anti-diabetic treatment (consider adding insulin), re-check within 24 hours. If grade improves then follow specific grade recommendations. If FPG is confirmed at Grade 4: • Discontinue patient from alpelisib/placebo • Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate • Initiate or intensify medication with appropriate anti-diabetic treatment (consider adding insulin) as per investigator's discretion
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until resolved, then ↓ 1 dose level

Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Investigations (Renal)	
Serum creatinine	
< 2 x ULN	Maintain dose level
2 – 3 x ULN	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue patient from alpelisib/placebo
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from alpelisib/placebo

Investigations (Hepatic)

Bilirubin

(*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)

Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level with LFTs* monitored as per protocol
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, ↓ 1 dose level • If resolved in > 7 days discontinue patient from alpelisib/placebo
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from alpelisib/placebo

AST or ALT

Confounding factors and/or alternative causes for increased transaminases like concomitant medications, infection, hepato-biliary disorder, obstruction, liver metastasis, etc. should be excluded before dose interruption/reduction

Grade 1 (> ULN – 3.0 x ULN)	Maintain dose level with LFTs* monitored per protocol
Grade 2 (> 3.0 - 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	For patients with grade 0 or 1 at screening Omit dose until resolved to ≤ baseline value If treatment delay is ≤ 7 days, restart at same dose If resolved in > 7 days, ↓ 1 dose level For patients with grade 2 at screening Maintain dose level with LFTs monitored per protocol
Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Baseline value, then If treatment delay is ≤ 7 days, restart at same dose If resolved in > 7 days, ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level

AST or ALT and concurrent Bilirubin

AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Permanently discontinue alpelisib/placebo

*LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT. For patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct

bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher) and GGT).
Patients with grade 0 or 1 at screening experiencing ALT/AST/bilirubin increase ≥ grade 2 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1. In case of any
occurrence of ALT/AST/bilirubin increase ≥ grade 3 the liver function tests must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1; hereafter the monitoring should be continued every other week or more frequently if clinically indicated until the end of treatment with study medication. Patients who
discontinued study treatment should be monitored weekly, including LFTs or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization (no CTCAE grade change over 4 weeks).

Investigations (Cardiac)

Cardiac – QTc prolongation

QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	First Occurrence: • omit alpelisib/placebo • Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. • Perform a repeat ECG within one hour of the first QTcF of > 500 ms or >60ms from baseline • If QTcF remains > 500 ms or >60ms from baseline, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input. • Once QTcF prolongation has resolved, alpelisib/placebo may be restarted at a one lower dose level Second Occurrence: Permanently discontinue patient from alpelisib/placebo

Cardiac - Left Ventricular Systolic Dysfunction

Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	-Maintain dose level, and continue alpelisib with caution -Repeat LVEF within 4 weeks or as clinically appropriate
Symptomatic, responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	-Omit alpelisib/placebo until resolved* (as defined below), then ↓ 1 dose level -LVEF measurement to be repeated, if not resolved* within 28 days permanently discontinue patient from alpelisib/placebo treatment
Refractory or poorly controlled, ejection fraction < 20%	Permanently discontinue patient from alpelisib/placebo

*the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥ 40% and
≤20% decrease from baseline.

Other Cardiac Events

Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue patient from alpelisib/placebo

Stomatitis/Oral mucositis

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

Investigations (Skin and subcutaneous tissue disorders)

Grade 1	-Maintain dose level. -Initiate antihistamine dosing. Recommend non-sedating regimen for at least 28 days. -Topical corticosteroid preparation** b.i.d. for affected areas for at least 28 days.
Grade 2	-Maintain dose level. -Initiate antihistamine dosing. Recommend non-sedating regimen during the daytime and sedating at QHS for at least 28 days. -Topical corticosteroid preparation** b.i.d. for affected areas for at least 28 days. -Oral corticosteroid (recommend prednisone 0.5-0.75 mg per kg q.d. or equivalent for 10 days). If rash resolves to Grade 0-1 within 10 days, oral corticosteroid may be discontinued, tapered dosing not needed. If oral prednisone administered continuously for >10 days, tapered dosing is indicated. Intravenous steroid administration can be substituted for oral administration. If rash is not grade ≤1 in 14 days, continue or readminister oral corticosteroid (recommend prednisone 0.5-0.75 mg q.d. or equivalent for 10 days; longer periods of dosing require tapered dosing).
Grade 3/Intolerable Grade 2	-Hold alpelisib/placebo dosing until rash resolved to Grade 0-1 and consider dermatology consult for skin biopsy and photographs. -Initiate antihistamine dosing. Recommend non-sedating regimen during the daytime and sedating at QHS for at least 28 days. -Topical corticosteroid preparation** b.i.d. for affected areas for at least 28 days. -Oral corticosteroid (recommend prednisone 0.5-0.75 mg q.d. or equivalent for 10 days). If rash resolves to Grade 0-1 within 10 days (and does not recur with redosing; see below for guideline on

	rechallenge), oral corticosteroid may be discontinued, tapered dosing not needed. If oral prednisone administered continuously for >10 days, tapered dosing is indicated. Intravenous steroid administration can be substituted for oral administration. -If rash is not grade ≤1 in 14 days, continue or readminister oral corticosteroid (recommend prednisone 0.5-0.75 mg q.d. or equivalent) until resolved and alpelisib/placebo is restarted. Upon rechallenge with alpelisib/placebo (once rash Grade ≤1), continue oral corticosteroid for at least 48 hours. If rash and/or pruritus do not recur in 48 hours, discontinue corticosteroid dosing. Antihistamine regimen should be continued for a minimum of 28 days after rechallenge with alpelisib/placebo. A dose reduction of one dose level is recommended if this is a second occurrence. Dose reduction is not necessary following the first occurrence of Grade 3 or intolerable Grade 2 rash. Grade 3: Consider exploratory skin biopsy
Grade 4	-Permanently discontinue patient from alpelisib/placebo and consider a dermatology consult. Treatment of rash should follow guidelines for Grade 3/intolerable Grade 2 rash above with the exception of rechallenge and with any additional measures needed. -Consider exploratory skin biopsy

Management of Pneumonitis

This patient receiving treatment with alpelisib will be routinely asked about and observed for the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). Patients who are suspected to have developed pneumonitis should suspend study treatment (alpelisib with or without any other agent in combination) immediately and undergo appropriate imaging (high resolution CT scans) and broncho-alveolar lavage and biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out. Management of pneumonitis which generally includes treatment with high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Consultation with a pulmonologist is highly recommended for any pneumonitis case during the study treatment. Alpelisib and any other drug (if suspected to be etiologically related to the AE of pneumonitis) should be permanently discontinued in all patients with confirmed pneumonitis. In case of documented pneumonitis, the guidelines in this table should be followed.

Pneumonitis	Required Investigations	Management of Pneumonitis	Study Treatment Modification
Any Grade	• Obtain appropriate imaging (e.g. high resolution CT scan) • Consider broncho-alveolar lavage (BAL) and biopsy if clinically appropriate • Infectious causes of interstitial lung disease should be ruled out	• Follow institutional practice for management of pneumonitis (e.g. treatment with high dose corticosteroids; concurrent antibiotic therapy if infectious causes are suspected). • Consultation with a pulmonologist is highly recommended	• Immediately interrupt both alpelisib with or without any other agent in combination for any case of suspected pneumonitis. • For all patients with confirmed pneumonitis • Alpelisib should be permanently discontinued • Any other agent should be permanently discontinued if suspected to be etiologically related to the pneumonitis

3) Any adverse event will be evaluated and treated by the investigator as deemed appropriate in light of the medical situation. All pertinent observations and treatments will be recorded, both on an outpatient and inpatient basis (should hospital admission be required). Should death occur on study, every effort will be made to obtain autopsy data with careful examination of suspected target organs such as the bone marrow and lungs, as well as examination of the tumor for possible chemotherapy induced changes.

9.0 CRITERIA FOR DISCONTINUING THERAPY

1) Increasing disease during therapy

2) The development of unacceptable toxicity as mentioned above

3) Change in the medical status of the patient such that the investigator believes that patient safety will be compromised.

4) Non-compliance by the patient with protocol requirements.

5) Patient refusal.

10.0 STATISTICAL CONSIDERATIONS

1) This is a compassionate use protocol. No statistics will be used. Only descriptive data will be collected as described above.

11.0 DATA AND PROTOCOL MANAGEMENT

1) Protocol Compliance: The attending physician and oncology research nurse must see each patient prior to each course of treatment. All required interim and pre treatment data should be available prior to each treatment course for the physician to make a designation as to tumor response and toxicity grade.

2) At the conclusion of the study, appropriate follow-up care will be provided for this patient.

12.0 ANALYSIS OF DATA

None will be performed. However, case reports may be drafted from the data observed in this compassionate protocol

13.0 REPORTING REQUIREMENTS

An adverse event is defined as any untoward medical occurrence in a patient administered alpelisib that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of alpelisib, whether or not related to it.

Medical conditions/diseases present before starting treatment with alpelisib are only considered adverse events if they worsen after starting treatment with alpelisib. The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit. 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.

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

Adverse event reporting includes but is not limited to the following:

1) Any serious and/or unexpected and severe (grade 4 non-hematologic toxicity) toxicity will be reported immediately to the study sponsor (Novartis) who, in turn, must notify the Chairman of the IRB (CFR 312.32).

2) Serious adverse events include toxicities which cause death, are life-threatening, result in inpatient hospitalization or prolongation of an existing hospitalization, cause a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. To ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient has provided informed consent and until 30 days after the patient has stopped participation to the IPP (defined as time of last dose of alpelisib taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 day period should only be reported to

Novartis if the Treating Physician or other involved health care professional suspects a causal relationship to the treatment with alpelisib. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the Treating Physician or other involved health care professional receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

3) Laboratory tests for hematology, chemistry will be performed to assess toxic effects of the study treatment. All laboratory tests performed will be assessed by the investigator as to their clinical significance. Any post-baseline laboratory value which is found to be clinically significant will be assessed by the investigator for a causal relationship to the study drug and the appropriate action taken.

4) Removal of a patient from the study because of adverse experiences or changes in laboratory test values, whether by the investigator or by the patient's own volition, should be reported promptly to the study sponsor (Novartis).

14.0 **REFERENCES**

Katso, R., et al. (2001). "Cellular function of phosphoinositide 3-kinases: implications for development, homeostasis, and cancer." Annu Rev Cell Dev Biol **17**: 615-675.

Liu, P., et al. (2009). "Targeting the phosphoinositide 3-kinase pathway in cancer." Nat Rev Drug Discov **8**(8): 627-644.

McCubrey, J. A., et al. (2006). "Roles of the RAF/MEK/ERK and PI3K/PTEN/AKT pathways in malignant transformation and drug resistance." Adv Enzyme Regul **46**: 249-279.

Samuels, Y., et al. (2004). "High frequency of mutations of the PIK3CA gene in human cancers." Science **304**(5670): 554.

Hennessy, B. T., et al. (2005). "Exploiting the PI3K/AKT pathway for cancer drug discovery." Nat Rev Drug Discov **4**(12): 988-1004.

Markman, B., et al. (2010). "Status of PI3K inhibition and biomarker development in cancer therapeutics." Ann Oncol **21**(4): 683-691.

Sansal, I. and W. R. Sellers (2004). "The biology and clinical relevance of the PTEN tumor suppressor pathway." J Clin Oncol **22**(14): 2954-2963.

Cheng, J. Q., et al. (1992). "AKT2, a putative oncogene encoding a member of a subfamily of protein-serine/threonine kinases, is amplified in human ovarian carcinomas." Proc Natl Acad Sci U S A **89**(19): 9267-9271.

Cheng, J. Q., et al. (1996). "Amplification of AKT2 in human pancreatic cells and inhibition of AKT2 expression and tumorigenicity by antisense RNA." Proc Natl Acad Sci U S A **93**(8): 3636-3641.

Shayesteh, L., et al. (1999). "PIK3CA is implicated as an oncogene in ovarian cancer." Nat Genet **21**(1): 99-102.

Hartmann, C., et al. (2005). "PIK3CA mutations in glioblastoma multiforme." Acta Neuropathol **109**(6): 639-642.

Li, V. S., et al. (2005). "Mutations of PIK3CA in gastric adenocarcinoma." BMC Cancer **5**: 29.

Lee, J. W., et al. (2005). "PIK3CA gene is frequently mutated in breast carcinomas and hepatocellular carcinomas." Oncogene **24**(8): 1477-1480.

Bachman, K. E., et al. (2004). "The PIK3CA gene is mutated with high frequency in human breast cancers." Cancer Biol Ther **3**(8): 772-775.

Levine, D. A., et al. (2005). "Frequent mutation of the PIK3CA gene in ovarian and breast cancers." Clin Cancer Res **11**(8): 2875-2878.

Wu, G., et al. (2005). "Somatic mutation and gain of copy number of PIK3CA in human breast cancer." Breast Cancer Research **7**(5): R609-R616.

Isakoff, S. J., et al. (2005). "Breast cancer-associated PIK3CA mutations are oncogenic in mammary epithelial cells." Cancer Res **65**(23): 10992-11000.

Ikenoue, T., et al. (2005). "Functional analysis of PIK3CA gene mutations in human colorectal cancer." Cancer Res **65**(11): 4562-4567.

Bader, A. G., et al. (2005). "Oncogenic PI3K deregulates transcription and translation." Nat Rev Cancer **5**(12): 921-929.

Engelman, J. A., et al. (2008). "Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers." Nat Med **14**(12): 1351-1356.

Appendix 1: Concomitant Medications

Table 1: List of medications to be used with caution during treatment with apelisib

Category	Drug Name
CYP2A6 substrates	Disulfiram, fadrozole, halothane, losigamone, methoxyflurane, nicotine, valproic acid
Sensitive CYP2C8 substrates[2]	Paclitaxel, repaglinide
Sensitive CYP2C9 substrates[2]	Phenytoin
Sensitive CYP2C19 substrates[2]	S-mephenytoin, R/S-lansoprazole, clobazam, omeprazole, tilidine
Moderate CYP3A Inhibitors	Amprenavir, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus paradisi fruit juice), imatinib, Schisandra sphenanthera[2], tofisopam, verapamil
Moderate CYP3A Inducers	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Gastric protection agents	Alpelisib is characterized by a pH-dependent solubility. Medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of alpelisib and hence its bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H_2-antagonists (e.g., ranitidine) and antacids. Alpelisib should preferably be dosed in a staggered manner, i.e., at least 1 hour before or 10 hours after dosing with a gastric protection agent. Note that some proton pump inhibitors may possibly inhibit BCRP (see below).
BCRP inhibitors	Alpelisib was identified as a substrate for the human BCRP. Co-administration of alpelisib with BCRP inhibitors may possibly increase systemic exposure and/or alter tissue uptake of oral alpelisib.The treatment with BCRP inhibitors should be kept as short as possible or, if possible, fully avoided.
Drugs with a possible risk for Torsades de Pointes / QT prolongation[4]	Alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, eribulin, escitalopram, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, levofloxacin, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, ondansetron, oxytocin, paliperidone, pasireotide, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tamoxifen, tizanidine, venlafaxine, voriconazole, ziprasidone
Hematopoietic growth factors	Hematopoietic growth factors (e.g. erythropoietins, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered prophylactically. Use of these drugs should be reserved to patients with severe neutropenia and anemia as per the labeling of these agents or as dictated by local practice (see also the guidelines established by the American Society of Clinical Oncology (ASCO)).
Corticosteroids	Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone may prolong or aggravate hyperglycemia (steroid-induced diabetes), which is a common adverse event for PI3K inhibitors such as alpelisib, they should be additionally used with caution and closely monitored.
Anticoagulation	Anticoagulants other than warfarin/coumarin derivates (Appendix 1, Table 12-1) or antiaggregation agents may be administered under the discretion of the investigator. However, caution is advised when alpelisib is co-administered with

Category	Drug Name
	anti-platelet pro-drugs such as clopidogrel, ticlopidine and prasugrel, which require metabolic activation by CYP3A4, CYP2C9 and CYP2C19. Alpelisib has the potential to inhibit some of these enzymes and may therefore decrease the metabolic activation and clinical efficacy of these pro-drugs. Patients using anti-platelet pro-drugs should be carefully monitored.

[1]Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria, or as specified in Section Concomitant Medications of this guideline document or listed in Appendix 2, Table12-2.
[2]Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
[3]NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[4] Please also refer to http://crediblemeds.org/ for a comprehensive list of agents that prolong the QT interval.

Table 2: List of prohibited medications during apelisib treatment

Category	Drug Name
Strong CYP3A Inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole
Strong CYP3A Inducers	Avasimibe[2,3], carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]
CYP3A substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
Sensitive CYP3A Substrates[4]	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, indinavir, levomethadyl, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simvastatin, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc
Other investigational and antineoplastic therapies	Other investigational therapies should not be used while the patient is treated within the IPP. Anticancer therapy [chemotherapy, biologic or radiation therapy, and surgery (unless specified in protocol - tbc)] other than the treatment with alpelisib must not be given to patients while the patient is treated within the IPP. If such agents are required for a patient then the patient must be discontinued from the IPP.
Herbal medications	Herbal preparations/medications are prohibited throughout the study, as a potential drug-drug-interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of alpelisib.
Warfarin and coumarin derivatives	Therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants are prohibited in this study. Warfarin has a narrow therapeutic range and alpelisib is a possible inhibitor of CYP2C8 and 2C9, the major metabolizing enzyme of warfarin. Therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

Category	Drug Name
Drugs with a known risk for Torsades de Pointes / QT prolongation[5]	Amiodarone, amitriptyline (2C19), arsenic trioxide, astemizole, cepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, clomipramine (2C19), disopyramide, dofetilide, domperidone, dronedarone (CYP3A4), droperidol, erythromycin, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozide, probucol, procainamide, quetiapine (3A4), quinidine, ritonavir (3A4), sotalol, sparfloxacin, tacrolimus (3A4), telithromycin (3A4), terfenadine, thioridazine, trazodone (3A4), vandetanib, vardenafil (3A4)

[1]NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes)

[2]Herbal product

[3]P-gp inducer

[4]Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when

[5] Please also refer to http://crediblemeds.org/ for a comprehensive list of agents that prolong the QT interval.