An open-label pilot study to evaluate the efficacy and safety of a combination treatment of Sonidegib and BKM120 for the treatment of advanced basal cell carcinomas

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List of abbreviations

AE	Adverse Event
AKT	See PKB (protein Kinase B)
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CK	Creatinine Kinase / Phosphokinase
CK-MB	Creatinine Kinase – Muscle and Brain isoenzyme
CR	Complete Response
CRD	Clinical Research and Development
CS	Cowden Syndrome
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
EGFR	Epidermal Growth Factor Receptor
18F-FDG	[18F]-Fluorodeoxyglucose
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
HDL	High density lipoprotein
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low density lipoprotein
LVEF	Left Ventricular Ejection fraction
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition Scan
PD	Pharmacodynamic
PET	Positron Emission Tomography
PI3K	Phosphatidylinositol 3'- kinase
PK	Pharmacokinetic
PKB	Protein Kinase B (or AKT)
PT	Prothrombin Time

PTEN	Phosphatase and Tensin homolog
PTT	Partial Thromboplastin Time (also known as APTT)
QTc	QT interval (corrected)
RBC	Red Blood Cells
REB	Research Ethics Board
RECIST	Response Evaluation In Solid Tumors
S6K	Protein Kinase S6
SAE	Serious adverse event
SOP	Standard Operating Procedure
SUV	Standardized Uptake Value
TTP	Time to Progression
ULN	Upper Limit of Normal
WBC	White Blood Count
WCBP	Women of Childbearing Potential
WHO	World Health Organization

1 Background

1.1 Disease Background

Basal cell carcinoma (BCC) is the most common human malignancy with an estimated 2 million cases diagnosed annually (American Cancer Society 2010). Most of these forms of skin cancer are highly curable if found and treated early. However, a fraction of these are highly aggressive and difficult-to-treat with conventional therapies. These can become life-threatening and even metastasize to distant organs. These BCCs are collectively termed advanced BCCs (aBCCs). Recently, the Smoothened inhibitor (SI) class of drugs has emerged as a highly targeted therapy for BCCs resulting in the ability to shrink BCCs while causing minimal collateral damage. (Sekulic *et al*., 2012) However, less than 50% of aBCCs respond to (SIs). Of those that respond, approximately 20% become resistant to SIs after 1 year. (Chang and Oro, 2012) Recently, our group has identified one mechanism of SI drug resistance, specifically increase in the PI3 kinase pathway (Chang et al., 2013, in press) Hence, we propose a preliminary proof-of-principle clinical trial to describe the overall response rate of aBCCs to combination SI and PI3K inhibitor treatment. We also will characterize the mean duration of response on this combination therapy. These data will be critical for future clinical studies using greater sample size.

1.2 Hedgehog Pathway and mechanism of action

Smoothened (Smo) is a G protein-coupled receptor-like molecule that positively regulates the Hedgehog (Hh) signal transduction pathway. Hh pathway activation (Figure 1) at or upstream of Smo is linked to the pathogenesis of several types of cancer. In particular, activating mutations in Hh pathway genes have been identified in patients with medulloblastoma (MB), basal cell carcinoma (BCC), and rhabdomyosarcoma. Aberrant

Figure 1. Schematic representation of the Hh pathway depicting mechanism of action of Sonidegib (http://www.novartisoncology.us/research/pipeline/Sonidegib.jsp)

upregulation of the Hh pathway without known mutation is linked to the pathogenesis of many other cancer types including pancreatic breast, esophageal, gastric, colorectal, glioblastoma, ovarian, sarcoma, acute and chronic leukemias, multiple myeloma, lymphoma and small-cell lung cancer (SCLC). Antagonists of Smo are hypothesized to block the growth of tumors that are dependent on Hh pathway activation. Furthermore, preclinical and emerging clinical data suggests Hh signaling may play an important role in many hematological cancers, such as acute and chronic leukemia, multiple myeloma and lymphomas.

Sonidegib is a potent, selective and orally bioavailable Smo antagonist. Treatment with sonidegib results in tumor regression *in vivo* in several genetically defined MB models. Efficacy in these tumor models is dose-related and correlates with inhibition of Hh pathway signaling, as measured by decreased Gli1 mRNA. Treatment with sonidegib in

combination with other therapeutic agents also shows *in vivo* efficacy in many tumor models including of pancreatic cancer, glioma, and SCLC.

Sonidegib is a potent antagonist of Hedgehog (Hh) - and Smoothened (Smo)-dependent signaling. Smo is a GPCR-like molecule that positively regulates the Hh signal transduction pathway. Hh signaling plays critical roles in the development and homeostasis of many human organs and tissues, including the skeletal system, gastrointestinal tract, kidney, and eye (McMahon, Ingham and Tabin 2003). In the resting state, the 12-pass transmembrane protein Patched (Ptch) inhibits activity of the divergent GPCR Smo. The Hh family protein ligands Sonic Hedgehog (SHH), Desert Hedgehog (DHH) and Indian Hedgehog (IHH) can all bind to and inactivate Ptch, leading to release of Smo repression. Active Smo signals via a cytosolic complex of proteins including Suppressor of Fused (SuFu) to the Gli1 family of transcription factors. Active Gli1 signaling can cause cell proliferation and differentiation.

Genetic activation of the Hh pathway at or upstream of Smo is linked to proliferation of several tumor types. Patients with a germline mutation in Ptch have activated Hh signaling and develop Gorlin's Syndrome, or basal cell nevoid syndrome (BCNS). Gorlin's patients present with skeletal and dental anomalies due to developmental patterning defects, together with a high incidence of BCC, pediatric MB, ovarian cysts and ovarian carcinoma. Moreover, somatic mutations in Ptch and Smo have been detected in human MB and BCC. Activating mutations in Ptch and Smo are found in 20% of sporadic pediatric MB (Lee *et al* 2003, Thompson *et al* 2006), and in >70% of sporadic BCC (Gailani *et al* 1996, Xie *et al* 1998). Smo antagonists exert dose-dependent anti-tumor activity in *vivo in* several genetically defined MB models that are driven by mutations in Ptch (Romer *et al* 2004).

Hedgehog overexpression, accompanied by increased expression of Hh target genes, is detected in a broad spectrum of human tumor biopsies and cell lines, including small cell lung cancer, gastric cancer, prostate cancer and pancreatic cancer. Growth of Hh-overexpressing tumors in xenograft models has been shown to be inhibited by treatment with cyclopamine, a small molecule antagonist of Smo (Watkins *et al* 2003, Thayer *et al* 2003, Karhadkar *et al* 2004, Berman *et al* 2003, Rubin and De Sauvage 2006, Clement *et al* 2007).

Since sonidegib may inhibit the growth of a wide range of cancers with aberrant upregulation of Hh signaling, the first-in-human study is a phase 1, multicenter, open-label, dose-escalation study of oral sonidegib in patients with advanced solid tumors. Given the germline mutation in Ptch in Gorlin patients, a proof of concept in Gorlin patients presenting with BCCs has been conducted.

1.3 PI3K Pathway and mechanism of action

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

The 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 and in many tumor types. 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. Moreover, preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers.
Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to:

a. Gain-of-function mutations of PI3K subunits (*PIK3CA* encoding the PI3K catalytic subunit p110α; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (eg, HER2, EGFR, RAS, Src-family proteins) or
b. Loss-of-function mutations or epigenetic alterations affecting negative regulators ofPI3K signaling (eg, loss of PTEN expression or function)

Together these observations suggest that PI3K pathway could be a critical therapeutic target for the treatment of patients with advanced solid malignancies who often have limited therapeutic options beyond institutional standard of care. Hence, the pan-PI3K inhibitor buparlisib (BKM120) treatment potentially addresses an unmet medical need in such patients. A schematic representation of these PI3K components is shown in Figure 2. In 2010, Buonamici, et *al demonstrated* that the PI3K signally pathway is increased in medulloblastomas resistant to SIs. Concurrent administration of BKM appeared to delay the onset of resistant. Recently, our group interrogated BCCs with demonstrated resistance to vismodegib, an SI. In both these tumors, the levels of PI3K were increased compared to normal skin (Figure 3), in *press*. Furthermore, this combination SI and PI3K inhibitor therapy is currently in phase 1 studies for safety in patients with solid tumors. In our patient population, a significant number of patients are resistant to SI monotherapy or develop resistance after SI treatment. Few good options exist for these patients. Our data suggests that combination therapy with SI inhibitor and PI3K inhibitor is likely to delay resistance in these patients and is the subject of this proposal.

Figure 2 Schematic representation of the PI3K pathway

Figure 3. PI3K signaling pathway is increased in both resistant tumors from a patient treated with a SI, vismodegib.

1.4 Sonidegib Compound Information

Sonidegib is a potent and highly specific oral selective, Smo antagonist from a novel structural classN-[6-(cis-2,6-dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy)-1,1'-[biphenyl]-3-carboxamide diphosphate and has been shown to potentially inhibit Hh and Smo-dependent proliferation *in vivo*. This compound has been studied extensively in non-clinical models and is currently being evaluated in clinical trials.

1.4.1 Preclinical Studies for Sonidegib

1.4.1.1 Pharmacodynamics of Sonidegib

Sonidegib potently inhibits both human and mouse Smo at low nanomolar concentrations (11 and 12 nM, respectively) in competitive binding in *vitro assays*. In a single dose pharmacokinetic–pharmacodynamic (PK-PD) study, 20 mg/kg Sonidegib resulted in >90% inhibition Gli1 mRNA expression in tumor samples that was sustained for over 24 hrs. Daily multiple doses of Sonidegib (20 mg/kg QD) caused >90% tumor regression in genetically defined *in vivo* MB xenograft models characterized by heterozygous deletion of PTCH.

1.4.1.1.1 Nonclinical pharmacokinetics and metabolism of Sonidegib

Sonidegib (free base or diphosphate salt) and [^{14}C] sonidegib were used in the pharmacokinetic (PK) studies. Total radioactivity in rat blood, plasma and excreta samples was determined using a liquid scintillation counter (LSC). Parent drug in plasma was determined by high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS). The lower limit of quantification (LLOQ) for sonidegib was 1 ng/mL in the 4 week rat or dog GLP toxicity study. The LLOQ was 0.05ng/mL in the 13 and 26 week rat and dog GLP studies using a 0.05 mL aliquot of plasma. Metabolite concentrations and metabolite patterns in plasma and excreta were obtained by HPLC with radioactivity detection. Metabolite structural elucidation was carried out using LC-MS or LC-MS/MS.

Quantitative whole body autoradiography (QWBA) was also performed on rat tissues.

In all species investigated, bioavailability of the compound was high (from 68.5% in mouse to ~100% monkey) with the Tmax occurring between 1.7 – 48 h. In the rat, following a single oral dose, absorption of sonidegib-related radioactivity was high but was eliminated very slowly from the circulation (T1/2 169 h) compared to sonidegib (T1/2 10.6 h). LGE899, the major metabolite of sonidegib, exhibited a half-life of 155 hours, suggesting that the remaining circulating radioactivity was essentially associated to this metabolite.

After an IV dose in male rats, mini-pigs, and dogs using [^{14}C] sonidegib, and after an IV dose in mice and monkeys using unlabeled sonidegib, the plasma clearance (CL) was low to moderate compared to their respective hepatic blood flows. The estimated plasma volume of distribution at steady state (Vss) was moderate to high (greater than total body water) in all species, indicating wide tissue distribution, which was consistent with the rat ADME tissue distribution results (Section 4.2.3 of IB). The terminal elimination T1/2 of sonidegib in plasma was moderate in mouse (~3-5h) and longer in the rat, dog, and monkey (Section 4.2.5 of Investigator Brochure).

Clearance of Sonidegib is primarily hepatic by CYP3A4. Sonidegib was extensively metabolized, with the major metabolic pathway being via mono- or dioxygenation, demethylation, and oxidation leading to carboxylic acid formation, dealkylation, and dehydrogenation monohydroxylation. The elimination of metabolites was mainly through the bile.

Studies with human liver microsomes demonstrated that Sonidegib is a competitive inhibitor of CYP2B6 (IC_{50} ~0.5 μM; K_i 0.045 μM), and CYP2C9 (IC_{50}~5 μM; K_i 1.7 μM), but showed very little or no inhibition of CYP1A2, 2A6, 2C8, 2C19, 2D6, 2E1 or 3A4/5 at concentrations of up to 100 μM. No apparent time-dependent inhibition of the major CYP450 enzymes was observed. Sonidegib is neither a substrate nor an inhibitor of P-glycoprotein (Pgp) or multi-resistance protein 2 (MRP2); but it has demonstrated inhibitory effects on breast cancer resistance protein (BCRP), with an estimated IC_{50} value

of 1.5 mM. The potential of Sonidegib and its metabolites to undergo covalent binding to cellular macromolecules was found to be low.
The toxicokinetics of sonidegib have been investigated in male and female rats (4-, 13-, and26-week studies). In all studies, the exposure increased with dose, there was also evidence of sonidegib accumulation following repeated dosing (1.6- to 5.6–fold). There was a general under-proportionality of exposure with increasing doses in the 4 week rat study (doses of 20, 100, and 600 mg/kg/day) and over-proportional increases in exposure with increasing doses in the 13 and 26 week studies (doses up to 20 mg/kg/day). In the 4 week rat study, there was evidence of a sex difference, with females having higher exposure (particularly at the higher doses and after multiple doses), but there was no evidence of a sex difference in either the 13 or 26 week studies.
Juvenile rats (14 days post-partum) were dosed with sonidegib at 1, 3, 10, and 30 mg/kg/ day for 5 weeks. On day one, the AUC0-24 increase was roughly dose-proportional from 3 to 30 mg/kg/day and slightly greater than dose-proportional from 1 to 3 mg/kg/day. In week 5, a slight tendency for a greater than dose-proportional increase in AUC0-24 was observed. The female showed slightly higher exposure compared with the male rats. No obvious accumulation was seen after 5 weeks of dosing except that a 40-80% increase of exposure (AUC) was observed at 30 mg/kg dose for both gender and at 10 mg/kg for female. The dose normalized AUC at 10 and 30 mg/kg after single or multiple dosing are similar to those achieved in adult rats at 20 mg/kg dose. The toxicokinetics in the dog (4, 13, and 26 week studies) were similar to the rat. In general, increasing doses showed under-proportional increases in exposure after single doses in the 4 week toxicology study, and over-proportional exposure with multiple dosing in the 13 and 26 week studies. There was no difference in exposure between male and female dogs, and there was evidence of accumulation (2- to 46-fold) following repeated dosing.

1.4.1.1.2 Safety pharmacology and toxicology of Sonidegib

The majority of adverse effects observed in toxicity studies in growing rats and dogs can be attributed to the pharmacologic action of sonidegib, and the effects in both species were similar. The most striking effects of sonidegib, which are consistent with literature reports on other Hh pathway inhibitors, were on bone and consisted of thinning or closure of growth plates in the sternum and femur and decreasing proliferating chondrocytes in the chostochondral junction of ribs. In addition, decreases in bone alkaline phosphatase were observed in dogs (Investigator Brochure]. The observations were more pronounced in rats, which is a species where the growth plate does not close. Similar observations have been reported for other Smo inhibitors in animal studies (eg, GliLuc transgenic mice, IHH transgenic mice) including thinning and early closure of the growth plate, shortened bones, inhibition of tooth growth and abnormal bone structures, particularly the femur and tibia (Maeda 2007, Kimura 2008). This is likely due to the role of the Hh pathway in bone development, particularly in the early stages of bone formation and growth (Kimura 2008). These effects are not likely to occur in the adult cancer patient population intended for the clinical studies due to the maturity of their skeletal system. However, it anticipated that Smo inhibition may likely affect the development of bones and teeth in growing children. Hence, monitoring for these effects will be required during therapy with Smo inhibitors in children. Preclinical cardiovascular safety pharmacology data do not indicate a clinical risk for QTc prolongation. There is also no indication of effects on the central nervous and respiratory systems from the preclinical data. Please refer to the Investigator's Brochure for more details on the non-clinical toxicity and safety of sonidegib.

1.4.2 Muscular system

In the phase 1 trial (LDE225X2101), dose-limiting skeletal muscle toxicities characterized by CTCAE Grade 3 or Grade 4 creatinine kinase (CK) elevation associated with muscle pain and elevated plasma myoglobin have been observed in a dose and exposure dependent manner. No evidence of cardiac muscle toxicity has been observed. The majority of cases of CTC Grade 3/4 elevated CK, occurred 3 to 6 weeks after continuous daily treatment with sonidegib. Following the discontinuation of sonidegib, the majority of DLTs resolved over a period of approximately 4-8 weeks. Re-challenge with sonidegib at a lower dose appeared not to cause subsequent CK elevation. The DLTs were described in some cases as rhabdomyolysis, however, no impairment in renal function was been observed in any of the affected patients.

In the CLDE225A2112 drug-drug interaction study, one patient developed rhabdomyolysis with renal failure, which necessitated treatment with hemodialysis, as described in Section 5.2.1.8. Muscular activities such as strenuous exercise that can result in significant increases in plasma CK levels should be avoided while on sonidegib treatment. Patients who are taking statins appear to be at increased risk of developing Grade 3/4 CK elevation and therefore statins should be avoided while taking sonidegib. If it is essential that the patient stays on a statin to control hyperlipidemia, only pravastatin may be used with extra caution.

Patients should be assessed for the development of muscle symptoms such as myalgia, myopathy and/or muscle spasms. Serum creatinine and plasma levels of CK, CK-MB, and myoglobin should be closely monitored during the first 8 weeks and throughout treatment with sonidegib. If clinically significant increases in CK levels are detected, serum creatinine must be checked and the patients must be monitored for signs and symptoms of rhabdomyolysis. Management using supportive therapy including adequate hydration may be considered according to standard medical practice, institutional and applicable protocol-specific guidelines.

1.4.3 Skeletal system

In the GLP toxicology studies of sonidegib conducted in growing rats and dogs there was thinning or closure of growth plates in the sternum and femur and decreased proliferation of chondrocytes in the costochondral junction of ribs. These effects are more likely to occur in children where the growth plate is open. However, the effect of sonidegib on mature bones is not known, since the toxicology studies were conducted in growing animals. It is possible that treatment with sonidegib could have effects on bone metabolism in addition to its effect on the growth plate. In the clinical setting, apparent growth plate thinning was observed in 2 pediatric patients (aged 4 and 11 years) after approximate 9 month treatment with single agent sonidegib for medulloblastoma. Therefore, pediatric patients should be observed using imaging techniques (such as knee and wrist x-rays), assessment of changes in serum bone markers including bone-specific alkaline phosphatase, osteocalcin and N-terminal propeptide (type 1 collagen, as well as any other protocol-specific guidance in order to assess the potential effects on bone.

1.4.4 Reproductive system

The effects of sonidegib on the male and female reproductive tract of young rats and dogs included delayed or arrested maturation of the testes, prostate, ovary and uterus in young dogs and uterine atrophy in rats. Protocol-specific guidelines regarding the participation of women of child-bearing potential, the use of contraceptives, and the prohibition of treatment of pregnant and lactating women are provided in the study protocol. Patients should be informed that treatment with sonidegib carries the potential risk of causing infertility. However, a single oral dose of sonidegib employed to study the pharmacokinetics in healthy subjects is not expected to have effects on male reproductive tissues or to impair fertility of male subjects.
Sonidegib has been found to be teratogenic. The investigator is therefore advised to make patients aware of this risk. To minimize the risk of teratogenic effects, sonidegib should not be given to pregnant or lactating women. In addition patients intended to be treated with sonidegib should be made aware of this risk and instructed to apply appropriate barrier contraceptive methods during treatment with sonidegib.

1.4.5 Gastro-intestinal system

GI mucosal toxicity was observed in preclinical toxicology studies. In preclinical studies, observations included extreme distention of the stomach and duodenum in rats that died early or were euthanized moribund at the highest doses (600 mg/kg). These findings were associated with visible hemorrhage in the stomach wall, loss of mucosa with inflammation, and ulcerations of the non-glandular mucosa. Emesis and diarrhea were also observed at high doses (1000 mg/kg) in preclinical studies in dogs. These effects are considered unlikely to be related to the pharmacologic mechanism of action of sonidegib and are instead hypothesized to reflect the very high oral doses of sonidegib given to animals, coupled with the low solubility and incomplete absorption from the GI tract, resulting in direct irritation of the mucosa.
In on-going clinical studies, nausea, vomiting, and diarrhea have been reported as AEs. Patients should be monitored for symptoms and signs of such toxicity and care should be taken to ensure that patients in whom such symptoms arise do not develop dehydration. Management using supportive therapy with anti-emetics and/or anti-diarrheal medications may be considered according to standard medical practice, institutional and applicable protocol-specific guidelines.

1.4.6 Renal system

Rats treated with high doses (600 mg/kg) of sonidegib developed acute tubular necrosis and prominent mineralization of the tubular epithelium.
The renal function of patients receiving sonidegib should be closely monitored, including serum creatinine, urine output, urine color and specific gravity. Attention should be given to the prevention and treatment of dehydration, particularly if the patient reports muscle symptoms or there is laboratory evidence of an increased CK.

1.4.7 Clinical experience with Sonidegib

1.4.7.1 **Pharmacokinetics and pharmacodynamics of Sonidegib**

The PK summary of sonidegib in adult patients with advanced solid tumors assessed in study (LDE225X2101] can be found in the Investigational Brochure in Table 5-3. The available preliminary PK data demonstrate that the median peak plasma concentrations of sonidegib occurs at 4 hours (range: 2-24 hours) after dosing. Plasma exposure to sonidegib (Cmax and AUC) after single dose administration increases dose proportionally from 100-800 mg and appears to plateau at higher dose levels (1500 mg to 3000 mg). On cycle 1 Day 15 C_{max} and AUC increase linearly with doses up to 400 mg/ day, and in a less than dose-proportional manner with higher doses (800 to 3000mg/ day). Sonidegib exposure at 400 mg BID demonstrates ~30% higher mean AUC on day 15 compared with exposure at 800 mg QD, and AUC at 750mg BID is approximately 18% greater than the AUC achieved at 1500 mg QD. The median accumulation index is 3-fold (range: 0.5-12), and 6-fold (range: 2.22-22.1.) for C_{max} and AUC, respectively, on cycle 1 Day 15 compared with the single PK run-in dose. Due to the long apparent terminal half-life of sonidegib, an accurate terminal half-life cannot be calculated using a non-compartmental approach. The estimated effective half-life, calculated on the basis of the accumulation index across dose groups, is greater than 4 days (range: 1-14 days). Successive measurements of plasma trough concentrations (C_{min}) over time suggest that steady-state appears to be achieved after 28 days of daily dosing. Trough levels on day 15 (pre-dose) correlate well with AUC and Cmax on day 15 during daily administration of sonidegib. The inter-patient coefficient of variation in sonidegib AUC is 40 to 58% across the dose range of 100 mg to 3000 mg/day. Exploratory analyses suggest that the odds of observing a CK DLT increase with AUC on day 15. In addition, the probability of a CK DLT is expected to be low (< 0.16) for exposure levels (AUC day 15) below 41 μM*hr (equivalent to an average steady state concentration of approximately 1. 7 μM).

Analyses of skin punch biopsies taken at baseline and at the end of the first treatment cycle (day 28) have shown evidence of potent target modulation, as measured by Gli1 mRNA, in a dose- and exposure-dependent manner. The available data shows that sonidegib caused up to 95% mean reduction in Gli1 expression in skin compared with baseline values. The maximum observed inhibition of the target in skin (as measured by Gli1 expression) was observed at 1500 mg QD. Based on the limited data on PD effect in tumor biopsies (n=4 paired samples), where up to 99% reduction in Gli1 expression was observed, skin is a good surrogate tissue for assessing target inhibition. On the whole, the changes in Gli1 expression in skin appeared to be highly variable, particularly within the 800 mg QD cohort, where a relatively large number of paired samples were obtained compared with the other doses.

Sonidegib, at 800 mg QD, demonstrated a mean reduction in Gli1 mRNA in skin of approximately 74% (n=13, range: 8.3% - 95.8%) compared with baseline values after 28 days of therapy. At 200 mg QD, approximately 68% (n=4, range: 25.9% - 89.3%) reduction in Gli1 expression in skin was observed, with 87% reduction in the MB patient who achieved objective partial response.

The FDA has not yet approved the drug for treatment of this indication, and IND application is currently in process.

1.4.7.2 **Clinical experience with Sonidegib**

Sonidegib is currently undergoing phase 1, 2, and 3 evaluation in clinical trials, to assess the safety, tolerability, PK, PD and potential efficacy of continuous once daily oral administration in patients with malignant solid tumors as part of monotherapy and combination studies. Data provided here are obtained from an active clinical trial database; therefore, they are preliminary and subject to change upon final QC review when the study is completed.

1.4.7.2.1 Human safety and tolerability data of Sonidegib

As of November 29, 2013, a total of 701 cancer patients have been treated with sonidegib, including 60 pediatric patients, in 11 Novartis sponsored clinical studies.
There were 6 studies conducted with 316 healthy or hepatically impaired volunteers receiving single-dose sonidegib. In addition, there are Investigator Initiated Trials (IIT) being conducted under their own respective INDs. Data from these IITs are not included in this IB, except for SUSAR reports attributed to patients in IITs.
The dose limiting toxicities observed in the first-in-human adult study in patients with advanced solid tumors (CLDE225X2101) were creatinine phosphokinase elevation, AST increase, and myoglobin increase. The most common treatment emergent toxicities reported in this study were nausea, muscle spasms, increased blood creatinine phosphokinase, vomiting, decreased appetite, dysgeusia, fatigue, asthenia and myalgia. Common toxicities observed in on-going studies are summarized in Section 5.2 of the Investigator's Brochure. In general, the safety profile in pediatric patients appeared to be similar to adult patients. Clinical response (CR and PR) was observed in basal cell carcinoma, and medulloblastoma in both adult and pediatric patients. In general, the safety profile in pediatric patients appeared to be similar to adult patients. Clinical response (CR and PR) was observed in basal cell carcinoma, and medulloblastoma in both adult and pediatric patients.
The pharmacokinetic data in patients with advanced solid tumors showed that the median Tmax occurs at 2-13 hours after single or repeated oral dosing of 100 to 3000 mg/day. Mean plasma exposure to sonidegib appeared to increase approximately dose proportionally up to 400 mg, but less than proportionally above 400 mg. The median effective elimination half-life of sonidegib calculated based on drug accumulation in patients was 11 days. The median terminal half-life estimated after a single dose in healthy subjects was 10 days.
DLTs occurred during Cycle 1 at the 800 mg and 1000 mg QD and 750 mg BID dose levels. The most common DLT was Grade 4 increase in CK, which typically occurred between Days 24-30 of the study.

In addition to the increases listed in in Table 1 below, 14 additional patients had Grade 3/4 increases in CK, consisting of 1 patient at 800 mg QD, 1 patient at 1000 mg QD. 3 patients

Table 1. Incidence of dose limiting toxicities in Study CLDE225X2101

Dose of Sonidegib	No. patients treated	Elevated plasma CK		
		No. patients with CTCAE Grade 3	No. patients with CTCAE Grade 4	Total (CTCAE Grade 3 or 4)
100 mg QD	5	0	0	0
200 mg QD	6	0	0	0
400 mg QD	4	0	0	0
800 mg QD	21	0	1	1
1000 mg QD	7	0	1	1
1500 mg QD	8	0	0	0
3000 mg QD	4	0	0	0
250 mg BID	12	0	0	0
400 mg BID	6	0	0	0
750 mg BID	5	0	3	3
Total	78	0	5	5

at 1500 mg QD, 3 patients at 3000 mg QD, 2 patients at 250 mg BID, 2 patients at 400 mg BID, and 2 patients at 750 mg BID. These DLTs occurred after cycle 1, however, they were considered as part of the clinical review that occurred as a part of each dose escalation decision. Consistent with the findings during Cycle 1, Grade 3 and 4 CK elevations occurring in later cycles were not observed at dose levels below 800 mg on the QD schedule. These data supported the choice of 800 mg QD and 250 mg BID as the MTDs.

Overall 102 of 103 patients (99.0%) experienced an AE during the study, and the majority of patients (78 patients, 75.7%) had AEs, which were suspected to be related to study drug. Approximately 60% of the patients experienced Grade 3 or Grade 4 AEs, and approximately one-half of patients experienced an SAE. Fourteen patients died during the study or within28 days after the last dose of sonidegib. Twelve of the patient deaths were related to disease progression. The other 2 deaths on study were cardiac arrest and sudden death, both were considered to be unrelated to sonidegib. Other than DLTs, there were no clinically significant changes in laboratory values, vital signs, or ECG parameters during the study.

As seen in Table 2 below, the most common preferred terms were nausea (47 patients, 45.6%), muscle spasms, increased blood creatinine phosphokinase (35 patients each, 34.0%), vomiting, (33 patients, 32.0%), decreased appetite, dysgeusia (31 patients each,

30.1%), fatigue (29 patients, 28.2%), asthenia and myalgia (24 patients each, 23.3%). Other AEs were reported in less than 20% of patients.

Table 2. Adverse events suspected to be related with sonidegib, occurring in >/=5% of patients in Study CLDE225X2101 October 2012

	800 mg QD* (n=26)	All doses** (n=103)
	Any grades n(%)	Any grades n(%)
Nausea	10 (38.5)	47 (45.6)
Dysgeusia	5 (19.2)	31 (30.1)
Weight decrease	5 (19.2)	18 (17.5)
Decreased appetite	5 (19.2)	31 (30.1)
Vomiting	10 (38.5)	33 (32.0)
Diarrhea	3 (11.5)	17 (16.5)
Constipation	3 (11.5)	18 (17.5)
Muscle spasms	9 (34.6)	35 (34.0)
Myalgia	5 (19.2)	24 (23.3)
Blood CK increased	8 (30.8)	35 (34.0)
AST increased	3 (11.5)	14 (13.6)
ALT increased	2 (7.7)	10 (9.7)
Fatigue	6 (23.1)	29 (28.2)
Asthenia	7 (26.9)	24 (23.3)
Alopecia	4 (15.4)	13 (12.6)
Lethargy	3 (11.5)	7 (6.8)
Anemia	3 (11.5)	18 (17.5)
Pyrexia	3(11.5)	15 (14.6)
Abdominal Pain	2 (7.7)	13 (12.6)
Insomnia	2 (7.7)	13 (12.6)
Dyspnoea	5 (19.2)	13 (12.6)
Dizziness	4 (15.4)	12 (11.7)
Abdominal pain upper	4 (15.4)	11 (10.7)
Back pain	2 (7.7)	11 (10.7)
Cough	1 (3.8)	11 (10.7)
Oedema peripheral	1 (3.8)	10 (9.7)
Headache	3 (11.5)	10 (9.7)
Hypoalbuminaemia	2 (7.7)	9 (8.7)
Blood bilirubin increased	1 (3.8)	8 (7.8)
Pain in extremity	1 (3.8)	8 (7.8)
Dyspnoea exertional	3 (11.5)	8 (7.8)
Urinary tract infection	1 (3.8)	7 (6.8)
Musculoskeletal pain	0 (0.0)	7 (6.8)
Hyperbilirubinaemia	2 (7.7)	6 (5.8)
Arthralgia	0 (0.0)	6 (5.8)
Muscular weakness	2 (7.7)	6 (5.8)
Somnolence	1 (3.8)	6 (5.8)
Pruritus	2 (7.7)	6 (5.8)

* Recommended phase 2 dose in adults

** All doses, including BID and QD schedule

1.4.7.2.2 Clinical efficacy data of Sonidegib

Responses (confirmed, RECIST v1.0) were observed in 8 patients, 1 patient (1.0%) with CR and 7 patients (6.8%) with PR (see Table 3 below). SD was the best response in 24 patients

Table 3. Summary of best overall response by treatment – CLDE225X2101

	100 mg QD	200 mg QD	400 mg QD	800 mg QD	1000 mg QD	1500 mg QD	3000 mg QD	250 mg BID	400 mg BID	750 mg BID	All
	N=6 n (%)	N=6 n (%)	N=5 n (%)	N=26 n (%)	N=11 n (%)	N=9 n (%)	N=10 n (%)	N=14 n (%)	N=8 n (%)	N=8 n (%)	N=103 n (%)
CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (1.0)
PR	1 (16.7)	1 (16.7)	0 (0)	3 (11.5)	1 (9.1)	0 (0)	0 (0)	1 (7.1)	0 (0)	0 (0)	7 (6.8)
SD	1 (16.7)	2 (33.3)	2 (40.0)	6 (23.1)	1 (9.1)	3 (33.3)	2 (20.0)	4 (28.6)	2 (25.0)	1 (12.5)	24 (23.3)
PD	3 (50.0)	3 (50.0)	3 (60.0)	11 (42.3)	6 (54.5)	3 (33.3)	3 (30.0)	6 (42.9)	4 (50.0)	2 (25.0)	44 (42.7)
Unknown	1 (16.7)	0 (0)	0 (0)	6 (23.1)	3 (27.3)	3 (33.3)	5 (50.0)	3 (21.4)	1 (12.5)	5 (62.5)	27 (26.2)

Best overall response is based on investigator's assessment of disease status using RECIST.

(23.3%), and PD was the best response in 44 patients (42.7%). Consistent with the mechanism of action of sonidegib, all responding patients had diagnoses of basal cell carcinoma (BCC) or medulloblastoma, cancers known to be driven by activation of the Hedgehog pathway. Of 16 patients with BCC, 1 patient achieved a CR and 5 patients achieved PR, for a response rate of 38% in this subset. Of the 9 patients with medulloblastoma, 2 patients achieved a PR, for a response rate of 22%. In addition one patient with medulloblastoma, whose only site of disease was bone metastases, had a metabolic PR by [18F]-FDG PET. The disease in this patient could not be evaluated by CT.

1.5 Buparlisib (BKM120)

NVP-BKM120 (buparlisib, BKM120) is a potent and highly specific oral panclass I PI3K inhibitor that is a 2, 6-dimorpholino pyrimidine derivatives. This

compound has been studied extensively in non-clinical models and is currently being evaluated in clinical trials.

1.5.1 Preclinical studies of Buparlisib

Buparlisib activity against class I PI3K (p110α, -β, -δ and -γ), Class III (Vps34), the class IV mTOR related PI3K or PI4Kβ, was assessed using either using a luciferase luminescence (class I or III PI3Ks and PI4Kβ) or a TR-FRET assay (Class IV mTOR). The IC50 in these assays is outlined below in Table 4:

Table 4. Inhibitory activities (IC50) of buparlisib against other PI3K or related kinases

Buparlisib significantly inhibits p110α and the most common p110α mutations (H1047R, E454K, E542K), p110β, p110δ and p110γ but not the related proteins Vps34, mTOR or PI4Kβ. Hence buparlisib is classified as a pure pan-class I PI3K inhibitor. Enzymatic characterization of the inhibitory properties of the compound revealed that buparlisib is a mixed inhibitor of PI3Kα with a strong competitive component (largest on Vmax). The cocrystal X-ray structure of buparlisib with PI3Kγ confirmed that buparlisib interacts with PI3K into the ATP catalytic cleft.

The PI3K pathway regulates the activity of the mTORC1 complex, when cells are challenged through mitogenic stimuli. In order to assess in cells the potential impact of the buparlisib on the mTORC1 complex, the compound was tested in TSC1 null cells. These cells express a constitutively activated mTORC1 complex that uncouples the mTOR pathway from the PI3K upstream input (Kwiatkowski 2003). When exposed to TSC1 null MEFS, buparlisib reduced the S235/236P-RPS6 levels with an IC50 of 1785 nM, in agreement with the data obtained in the mTOR biochemical assay. In contrast, and as expected the allosteric mTORC1 inhibitor RAD001 displayed sub-nanomolar inhibitory activity in this assay.

In contrast to molecules with distinct mechanism of action (BCR-Abl inhibitor STI571, mTORC1 allosteric inhibitor RAD001), buparlisib is able to decrease the phosphorylation status of various either direct (GSK3β, FKHRL1/FOXO3a) or indirect downstream Akt effectors (p70S6K, through mTOR) in the PTEN null U87MG cell line, as efficiently as prototypical PI3K inhibitors such as LY294002 and Wortmannin.

Forkhead transcription factors (such as FKHRL1) are re-located from the nucleus to the cytosol upon phosphorylation by Akt. Treatment of U2OS cells stably expressing GFP - FKHRL1 chimera to GFP with buparlisib produced a strong nuclear localization of the fluorescence signal, in agreement with the reduction of the phosphorylated FKHRL1 levels. Signaling pathways from membrane receptors to nuclear transcription factors involve many different players such as kinases or molecular adaptors. To test whether buparlisib does influence other signaling molecules outside of the PI3K pathway, induction of various pathways (mitogenic with EGF and PDGF, stress pathways with anisomycine and interleukine pathways with IL-4) were interrogated in the presence of the compound. In all cases, buparlisib showed specific PI3K pathway attenuation, as demonstrated by specific attenuation of S473P-Akt levels, without affecting the non PI3K driven read –outs such as activated receptors (EGFR, PDGFR), MAPK kinases (ERK, JNK and p38) or Jak cytosolic tyrosine kinases responsible for Stat transcription factor phosphorylation.

1.5.1.1 **Preclinical Safety of Buparlisib**

Safety pharmacology studies in rats revealed no effects on neuronal (behavior) or respiratory functions. Cardiac safety studies, conducted *in vitro* and *in vivo*, did not indicate a prominent electrophysiological risk. In the isolated rabbit heart, effects pointing towards a shortened repolarization were seen only at 10 µM. Buparlisib inhibited hERG channel activity significantly at concentrations ≥ 100 µM (IC_{50}: 190 µM). No relevant electrophysiological effect was seen in dogs. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, observed in two dog telemetry studies.

Repeated-dose studies (up to 13 weeks of duration) were performed in rats and dogs. In rats, clinical pathology and histopathology findings showed a decrease in lymphocyte counts in the peripheral blood, decreases in germinal center development in different lymph nodes, and lymphocytolysis in the thymus. In dogs, similar findings occurred. In both species, erythropoiesis was affected, as evidenced by reduced erythrocyte counts, accompanied by bone marrow depression observed in rats.

The pancreas was seen to be affected by treatment with buparlisib, particularly in dogs, where acinar cell toxicity was seen in the exocrine part of this organ. In addition, in one of the four recovery animals minimal acinar cell atrophy was observed after four weeks treatment-free period. In rats, in the 4-week study, no pancreas toxicity was observed (however, in the 2-week dose range finding study, at higher doses, there were histopathological findings of the endocrine as well as the exocrine pancreas).

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

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

After up to 2 weeks of treatment with up to 2.5 mg/kg/day, decreased levels of glutamate, dopamine, serotonin and epinephrine as well as elevated levels of glutamine, GABA (gamma-amino butyric acid) and HIAA (5-hydroxyindoleacetic acid, a serotonin breakdown product) were seen in rats. The increased levels of HIAA and decreased levels of serotonin indicates an increased serotonin breakdown, pointing to a potential perturbation of the serotonin release and/or re-uptake. Generally, the decreased levels of glutamate, dopamine, serotonin and epinephrine points to an exhaustion of these neurotransmitters. No such effects were seen in cerebrospinal fluid (CSF) or plasma of those animals.

Both in vitro and in vivo, buparlisib elicited a genotoxic potential. While no evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro, a potential for genotoxicity was concluded based on the observation of an aneugenic potential, seen in this latter experiment. In line with this result, buparlisib treatment resulted in an elevated frequency of micronucleated polychromatic erythrocytes in the bone marrow of rats. Data indicate the absence of a relevant photoxic potential of buparlisib.

In conclusion, the majority of the observed effects were related to the pharmacological activity of buparlisib as an inhibitor of PI3K, such as a potential influence on glucose/insulin homeostasis and the risk of increased blood pressure. Main target organs of toxic effects were bone marrow and lymphoid tissue, pancreas, and male as well as, to a lesser extent, female reproductive organs. Further, neurotransmitter fluctuations were seen in the brain of rats, not visible in plasma or cerebrospinal fluid.
Please refer to the Investigator's Brochure for additional information on the preclinical testing of buparlisib.

1.5.1.2 **Pharmacodynamics of Buparlisib**

Buparlisib inhibits wild-type PI3Kα (IC_{50}: 35 nM), with at least 50-fold selectivity towards this target compared to other protein kinases as well as against somatic PI3Kα activating mutants (H1047R-, E542K-, and E545K-p110α), the other three PI3K paralogs as well as the direct downstream effector AKT. Buparlisib does not inhibit the related kinases mTOR or Vps34, nor does it inhibit other receptors and ion channels profiled (IC_{50} >10 μM). Buparlisib demonstrates significant tumor growth inhibition in relevant tumor xenografts in mice and rats when administered orally, including models of renal cell cancer (RENCA, 786-0, Caki-1), glioblastoma multiforme (U87MG), prostate cancer (PC3M), lung cancer (A549, NCI-H1975), ovarian cancer (A2780), colorectal cancer (HCT116, HCT-15) and melanoma (A2058, A375). *In vivo* PK/PD analyses of tumor tissues shows a good correlation between exposure, PI3K pathway blockade (S473P-Akt levels), and anti-tumor activity.

1.5.1.2.1 Nonclinical pharmacokinetics and metabolism of Buparlisib

Buparlisib showed favorable pharmacokinetic properties in all animal species tested. The absorption of [$_{14}$C]-buparlisib-related radioactivity was >84% in the rat. Oral bioavailability was high in rats (73%), was complete in dogs, and was moderate in monkeys (42%). The estimated steady state plasma volume of distribution (Vss) was high (3.0-3.5 L/kg) in all species tested, suggesting a wide tissue distribution. Buparlisib was found to cross the blood brain barrier in rats with a tissue-to-plasma ratio of approximately 2 (Novartis internal data). Buparlisib is moderately bound to plasma protein in all species examined (about 80%).
In vitro metabolism studies using human liver microsomes showed that oxidative phase 1 metabolism of buparlisib was predominantly mediated by CYP3A4 (estimated fm > 0.9). Formation of a buparlisib N-glucuronide conjugate (phase 2 metabolism) via the UDP-glucuronosyltransferase-1 family, polypeptide A4 (UGT1A4) was also observed in human liver microsomes supplemented with uridine 5'-diphosphoglucuronic acid (UDPGA). Buparlisib and metabolites have a low potential for covalent binding to protein. Buparlisib was determined to be a weak reversible inhibitor of CYP3A4 (IC50 = 8 μM, Ki = 13.4 μM unbound) at concentrations reached in the clinic. Buparlisib very weakly inhibited the CYP2C family (2C8, 2C9 and 2C19) with IC50 values ranging from 35-65 μM (34-59 μM unbound). Buparlisib did not show time-dependent inhibition of CYP450 enzymes. In GLP toxicology studies, buparlisib exposure in terms of AUC0-24h and Cmax increased in a dose proportional manner in rat and dog. Results from the rat ADME study showed that radioactivity was mainly excreted into the feces. Renal

excretion was minor. There was no noticeable drug accumulation in dog or male rats after 13 weeks of daily dosing. There was a slight accumulation in female rat (< 2 fold).
Further information concerning the pharmacokinetic and pharmacodynamics properties of buparlisib may be found in the Investigator Brochure.

1.5.1.2.2 Safety pharmacology and toxicology of Buparlisib

Safety pharmacology studies in rats revealed no effects on neuronal (behavior) or respiratory functions. Cardiac safety studies, conducted in vitro and in vivo did not indicate a prominent electrophysiological risk. No relevant electrophysiological effect was seen in dogs. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, which was observed in two dog telemetry studies. In rats and dogs, clinical pathology and histopathology findings showed quantitative reductions of lymphoid and erythroid counts and lymphoid tissue hypoplasia.
The pancreas was seen to be affected by treatment with buparlisib, particularly in dogs, where acinar cell toxicity was seen in the exocrine part of this organ. At higher doses in the 2-week dose-range-finding study in rats, there were histopathological findings in both the endocrine as well as the exocrine pancreas.
Male sexual organs and associated tissues were found to be targets of toxicity in both rats and dogs. Changes included minimal to slight germ cell depletion, formation of spermatic giant cells and abnormal spermatids, and cellular debris in epididymal tubules. Testicular toxicity did not fully reverse after the 4-week treatment-free period in rats (highest dose), although a clear trend towards recovery was seen. In individual female rats, minimal to slight cyst formation occurred in the Graafian follicles. In dogs, there was no effect on female sexual organs.
Glucose homeostasis was affected in various species (mice, rats, dogs), as expected from the mode of action of buparlisib. However, these effects were minimal in both rats and dogs at the doses used in the 4-week studies.
Other safety considerations include:

- ♦♦ After up to 2 weeks of treatment with up to 2.5 mg/kg/day of buparlisib, alterations in the levels of multiple brain neurotransmitters were seen in rats.
- ♦♦ No evidence for a direct DNA interaction was found in an Ames test and two chromosome aberration tests in vitro with buparlisib. However, evidence of a genotoxic potential with buparlisib has been seen in vitro and in vivo and is likely due to an aneugenic effect.
- ♦♦ No phototoxic potential or any effect on wound healing has been identified with buparlisib in pre-clinical studies.

In conclusion, the majority of the observed effects were related to the pharmacological activity of buparlisib as an inhibitor of PI3K, such as a potential influence on glucose homeostasis and the risk of increased blood pressure.
Please refer to the Investigator's Brochure for additional information on the preclinical testing of buparlisib.

1.5.1.2.3 Pharmacodynamic biomarkers of Buparlisib

The preclinical *in vivo* studies with xenografted tumors in mice indicate that detectable inhibition of AKT phosphorylation, which is an accurate readout of PI3K activity, as well

as further suppression of downstream signaling (eg, phosphorylation of S6) was obtained soon after buparlisib administration. PI3K is known to serve a pivotal role in the regulation of glucose homeostasis, and preclinical studies in which oral glucose and intraperitoneal insulin tolerance tests were performed suggesting post-treatment induction of insulin insensitivity/resistance. Therefore, throughout the trial the circulating levels of several markers for glucose metabolism (eg, glucose, insulin, C-peptide) will be assessed as an additional measure of PI3K signaling modulation.

1.5.2 Clinical experience with Buparlisib

1.5.2.1 Pharmacokinetics and pharmacodynamics of Buparlisib

Pharmacokinetic data observed so far showed that buparlisib is rapidly absorbed after oral administration with mean peak plasma concentrations (C_{max}) ranging between 0.5 to 4 h post dose (t_{max}). The median t_{max} at the MTD dose (100 mg daily) was about 1 hour. After reaching C_{max}, buparlisib plasma concentrations decreased in a bi-exponential manner. Apparent total body clearance from plasma (CL/F) was low: ~5.0 L/h, indicating that buparlisib is a low clearance drug. Buparlisib accumulated ~3-fold in achieving steady-state, consistent with an effective half-life of ~40 h. Steady-state can be expected to be reached after approximately 7-10 days of daily dosing in most patients. Approximate dose-proportional increase in C_{max} and AUC was found in the dose range of 12.5-150 mg. Intersubject variability in C_{max} and AUC differed at each dose level but was relatively low and generally around 40%. Doses of 50mg/day and above led to steady-state drug exposure (AUC0-24,.SS) > 10,000 ng*h/mL, a target efficacious exposure level estimated preclinically.
Due to the difficulty to obtain fresh tumor tissue during treatment, pharmacodynamic measurements were limited to surrogate tissues such as skin and blood. The parameters assessed have been selected for their relevance to PI3K/mTOR signaling modulation: phosphorylated S6 ribosomal protein in the skin (S6 is a well-known downstream target of mTOR/PI3K pathway) and C-peptide and glucose levels in the blood (PI3K/ mTOR signaling has a critical role in glucose metabolism). A formal analysis of these assessments is currently ongoing. Consistent suppression of S6 activation in skin was evident at the highest doses tested (100 and 150mg/day) with 30 to 80% decrease from baseline levels. Occasional increases of C-peptide have been seen at all doses, while hyperglycemia was one of the DLTs suggesting potential impairment of glucose transport and utilization by the tissues (insulin resistance). More information is provided in the Investigator's Brochure.

1.5.2.2 Clinical Experience with Buparlisib

As of September 2013, a total of 1469 patients were enrolled into twenty two Novartis sponsored clinical studies of buparlisib, including 3 blinded phase 2 and phase 3 studies:

- Phase 1 single agent studies CBKM120X2101 (First in man dose escalation in solid tumors) and CBKM120X1101 (Japanese dose escalation in solid tumors), CBKM120Z2102 (Chinese dose escalation in solid tumors), CBKM120C2110 (bioavailability of BMK120 tablet formulation in healthy subjects), CBKM120C2104 (Single dose in hepatic impairement), CBKM120C2106 (two doses of 50mg in healthy subjects), CBKM120C2111 (two doses of 30mg

in healthy subjects) and CBKM120C2102 (one dose of 100mg in healthy subjects)

- ♦♦ Phase 2 single agent studies CBKM120C2201 (endometrial cancer) and CBKM120D2201 (non-small cell lung cancer)
- ♦♦ Phase 1 combination studies CBKM120B2101 (buparlisib plus GSK1120212), CBKM120X2107 (buparlisib plus trastuzumab), CBEZ235A2118 (buparlisib plus paclitaxel), and CMEK162X2101 (buparlisib plus MEK162), CBKM120E2101 (buparlisib plus radiation and temozolimide for gliobastoma), CLDE225X2114 (dose escalation of buparlisib plus sonidegib), CSTI571X2101 (buparlisib plus imatinib), CINC424A2104 (buparlisib plus INC424) and CBEZ235D2101 (buparlisib plus BEZ235)
- ♦♦ Phase 2 combination study CBKM120F2202 (buparlisib plus paclitaxel in breast cancer)
- ♦♦ Phase 3 combination studies CBKM120F2302 (buparlisib/placebo plus fulvestrant in breast cancer) and CBKM120F2303 (buparlisib plus fulvestrant in breast cancer)

1.5.2.2.1 Human safety and tolerability data of Buparlisib

Study recruitment in study CBKM120X2101 has been completed with forty (40) patients included in the dose escalation phase at 6 dose levels (all once daily) (12.5 mg (1 patient); 25 mg (2), 50 mg (5), 80 mg (11), 100 mg (17), 150 mg (4)). Dose limiting toxicities were hyperglycemia, skin rash, epigastric pain, mood disorder, joint pain. The MTD for buparlisib given as single agent, once daily was established at 100 mg/day. Fortythree additional patients were treated in the expansion cohort at 100 mg/day. At the cutoff date of 4th July 2011 patient characteristics of 82 patients analyzed were as follows: median age 55 years (range 30–78); ECOG performance status 0/1/2 for 35/46/1 patients, respectively. The safety experience for this single agent trial of buparlisib is described in Table 5 below.

Table 5. Most frequent AEs (≥ 15%) related to study drug in study CBKM120X2101 (n=81)

Event	All grades	Grade 3-4
Fatigue/asthenia	31(38.3%)	3 (3.7%)
Decreased appetite	24 (29.6%)	-
Diarrhea	24 (29.6%)	3 (3.7%)
Hyperglycemia	24 (29.6%)	4 (4.9%)
Nausea	24 (29.6%)	-
Rash	22 (27.2%)	4 (4.9%)
Mood altered/emotional disorder/ affective disorder	17 (21.0%)	4 (4.9%)
Anxiety	14 (17.3%)	1 (1.2%)

Depression	14 (17.3%)	1 (1.2%)

A second single agent trial, CBKM120X1101 was a phase 1 dose escalation study in Japanese patients with advanced solid tumors with dose levels ranging from 25 to 100 mg/day. Enrolment of 15 patients has been completed, including 9 patients at 100 mg/day. One DLT (G4 hepatic function abnormal) was observed in the 100mg/day group. The most common G3 or G4 adverse events occurring in at least 2 patients were hepatic function abnormal in 6 patients including transaminase increase in 2 patients, G3 anemia in 2 patients, hypokalemia in 2 patients. The recommended phase 2 dose (RP2D) for Japanese has been determined at 100 mg/day, as in the western population.
Buparlisib in combination with trastuzumab is currently investigated in a phase 1b/1 CBKM120X2107 study in patients with HER2+ MBC who acquired trastuzumab resistance. The phase 1b part of the study has been presented. In this study trastuzumab is given at fixed dose of 2 mg/kg/week (with a 4 mg/kg/week loading dose). In the dose escalation phase, 17 patients with MBC have been enrolled at the cutoff date of September 30_{th}, 2011: 5 patients at 50 mg/day and 12 patients at 100 mg/day. The recommended phase 2 dose for buparlisib was declared at 100 mg/day. The median age was 47 years (range 28 -70). Most of the patients have been heavily treated (range of prior chemotherapy lines 1-8). With the completion of escalation phase, buparlisib in combination with trastuzumab has shown an acceptable safety profile. Grade 3 adverse events reported with a suspected relationship to buparlisib were asthenia, ALT increase, hypersensitivity hyperglycemia, mood altered, affective disorder, photosensitivity reaction and rash in 1-2 patients each. No drug related G4 toxicity has been observed so far. The trial is currently recruiting the phase 2 part.
Details on liver toxicity, mood alterations, pneumonitis and hyperglycemia as side effects of buparlisib are presented below.

Liver Toxicity of Buparlisib

Liver function test (LFT) alterations observed during ongoing studies were mostly transaminase enzyme increases (ALT and/or AST). Only a few of the patients with LFT alterations had other simultaneous observations like bilirubin increase or clinical symptoms related to impaired liver function. To be noted, no case fitting Hy's law has been observed so far.
Liver toxicity observed at 100 mg/day, regardless of study drug relationship, in ongoing buparlisib studies are summarized in Table 6.

Table 6. Numbers of patients with liver toxicity occurred at 100 mg/day in ongoing buparlisib studies

Study Number (N = patient treated with 100 mg/d buparlisib)	**All grades**	**Grade 3-4**
CBKM120X2101 (N = 55)	22 (40%)	13 (23%)
CBKM120X1101 (N = 9)	4 (44%)	4 (44%)
CBKM120C2201 (N = 50)	10 (20%)	6 (12%)

CBKM120X2107 (N = 12)	2 (16%)	2 (16%)
CBEZ235A2118 (N = 6, buparlisib-treated only)	0 (0%)	0 (0%)

Based on these findings, conservative selection criteria and guidelines to monitor and to follow patients with LFT alterations (including dose and schedule modifications) are currently implemented in study protocols investigating buparlisib.

Mood alteration of Buparlisib

Recently, a number of publications demonstrated that the modulation of AKT/GSK3 signaling pathway by neurotransmitters is important for the regulation of behavior. Preclinical studies conducted in rats to investigate the effect of buparlisib on different neurotransmitters have shown that repeated administration of buparlisib resulted in an enhanced decrease in glutamate, dopamine, serotonin and epinephrine as well as in an enhanced increase in GABA and HIAA.
Reversible mild to moderate mood disorders observed at 100 mg/day, regardless of study drug relationship, in ongoing buparlisib studies are summarized in the Investigator's Brochure. (see also Table 7 below)

Table 7. Numbers of patients with mood disorders occurred at 100 mg/day in ongoing buparlisib studies

Study Number (N = patient treated with 100 mg/d buparlisib)	All grades	Grade 3-4
CBKM120X2101 (N = 55)	11 (20%)	2 (3%)
CBKM120X1101 (N = 9)	4 (44%)	0 (0%)
CBKM120C2201 (N = 50)	6 (12%)	0 (0%)
CBKM120X2107 (N = 12)	7 (58%)	2 (16.7%)
CBEZ235A2118 (N = 6, buparlisib-treated only)	0 (0%)	0 (0%)

These adverse events are currently under investigation. Nevertheless, until a more complete understanding of this AE is compiled and in order to lower the risk, protocol guidelines disqualify patients with an active and/or history of major psychiatric disorder. In addition, throughout the trial patients must be closely monitored using self-rating questionnaires (ie, PHQ-9 and GAD-7), when required a psychiatrist should be consulted and the use of standard available medication should be considered as per investigator's discretion.
Across the ongoing studies of buparlisib, 4 patients experienced other psychiatric toxicities related to buparlisib: confusional state in 3 patients (Grade 3 in 1 patient) and mental status change in 1 patient (Grade 3). With regards to the confusional state, in one case it has been considered as a symptom related to mood disorders, cholangitis and brain metastases, and in the remaining two cases, the confusional state occurred in a context of infection and

gastrointestinal disorders. In two out of the three cases, the event improved/resolved after study drug interruption. Further information is being collected for the latest reported case.

Lung Toxicity and Pneumonitis in buparlisib

Lung changes compatible with pneumonitis have not been observed in the preclinical setting. Among the current studies, lung toxicity has been observed in 2 patients and reported as pneumonitis, including a fatal outcome reported in one patient in a complex clinical context, combining progression of lung lesions and aspergillosis infection The currently available data do not enable a clear assessment about the causal relationship of pneumonitis with buparlisib treatment. Newly appearing or significant changes in pulmonary symptoms (which cannot be explained by the underlying disease), should be carefully followed with appropriate management as per institutional guidelines and the guidelines provided in the protocol.

Hyperglycemia events in buparlisib

The PI3K/Akt pathway plays a significant role in regulating glucose metabolism, particularly by regulating glucose transport into adipocytes and muscle tissue. Therefore, hyperglycemia is considered as an "on target" effect of buparlisib. Regular monitoring of insulin C-peptide is implemented in buparlisib protocols to evaluate this pharmacodynamics effect. Transient increases of plasma glucose levels have been reported commonly in patients treated with buparlisib. Hyperglycemia observed at 100 mg/day, regardless of study drug relationship, in ongoing buparlisib studies are summarized in Table 8.

Table 8. Number of patients with hyperglycemia occurred at 100 mg/day in ongoing BKM studies

Study Number (N = patient treated with 100 mg/d buparlisib)	All grades	Grade 3-4
CBKM120X2101 (N = 55)	17 (30.9%)	2 (3.6%)
CBKM120X1101 (N = 9)	2 (22.2%)	1 (11.1%)
CBKM120C2201 (N = 50)	31 (62.0%)	12 (24.0%)
CBKM120X2107 (N = 12)	4 (33.3%)	2 (16.7%)
CBEZ235A2118 (N = 6, buparlisib-treated only)	2 (33.3%)	1 (16.7%)

The highest rate of hyperglycemia (62.0%) was reported in CBKM120C2201, a phase 2 study conducted in patients with advanced endometrial carcinoma, as this was the only study among those listed allowing the enrollment of patients with controlled diabetes mellitus. However, so far, there were only two patients that experienced a Grade 4 hyperglycemia, and they both were treated at the highest dose level (150 mg/day) in the CBKM120X2101 study. Detailed guidelines to monitor and manage patients who develop hyperglycemia are provided in the Investigator's Brochure. Specifically, with regards to appropriate concomitant medication, considering that in *vitro studies* have shown that buparlisib may inhibit insulin-stimulated glucose uptake, the first recommended approach

is to use oral anti-diabetics (eg, metformin) who increases muscle and fat glucose uptake. The addition of insulin can be considered based on the guidelines of American Diabetes Association included as reference in the current protocol.

1.5.2.2.2 Human pharmacokinetic and metabolism data of buparlisib

Preliminary clinical pharmacokinetic data of buparlisib after single and multiple daily dosing is available from the first-in-human trial CBKM120X2101. Buparlisib was administered as a capsule (doses ranging between 12.5 and 150 mg) and full pharmacokinetic profiles were collected on Day 1, Day 8 and Day 28 of Cycle 1.
Buparlisib was rapidly absorbed, with the median time to reach the peak plasma concentration (Tmax) ranging from 1.0 to 1.75 hours following administration. Tmax was independent of dose and was not altered after multiple oral doses. Variability in systemic drug exposure was moderate at all dose levels. At 100 mg the variability in systemic drug exposure and Cmax (CV %) at steady-state was moderate, about 36% and 25%, respectively.
During once daily dosing, plasma buparlisib concentrations were found to accumulate in reaching steady-state. After one week of oral daily dosing (day 8), both Cmax and AUC0-24h were approximately 3-fold higher than after a single dose (day 1). The mean accumulation ratio (Racc) of buparlisib at 100 mg was 2.7 and 3.3 on days 8 and 28, respectively, indicating the absence of significant drug accumulation after day 8. The decay in buparlisib plasma concentration over time was bi-exponential, with an apparent long terminal half-life. The mean T1/2,acc (effective half-life, obtained from drug accumulation) calculated from exposure data at day 28 ranged between 38 and 49 hours across all dose levels. T1/2,acc was found to be independent of dose. Based on the effective half-life, steady state buparlisib plasma levels can be expected to be reached after 1 week of daily dosing.
Furthermore the preliminary PK data within the Japanese population CBKM120X1101 show no significant differences in Cmax or AUC0-24h with the Caucasian population CBKM120X2101. A preliminary population PK analysis, including data from studies CBKM120X2101 and CBKM120X1101 confirmed those findings (Novartis internal data).
In study CBKM120B2101, buparlisib was administered with GSK1120212 (a MEK inhibitor). Single dose pharmacokinetics of buparlisib appeared to be unaffected by concomitant administration of GSK1120212. Concurrent chronic daily administration of both drugs, however, consistently resulted in a dose- and time-dependent decrease in buparlisib systemic drug exposure. After 28 days of once daily combination treatment of buparlisib with GSK1120212 (1.5-2.0 mg), exposure of buparlisib at system steadystate was decreased by approximately 45-50%, when compared to the mean value determined from CBKM120X2101. Decrease in exposure was less pronounced at lower doses of GSK1120212 (0.5- 1 mg) (approximately 25%). The overall drug clearance of buparlisib increased up to 2-fold in the presence GSK1120212. This dose and time dependent effect of GSK1120212 on buparlisib oral clearance is most likely explained by induction of CYP3A4, a property of GSK1120212, which has been demonstrated *in vitro*. These findings are also consistent with a high dependence of buparlisib clearance on CYP3A4 activity. Similar changes in the pharmacokinetics of buparlisib could be expected to occur when other inducers of CYP3A4 are combined with buparlisib treatment (see concomitant medication). The pharmacokinetics of GSK1120212 was not altered by buparlisib.
In study CBKM120X2107 a daily dosing regimen of buparlisib was tested in combination with weekly infusions of trastuzumab in patients with relapsed HER2-overexpressing

breast cancer. Preliminary pharmacokinetic data indicated that the systemic drug exposure (Cmax and AUC) of oral buparlisib in combination with trastuzumab was similar to the single agent data. Trastuzumab trough levels were consistent with those previously reported to be therapeutic (ie, generally greater than 20 μg/ml).

1.5.2.2.3 Clinical efficacy data on buparlisib

Sixty-six patients were evaluable for response in study CBKM120X2101 where all patients in the expansion cohort were required to have mutated and/or amplified PIK3CA and/or mutated PTEN or null/low PTEN protein expression: partial tumor responses (PR) were observed in 3 patients, one of which was a RECIST v1.0 confirmed PR in a patient with triple negative breast cancer and the other 2 not confirmed (1 patient with metastatic breast cancer and 1 patient with parotid carcinoma).

The first patient was a 61 year-old female with poorly differentiated ductal metastatic breast cancer assessed as triple negative (ER-, PgR-, HER2-), PI3KCA wild type, PTEN IHC positive. Since 2006 she received many previous anticancer agents (cyclophosphamide, doxorubicin, gemcitabine, docetaxel, paclitaxel, vinorelbine, capecitabine, etoposide, anastrazole). As progressive disease developed (bulky lymph node involvement and local breast relapse), she was enrolled (April 2009) in the phase 1 study of buparlisib in the 100 mg/day cohort. A metabolic response (61% decrease in SUV) was observed after 2 cycles, followed by a RECIST partial response (66% tumor shrinkage) after 4 cycles. This patient continues to receive treatment beyond 32 cycles.

The second patient was a 52 year-old female with moderately differentiated ductal metastatic breast cancer, assessed as ER positive, HER2 negative, PI3KCA mutated (E545K& H1047Y), PTEN IHC positive. She had been previously treated with several antineoplastic agents. When she received buparlisib at 100 mg/day (January 2010), she had measurable metastases in the brain, lung and liver. At the second radiological assessment after receiving 4 cycles of buparlisib treatment, a 45% reduction of the sum of the lesions was recorded. The TTP for this patient was 24 weeks.

The third patient was a 45 year-old man with Grade 4 parotid gland ductal carcinoma, PI3KCA wild type, PTEN IHC positive. He had been previously treated with doxorubicin and adriamycin. After disease progression was observed on this regimen he was enrolled in the 100mg/day cohort (July 2010) in the CBKM120X2101 study. At the first radiological assessment after receiving 2 cycles of buparlisib treatment, a 33% reduction of the sum of the lesions was recorded. The TTP for this patient was 16 weeks.

As of the data cut-off 04July2011, preliminary analysis shows forty-five percent of patients (30 of 66 evaluable) had stable disease as best response, with 20 patients (30%) with a disease stabilization of 3 months or longer. A trend towards better activity (longterm stabilizations) has been observed at the higher dose cohorts, also expressed in metabolic FDG-PET response. However, considering the impact of a PI3K inhibitor on glucose metabolism, further data needs to be acquired to understand whether the current FDG-PET assessment data can be used as a predictive factor for efficacy.

With regards to pharmacodynamic markers observed in study CBKM120X2101, down regulation of pS6 in skin by 30-80% was demonstrated in 28 out of the 38 evaluable patients at 100 and 150 mg/d and more than 25% FDG-PET signal decrease in patients at doses greater than the MTD.

With regards to the PI3K pathway activation, of the two responders described above, one had a tumor with the PIK3CA mutation. Moreover, 18 patients had a stable disease lasting for 16 weeks or longer, including 8 patients who had tumors with an activated PI3K

pathway. These data are promising and continued exploration of the activity of buparlisib in patients with activated PI3K pathway is warranted.
More specifically, in CBKM120X2101, 25.3% (21/83) of patients had metastatic breast cancer. At the cut-off date of 4th July 2011, twenty breast cancer patients were evaluable for objective tumor response by RECIST 1.0. Two breast cancer patients (11%), described above exhibited partial responses. For these 2 patients, the treatment duration was 27+ (ongoing) and 5 months, respectively. An additional 8 breast cancer patients (40%) had stable disease. Median progression-free survival was 60 days and the 6-month PFS rate was 3 3%.
Please refer to the Investigator's Brochure for additional information on the available clinical experience with buparlisib.

1.5.2.2.4 Clinical safety data on combination of sonidegib plus buparlisib

The combination maximum tolerated dose (MTD) and/or recommended dose expansion (RDE) of sonidegib + buparlisib when co-administered orally, was determined in Study LDE225X2114, an ongoing phase 1b, multi-center, open label, dose escalation study of oral sonidegib in combination with buparlisib in patients with advanced solid tumors (metastatic breast cancer, advanced pancreatic adenocarcinoma, metastatic CRC and recurrent GBM). The RDE was determined based on observed rates of dose limiting toxicities (DLTs) during the first 6 weeks (42 days) of the combination treatment of sonidegib and buparlisib, using a Bayesian Logistic regression Model (BLRM) with Overdose Control (EWOC). The dose escalation phase was completed in December 2013 with 46 patients enrolled across 5 cohorts. The RDE was declared as 400 mg sonidegib QD + 80 mg buparlisib QD.
In a recent randomized double-blind study of sonidegib in patients with locally advanced (La) or metastatic (m) basal-cell carcinoma (BCC), 230 patients were randomized in a 2:1 fashion to receive either 200 mg QD or 800 mg QD of sonidegib. The primary endpoint of objective response rate was met in both arms with both doses achieving meaningful disease control and sustained duration of responses. The 200mg arm had a more favorable risk-benefit profile with respect to toxicities. Therefore, the doses of sonidegib and buparlisib for the current study will be 200mg QD of sonidegib and 80mg QD of buparlisib.

1.6 Study Rationale

Mutations in hedgehog pathway genes are clearly associated with development of BCCs and recent, exciting early phase clinical studies in locally advanced or metastatic BCCs using drugs which target the hedgehog pathway have shown potent and dramatic anti-tumor results (Sekulic *et al*; 2012, Von Hoff, *et al,* 2009). Another example of a Smoothened inhibitor is Sonidegib, which appears to be well-tolerated and possess anti-tumor activity in advanced solid tumors in a phase 1 and 2 clinical trials which are ongoing.
Nevertheless, a significant subset of BCC patients with locally advanced or metastatic BCC treated with Smoothened inhibitors do not respond to the drug, and their tumors become progressive (by estimate, approximately 50% of individuals treated with GDC0449 did not respond to the study drug) (Von Hoff *et al*, 2009; Sekulic *et al*, 2012). In addition approximately 20% of advanced BCCs which initially respond develop resistance to SI monotherapy (Chang and Oro, 2012). Several mechanisms for resistance to Smoothened inhibitors have been postulated. In particular, gene expression data from resistant tumors (Chang *et al*., 2013) have suggested that increased phosphatidylinositol-3-kinase (PI3K)

signaling may be a potential resistance mechanism in BCCs. The role of this pathway in other solid tumors has been reported as well (Zhu *et al,* 2010; Buonamici, *et al.,* 2010). Subsets of cancers have been reported to become dependent on PI3K pathway signaling ("pathway addicted", Weinstein *et al*, 2008) as a result of mutations of the PIK3CA gene itself or of regulators of PI3K (eg, PTEN, HER2) NVP-BKM120 (buparlisib) is an oral phosphatidylinositol-3-kinase (PI3K) inhibitor. The PI3K/AKT pathway regulates cell proliferation, growth, survival and apoptosis. Experiments in mice with mutations of the hedgehog pathway leading to medullo-blastoma found that tumor resistance to Smoothened antagonists could be delayed or prevented with the concomitant use of buparlisib (Buonamici, *et al,* 2010). This effect appeared to be more pronounced when combination therapy was initiated at the start of treatment before development of resistance.

As more and more patients with BCCs are treated with Smoothened inhibitors, the presence of resistant tumor populations has become a critical issue. This pilot study will provide vitally important information regarding the potential of dual treatment with PI3K inhibitor (buparlisib) PLUS Smoothened inhibitor (Sonidegib) to address resistance.

It is currently unclear whether the clinical efficacy of combination therapy (termed LB therapy) is more pronounced if it is instituted at the outset versus after resistance is clinically apparent.

2 Study objectives

Primary Objective

To estimate the overall response rate (ORR) of sonidegib in combination with buparlisib (hereby referred to as "LB therapy") for patients with locally advanced or metastatic BCC in Smoothened inhibitor naive patients (Cohort 1) and those whose disease is refractory or relapsed on Smoothened inhibitor monotherapy (Cohort 2).

Secondary Objectives

- To estimate the median duration of response, on or after LB therapy
- To assess the safety and tolerability of LB therapy
- To assess the histopathologic effect of LB therapy in tumor biopsies obtained at baseline and following 12 weeks of treatment
- To assess the effect of LB therapy on gene expression including Hedgehog pathway and PI3K pathways.
- To assess correlation between gene mutations in Smoothened, Sufu, PTCH, Gli1,2 and gene expression profiles and response to LB therapy

3 Exploratory Investigational plan

3.1 Overall study design

This is an open-label, single-center 2-cohort pilot study, as shown in Figure 4. All patients will receive LB therapy until evidence of progression, intolerable toxicities or withdrawal from the study.

3.2 Study population

Figure 4. Study Design

3.2.1 Patient population

Adult patients with locally advanced or metastatic BCC.
The study will accrue 12 patients with locally advanced or metastatic basal cell carcinoma who are naïve to Smoothened inhibitors (COHORT 1) and 12 patients are refractory or resistant to non-Sonidegib SI (COHORT 2). This is an exploratory descriptive study.

3.2.2 Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must me*et al*l inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment.

3.2.2.1 **Inclusion criteria**

Patients eligible for enrollment into the treatment phase of this study **must meet all** of the following criteria:

1. Able to understand and sign informed consent
2. Age ≥ 18 years
3. ECOG performance status ≤ 2
4. Patients with metastatic BCC, histologic confirmation of distant BCC metastasis
5. Patients with metastatic disease, target lesion must be measurable using CT or MRI
6. Patients with locally advanced BCC are required to have disease that is considered inoperable due to significant functional compromise or to have a medical contraindication to surgery
7. Patients with nevoid BCC syndrome (Gorlin syndrome) may enroll in this study but must meet the criteria for locally advanced or metastatic disease listed above
8. **COHORT 2 ONLY**: A Smoothened inhibitor must have been previously administered as monotherapy)
9. Adequate bone marrow function as shown by:
    a. ANC ≥ 1.5 x 109/L,
    b. Platelets ≥ 80 x109/L,
    c. Hb > 9 g/dL or values ≥ LLN for site-specific lab
10. Total calcium (corrected for serum albumin) within normal limits
    (biphosphonate use for malignant hypercalcemia control is not allowed)
11. Magnesium ≥ the lower limit of normal
12. Potassium within normal limits for the institution
13. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within normal range (or ≤ 3.0 x upper limit of normal (ULN) if liver metastases are present)
14. Serum bilirubin within normal range (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 Syndrome)
15. Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min
16. Serum amylase ≤ ULN
17. Serum lipase ≤ ULN

18. Fasting plasma glucose ≤ 120 mg/dL (6.7 mmol/L)
19. Negative serum pregnancy test within 72 hours before starting study treatment in women with childbearing potential
20. INR ≤ 2

3.2.2.2 Exclusion criteria

Patients eligible for enrollment into the treatment phase of this study **must not meet any** of the following criteria:

1. Patients who have received prior treatment with a P13K inhibitor
2. Patients with a known hypersensitivity to buparlisib or to its excipients
3. Patients with untreated brain metastases are excluded. However, patients with metastatic CNS tumors may participate in this trial, if the patient is > 4 weeks from therapy completion (incl. radiation and/or surgery), is clinically stable at the time of study entry and is not receiving corticosteroid therapy
4. Patients with acute or chronic liver, renal disease or pancreatitis
5. Patients with baseline creatinine kinase (CK) > upper limit of normal (ULN)
6. Patients with the following mood disorders as judged by the Investigator or a psychiatrist, or as a result of patient's mood assessment questionnaire:
   - ♦♦ Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (immediate risk of doing harm to others)
   - ♦♦ ≥ CTCAE Grade 3 anxiety
   - ♦♦ Meets the cut-off score of ≥ 12 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, or selects a positive response of "1, 2, or 3" to question number 9 regarding potential for suicidal thoughts in the PHQ-9 (independent of the total score of the PHQ-9)
7. Patients with diarrhea ≥ CTCAE Grade 2
8. Patient has active cardiac disease including any of the following:
   - ♦♦ Persistent Left ventricular ejection fraction (LVEF) < 50% as determined by prior Multiple Grated acquisition (MUGA) scan or echocardiogram (ECHO)
   - ♦♦ QTc > 450 msec on screening ECG (using the QTcF formula)
   - ♦♦ Angina pectoris that requires the use of anti-anginal medication
   - ♦♦ Ventricular arrhythmias except for benign premature ventricular contractions
   - ♦♦ Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication
   - ♦♦ Conduction abnormality requiring a pacemaker
   - ♦♦ Valvular disease with document compromise in cardiac function
   - ♦♦ Symptomatic pericarditis
9. Patient has a history of cardiac dysfunction including any of the following:
   - ♦♦ Myocardial infraction within the last 6 months, documented by persistent elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LVEF function
   - ♦♦ History of documented congestive heart failure (New York Heart Association functional classification III-IV)
   - ♦♦ Documented cardiomyopathy

10. Patient has poorly controlled diabetes mellitus (defined as HgA1c > ULM), steroid-induced diabetes mellitus or insulin dependent diabetes mellitus.
11. Other concurrent severe and/or uncontrolled concomitant medical conditions (eg, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol

♦♦ Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude pneumonitis or pulmonary infiltrates.

12. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of buparlisib (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). Patients with unresolved diarrhea will be excluded as previously indicated
13. Patients who have been treated with any hematopoietic colony-stimulating growth factors (eg, G-CSF, GM-CSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated at least 2 weeks prior to enrollment, may be continued.
14. Patients who are currently receiving treatment with medication with a known risk 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. Please refer to Table 16 for a list of prohibited QT-prolonging drugs with risk of Torsades de Pointes.
15. Patients receiving chronic treatment with steroids or another immunosuppressive agent.

    ♦♦ **Note:** Topical applications (eg, rash), inhaled sprays (eg, obstructive airways diseases), eye drops or local injections (eg, intr-articular) are allowed. Oral or systemic liver enzyme inhibitors such as topical antifungal creams are allowed. Patients with previously treated brain metastases, who are on stable low dose corticosteriods treatment (eg, dexamethasone 2 mg/day, predisolone 10 mg/day) for at least 14 days before start of study treatment are eligible.

16. Patients who have taken herbal medications and certain fruits within 7 days prior to starting study drug. Herbal medications include, but are not limited to St. John's Wort, Kava, and ephedra (ma huang), dehydroepiandrosterone (DHEA), gingko biloba, yohimbe, saw palmetto, and ginseng. Fruits include the CYP3A inhibitors Seville oranges, grapefruit, pummelos, or exotic citrus fruits.
17. Patients who are currently treated with drugs known to be moderate and strong inhibitors or inducers of isoenzyme CYP3A, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. Please refer to Table 15 for a list of prohibited inhibitors and inducers of CYP3A (Please note that co-treatment with weak inhibitors of CYP3A is allowed).
18. Patients who have received chemotherapy or targeted anticancer therapy ≤ 4 weeks (6 weeks for nitrosourea, antibodies or mitomycin-C) prior to starting study drug must recover to a Grade 1 before starting the trial
19. Patients who have received any continuous or intermittent small molecule therapeutics (excluding monoclonal antibodies) ≤ 5 effective half-lives prior to starting study drug or who have not recovered from side effects of such therapy
20. Use of statin drugs or other medications known to associate with rhabdomyolysis. These drugs must be discontinued at enrollment.

21. Patients who have received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
22. Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
23. Patients who are currently taking therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulant. Low molecular weight heparin is allowed.
24. Women who are pregnant or breast feeding or adults of reproductive potential not employing an effective method of birth control. Double barrier contraceptives must be used through the trial by both sexes. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (ie, who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 72 hours prior to initiating treatment.

♦♦ 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 (eg, age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL (*for US only*: and estradiol < 20 pg/mL) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. 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.

♦♦ Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through 20 months after the final dose of study treatment.. For males with partners with childbearing potential, highly effective contraception is required for 6 months. The highly effective contraception is defined as either:

I. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

II. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. 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 subjects on the study, the vasectomised male partner should be the sole partner for that patient.

IV. Use of a combination of any two 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 contraception, injected or implanted hormonal methods are not allowed as buparlisib potentially decreases the effectiveness of hormonal contraceptives.
- ♦♦ Fertile males, must use highly effective (double barrier) methods of contraception (eg, spermicidal gel plus condom) for the entire duration of the study, and continuing using contraception and refrain from fathering a child for 6 months following the study drug. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the study treatment via seminal fluid. Female partner of male study subject should use highly effective contraception during dosing of any study agent and for 16 weeks after final dose of study therapy.

  Note: Hormonal contraception methods (eg, oral, injected, implanted) are not allowed as it cannot be ruled out that the study drug decreases the effectiveness of hormonal contraception.

  Note: Woman are considered post-menopausal and not child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ mL and estradiol< 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. 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

25. Known diagnosis of human immunodeficiency virus (HIV) infection, Hepatitis B or Hepatitis C
26. History of another malignancy within 3 years, except cured basal cell carcinoma of the skin or excised carcinoma in situ of the cervix
27. Patient is unable or unwilling to abide by the study protocol or cooperate fully with the investigator

4 Treatments

4.1 Dose modification, interruption or discontinuation of treatment

If an adverse event is clearly associated to one of study drugs, the dose adjustment directed for that study drug will be followed; however, if the causality is not clear, then it may be necessary to adjust both study drugs. Dosing adjustments will be discussed with the sponsor. If a patient experiences a DLT then treatment with Sonidegib plus buparlisib must be stopped and the patient may be discontinued from the study. However, following resolution of the DLT to CTCAE Grade 1 or to the patient's baseline value, the patient may continue to receive study treatment with a 50% dose reduction for either sonidegib, buparlisib or both, if appropriate, at the discretion of the investigator and after discussion with the Sponsor.

If a patient requires a dose delay of > 21 days due to an sonidegib- or buparlisib-related toxicity, then the patient must be discontinued from the study; however, if the patient is obtaining clinical benefit (ie, SD, PR, or CR), the patient may continue treatment at the same or at a reduced dose following discussion between the investigator and Novartis. All patients will be followed for AEs and SAEs for 30 days following the last dose of sonidegib and/or buparlisib. If the administration of

study treatment was interrupted for reasons other than toxicity, then treatment with Sonidegib and buparlisib may be resumed at the same dose.
Patients who experience hematologic, renal, hepatic, or muscle toxicities should receive follow up and dosing modifications for sonidegib as per Table 9 and 10 below. Specific instructions for follow-up and dosing modifications for sonidegib are described in detail in Table 9. Patients who experience muscle toxicity, regardless of whether the toxicity meets the criteria described for a DLT, should be receive follow-up and dosing modifications specified in Table 9 below.

Table 9. Recommended dose modifications and dose delays for suspected sonidegib treatment-related toxicities**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Hematologic	
Neutropenia (ANC)	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 or 4 (ANC < 1000 - 500/mm^3 or < 500/mm^3)	Omit dose until resolved to ≤ Grade 1, then: ♦♦ If resolved in ≤ 7 days, implement 50% dose reduction ♦♦ If resolved in > 7 days, discontinue drug ♦♦ If a Grade 4 event, consider hospitalization if appropriate
Thrombocytopenia (PLT)	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 or 4 (PLT < 50,000 - 25,000/mm^3 or < 25,000/mm^3)	Omit dose until resolved to ≤ Grade 1, then: ♦♦ If resolved in ≤ 7 days, implement 50% dose reduction ♦♦ If resolved in > 7 days, discontinue drug ♦♦ If a Grade 4 event, consider hospitalization if appropriate

Febrile Neutropenia	
Grade 3 (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then implement 50% dose reduction
Grade 4 Life-threatening consequences; urgent intervention indicated	• Consider hospitalization • Discontinue drug

Table 9. Recommended dose modifications and dose delays for suspected sonidegib treatment-related toxicities**

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Muscle Toxicity	
Elevated creatinine phosphokinase (CK)	
Asymptomatic (no new-onset muscle pain/spasm or worsening of pre-existing muscle pain/spasm) CTCAE Grade 1 or 2 CK elevation	♦♦ For CTCAE Grade 1 CK elevation, continue treatment on same dose and continue monitoring as per schedule of assessments ♦♦ For CTCAE Grade 2 CK elevation, continue on same dose level of sonidegib. CK should be measured weekly until resolution to ≤ Grade 1.
Symptomatic (new-onset or worsening of pre-existing muscle pain/spasm) with CTCAE Grade 1 or 2 CK elevation	♦♦ For CTCAE Grade 1 CK with muscle pain/spasm ≥ CTCAE Grade 1, continue treatment at same dose and measure CK weekly until CK returns to normal or baseline value or muscle pain/spasm resolves ♦♦ For CTCAE Grade 2 CK with muscle pain/spasm ≥ CTCAE Grade 1, continue treatment at same dose level of sonidegib. CK should be measured weekly until CK is ≤ CTCAE Grade 1
CTCAE Grade 3 or 4 CK elevation (with or without muscle pain/spasm)	♦♦ Omit sonidegib dose, check blood myoglobin and monitor renal function. Measure CK weekly until resolution to Grade ≤ 1 ♦♦ Consider performing electromyography, MRI scan of symptomatic muscle group(s) and muscle biopsy ♦♦ If renal function is not impaired and resolution to ≤ CTCAE Grade 1 occurs within 21 days, consider resuming treatment at a reduced dose; CK should be measured weekly for 2 months after re-administration of sonidegib ♦♦ Patients who experience renal impairment (serum

	creatinine > 2x ULN) should be permanently discontinued from the study ♦♦ If a Grade 4 event, consider hospitalization if appropriate

Table 9. Recommended dose modifications and dose delays for suspected sonidegib treatment-related toxicities**

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Muscle pain/spasm (new onset or worsening of preexisting muscle pain/spasm)	♦♦ For CTCAE Grade 1 muscle pain/spasm, continue treatment on the same dose and planned assessments ♦♦ For CTCAE ≥ Grade 2 muscle pain/spasm, measure CK weekly until muscle pain resolves to ≤ Grade 1. If CK is elevated, follow guidance for CK elevation as described above. Continue treatment with sonidegib ♦♦ For new-onset CTCAE Grade 3 muscle pain/spasm, interrupt sonidegib. Collect blood sample for CK measurement at the time of dose interruption. Provide symptomatic treatment. Measure CK weekly until the muscle pain/spasm resolves to ≤ Grade 1 and resume therapy at a reduced dose. Measure CK weekly for 2 months after re-administration.
Renal	
Serum creatinine	
Serum creatinine <1.5 x ULN	Maintain dose level
Serum creatinine 1.5-3 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 implement 50% dose reduction (consider checking serum CK, if not already done)
Grade 3 Serum creatinine > 3.0 - 6.0 x ULN	Omit dose until resolved to ≤ Grade 1 then implement 50% dose reduction
Grade 4 Serum creatinine > 6.0 x ULN	Omit dose and discontinue study drug. Consider hospitalization if appropriate
Hepatic	
Bilirubin	
Total bilirubin <1.5 x ULN	Maintain dose level

Total bilirubin 1.5-3 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 implement 50% dose reduction
Grade 3 Total bilirubin > 3.0 - 10.0 x ULN	Omit dose until resolved to ≤ Grade 1, then implement 50% dose reduction
Grade 4 Total bilirubin > 10.0 x ULN	Discontinue study drug. Consider if hospitalization is appropriate.

Table 9. Recommended dose modifications and dose delays for suspected sonidegib treatment-related toxicities**

Worst toxicity CTCAE grade*(value)	During a cycle of therapy
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 baseline then: ♦♦ If resolved in ≤ 7 days, then maintain dose level ♦♦ If resolved in > 7 days, then implement 50% dose reduction
Grade 4 (> 20.0 x ULN)	Omit dose until resolved to ≤ Grade 1 or baseline, then implement 50% dose reduction. Consider if hospitalization is appropriate
Cardiac	
Cardiac - prolonged QTc interval Grade 3 (QTcF > 500 msec or >60 ms from baseline on at least 2 separate ECGs taken within 1 hour)	First Occurrence: ♦♦ Omit dose ♦♦ 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 ♦♦ If QTcF remains > 500 ms, repeat ECG as clinically indicated but at least once a day until the QTcF returns to < 480 ms. ♦♦ Once QTcF prolongation has resolved, study treatment may be restarted with a 50% dose reduction Second Occurrence: ♦♦ discontinue patient from study drug

Cardiac - prolonged QTc interval Grade 4	Discontinue patient from study drug

Table 9. Recommended dose modifications and dose delays for suspected sonidegib treatment-related toxicities**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Other Cardiac Events	
Grade 1	Maintain dose level
Grade 2	Implement 50% dose reduction of buparlisib
Grade 3	Omit dose and discontinue study drug
Grade 4	Omit dose and discontinue study drug. Consider if hospitalization if appropriate
Other adverse events**	
Grade 1	Maintain dose level
Grade 2	Implement 50% dose reduction
Grade 3	Omit dose and discontinue study drug
Grade 4	Omit dose and discontinue study drug Consider if hospitalization if appropriate
All dose modifications should be based on the worst preceding toxicity.	
If the dose-limiting toxicity recurs in a patient following dose reduction, then further therapy with sonidegib will not be continued.	
If a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose because of a sonidegib-related toxicity, then the patient must be discontinued from the study.	
*Common Toxicity Criteria for Adverse Events (CTCAE Version 4.0).	

** If the investigator deems that a recommended dose reduction or the recommendation to maintain the same dose level is not in the best interest of the patient, this decision may be discussed with Novartis on a case-by-case basis.

Criteria for follow-up and dosing modifications for buparlisib are described in detail in Table 10.

For overlapping toxicities of sonidegib and buparlisib, specifically hematologic, renal and hepatic toxicities, BOTH sonidegib and buparlisib will be reduced or discontinued depending on toxicity grade per the guidelines listed below for each drug (Tables 9 and 10).

Table 10. Recommended dose modifications and dose delays for suspected buparlisib treatment-related toxicities

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Hematologic	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 or 4 (ANC < 1000 - 500/ mm^3 or < 500/mm^3)	Omit dose until resolved to ≤ Grade 1, then: ♦♦ If resolved in ≤ 7 days, implement 50% dose reduction ♦♦ If resolved >7 days, discontinue drug If a Grade 4 event, consider hospitalization if appropriate
Thrombocytopena	
Grade 1 (PLT < LLN - 75 x 10^9/L)	Maintain dose level
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 implement 50% dose reduction
Grade 4 (PLT < 25 x 109/L)	Omit dose until resolved to ≤ Grade 1, then implement 50% dose reduction. Consider if hospitalization is appropriate
Renal	
Serum creatinine	
Serum creatinine <1.5 x ULN	Maintain dose level
Serum creatinine 1.5-3 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 implement 50% dose reduction (consider checking serum CK, if not already done)
Table 10. Recommended dose modifications and dose delays for suspected buparlisib treatment-related toxicities	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Grade 3 Serum creatinine > 3.0 - 6.0 x ULN	Omit dose until resolved to ≤ Grade 1 then implement 50% dose reduction
Grade 4 Serum creatinine > 6.0 x ULN	Omit dose and discontinue study drug. Consider hospitalization if appropriate
Hepatic	
Bilirubin (*for patients with Gilbert syndrome these dose modifications apply to changes in direct bilirubin only) will be fractionated if elevated	

Total bilirubin <1.5 x ULN	Maintain dose level
Total bilirubin 1.5-3 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 implement 50% dose reduction
Grade 3 Total bilirubin > 3.0 - 10.0 x ULN	Omit dose until resolved to ≤ Grade 1, then implement 50% dose reduction
Grade 4 Total bilirubin > 10.0 x ULN	Discontinue study medication Consider if hospitalization is appropriate
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 baseline then: ♦♦ If resolved in ≤ 7 days, then maintain dose level ♦♦ If resolved in > 7 days, then implement 50% dose reduction
Grade 4 (> 20.0 x ULN)	Discontinue study drug Consider if hospitalization is appropriate
AST or ALT and concurrent Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue study drug
*(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). **Monitoring** (*for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase (fractionated if alkaline phosphatase is Grade 2 or higher) and GGT). In case of any occurrence of ALT/AST/ bilirubin* increase ≥ **Grade 2** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ Grade 1** In case of any occurrence of ALT/ AST/ bilirubin* increase ≥ **Grade 3** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ Grade 1**; hereafter the 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).

Endocrine / Metabolic
Fasting Plasma Glucose (FPG) during a cycle of therapy

Maintain dose level, check FPG every week initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion.
Instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association during the study.
Consider use of oral anti-hyperglycemic therapy such as metformin blood finger stick every day and if blood glucose levels are worsening for 2 consecutive days FPG assessment is recommended.
Check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks.

First occurrence:

If signs and symptoms of hyperglycemia (e.g. mental status changes, excessive thirst, polyuria), omit buparlisib immediately and manage as per Grade 3 hyperglycemia.
If asymptomatic, maintain dose and recheck FPG within 24 hours. If grade worsens to grade 3 or 4 follow specific Grade recommendations. If grade improves to grade 1 follow Grade recommendations. If FPG remains at Grade 2, reduce study drug dose to 50% of prior dose and check FPG every week initiate or intensify medication with appropriate anti-diabetic treatment as per investigator's discretion.
Instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association during the study.
Consider use of oral anti-hyperglycemic therapy such as metformin blood finger stick every day and if blood glucose levels are worsening for
2 consecutive days FPG assessment is recommended. Check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks.

Second occurrence:

Discontinue study drug

Table 10. Recommended dose modifications and dose delays for suspected buparlisib treatment-related toxicities

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Grade 3 (> 250-500 mg/dL)	**First Occurrence**: Immediately omit buparlisib, initiate or intensify medication with appropriate

(> 13.9-27.8 mmol/L)	anti-diabetic treatment, recheck FPG within 24 hours. If Grade worsens to grade 4 then follow grade 4 recommendations. If Grade improves to grade 1 or 2 follow grade 1 or 2 guidelines. If FPG remains at Grade 3*: Administer intravenous hydration and intervention for electrolyte/ ketoacidosis/hyperosmolar disturbances as clinically appropriate Discontinue study drug Monitor FPG at least twice weekly until FPG resolves to ≤ Grade 1 Initiate or continue anti-diabetic treatment as appropriate Instruct patient to follow dietary guidelines according to local and/ or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study Consider use of oral anti-hyperglycemic therapy such as metformin Check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks For non-fasting plasma glucose >250-500 mg/dL (> 13.9 - 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, omit buparlisib and following guidance for management of Grade 3 fasting plasma glucose (FPG)

Table 10. Recommended dose modifications and dose delays for suspected buparlisib**** treatment-related toxicities**

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Grade 4 (> 500 mg/dL) (>27.8 mmol/L)	Discontinue study drug Consider hospitalization if appropriate. Initiate or intensify medication with appropriate anti-diabetic treatment, re-check within 24 hours, if grade improves then follow specific grade

	recommendations. If FPG is confirmed at Grade 4: Administer intravenous hydration and intervention for electrolyte/ ketoacidosis/hyperosmolar disturbances as clinically appropriate Instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study Consider use of oral anti-hyperglycemic therapy such as metformin. Check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks if clinically indicated For non-fasting plasma glucose > 500 mg/dL (> 27.8 mmol/L) accompanied by signs/symptoms of hyperglycemia (for example, mental status changes, excessive thirst, polyuria), or presence of blood or urine ketones, discontinue buparlisib and following guidance for management of Grade 4 fasting plasma glucose (FPG).
	Cardiac
	Cardiac - Left Ventricular systolic dysfunction
Grade 1 or 2 Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Reduce buparlisib dose by 50% Repeat LVEF within 4 weeks or as clinically appropriate

Table 10. Recommended dose modifications and dose delays for suspected buparlisib treatment-related toxicities**

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Grade 3 Symptomatic, ejection fraction responsive to intervention, ejection fraction 20-39% or > 20% drop from baseline	Discontinue buparlisib LVEF measurement to be repeated within 4 weeks or as clinically appropriate

Grade 4 Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support or heart transplant indicated; ejection fraction < 20%	Discontinue buparlisib Hospitalize if appropriate
*the event is considered resolved when the patient is asymptomatic, has a resting ejection fraction ≥40% and ≤20% decrease from baseline.	
Cardiac – QTc prolongation	
Cardiac - prolonged QTc interval ≥ Grade 3 (QTcF > 500 msec or >60 ms from baseline on at least 2 separate ECGs taken within 1 hour)	Refer to Table 9 Recommended dose modifications for sonidegib.
Other Cardiac Events	
Grade 1	Maintain dose level
Grade 2	Implement 50% dose reduction of buparlisib
Grade 3	Omit dose and discontinue study drug

Table 10. Recommended dose modifications and dose delays for suspected buparlisib treatment-related toxicities

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Grade 4	Omit dose and discontinue study drug Consider hospitalization if appropriate

Other
Mood alteration
* Mood questionnaire scores should be considered when assigning the AE Grade but psychiatric consult, if required, may determine the grade

Grade 1 Mild mood alteration (or Grade 2 anxiety if present at baseline)	Maintain dose level **Note**: If question 9 (suicidal ideation) on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score
Grade 2 Moderate mood alteration (for Anxiety only, if worsened from baseline) and if there is no concurrent medical condition that accounts for an acute increase the PHQ score.	Institute appropriate co-medication under the guidance of the psychiatrist. Maintain dose level. If the condition does not resolve to ≤ Grade 1 within 14 days despite medical treatment; then implement 50% dose reduction (continue to co-medicate) Note: If question 9 (suicidal ideation) on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score
Grade 3 Severe agitation; hospitalization not indicated	Discontinue study medication ***Note***: If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue study medication. Consider hospitalization if appropriate ***Note:*** If question 9 on the PHQ-9 has a positive response, or worsens in severity, the patient should be referred for psychiatric consult regardless of the total questionnaire score

Table 10. Recommended dose modifications and dose delays for suspected buparlisib treatment-related toxicities

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Rash	
Grade 1 Macules /papules covering <10% BSA with or without symptoms (e.g. pruritus, burning)	Maintain dose level. Consider to initiate appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)

Grade 2 Macules/papules covering 10-30% BSA with or without symptoms; limiting instrumental ADLs	Reduce study drug dose to 50% of prior dose. Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids)
Grade 3 Macules/papules covering >30% BSA with or without associated symptoms, limiting self-care ADLs	Discontinue study drug According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate
Grade 4	Discontinue buparlisib. Consider if hospitalization is appropriate According to the investigators discretion, a paired skin biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) if clinical appropriate.

Table 10. Recommended dose modifications and dose delays for suspected buparlisib treatment-related toxicities**

Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Fatigue (asthenia)	
Grade 1 Fatigue relieved by rest	Maintain dose level
Grade 2 Fatigue not relieved by rest; limiting instrumental ADL	Reduce study drug dose by 50% of prior

Grade 3 Fatigue not relieved by rest; limiting self care ADL	Discontinue study drug
Grade 4	Discontinue buparlisib. Consider if hospitalization is appropriate
Pneumonitis	
Please see Section 4.1.2.3.2; Table 14; and/or buparlisib Investigator Brochure Section 6.2.6.1.1.	
Other adverse events	
Grade 1	Maintain dose level
Grade 2	Implement 50% dose reduction
Grade 3	Omit dose and discontinue study drug
Grade 4	Omit dose and discontinue study drug Consider if hospitalization if appropriate
Other notes:	
Table 10. Recommended dose modifications and dose delays for suspected buparlisib treatment-related toxicities	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Note: Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic	
All dose modifications should be based on the worst preceding toxicity.	
If the dose-limiting toxicity recurs in a patient following dose reduction, then further therapy with sonidegib will not be continued.	
If a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose because of a sonidegib-related toxicity, then the patient must be discontinued from the study.	
** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.	

4.1.1 Monitoring of buparlisib suspected toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant 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. If the patient requires more than 1 dose reductions, the patient should be discontinued from the study (ie, patients cannot be treated below a 50% dose reduction). All patients must be followed for adverse events and serious adverse events for 28 days following the last dose of buparlisib. All SAEs must be reported to Novartis as detailed in Section 4.3.4.2.

4.1.2 Known Undesirable Side Effects of buparlisib

4.1.2.1 **Neuropsychiatric events**

In an ongoing phase 1a study of buparlisib in patients with solid tumors (CBKM120X2101), neuro-psychiatric adverse events, including reversible and generally mild to moderate mood alterations, described as anxiety, agitation with crying episodes and depression have been reported in patients treated with buparlisib. In this study, three out of five patients with moderate to severe mood alterations had a history of depression and/or anxiety. All patients with a documented medical history of depression/anxiety also developed mood alterations while treated with buparlisib at the 100 mg dose level and thus reflecting a potential risk group of patients.
In order to lower the risk of experiencing significant mood alterations within the proposed study, cancer patients with an active or history of major depressive episode, bipolar disorder, obsessive-compulsive disorder, schizophrenia, a history of suicide attempt or ideation, or homicide/homicidal ideation as judged by the investigator and/or based on recent psychiatric assessment will not qualify for study participation. Patients with corresponding symptoms CTCAE Grade $\geq$ 2 should immediately be examined by a psychiatrist and closely followed medically. Medical treatment with mood stabilizers (2nd generation antipsychotics) such as olanzapine and quetiapine may be applied as per investigator's discretion and following consultation of a psychiatrist.

4.1.2.1.1 Management of mood alteration

Patient self-rating mood questionnaires GAD-7 (anxiety) (see Table 11) and PHQ-9 (depression) (see Table 12) will be used:

- ♦♦ to support assessment of eligibility at Screening
- ♦♦ to monitor for newly occurring or worsening mood alterations during the study.

The following grading system will be used for this study:

At Screening, a patient as judged by the investigator or who meets the cut-off score of ≥ 12 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, or select a positive response of '1, 2, or 3' to question number 9 regarding suicidal thoughts or ideation will be excluded from the study.
During the study, patients who meet the cut-off score of ≥ 10 (≥ CTCAE Grade 2 mood alteration) in either questionnaire or indicate a positive response by selecting '1, 2, or 3' to question number 9 on the PHQ-9 must see a psychiatrist for advice on the most appropriate medical treatment must see a psychiatrist for diagnosis and determination of most appropriate medical treatment. For anxiety, this applies only if status has worsened from baseline. Patients who experience ≥ Grade 2 mood alteration will be followed by patient self-rating mood scale and will be seen weekly by the psychiatrist until resolved ≤ Grade 1 or baseline (for anxiety), if there is no concurrent medical condition that accounts for an acute increase the PHQ score. Questionnaire responses will be checked by the psychiatrist at the weekly visits (until resolution to Grade 1 or baseline (for anxiety).

Table 11. GAD-7 anxiety scale

Over the last 2 weeks, how often have you been bothered by the following problems? (Use "./"to indicate your answer"	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Column totals:		+	+	+

= Total Score

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all

Somewhat difficult

Very

Difficult

Extremely

Difficult

Table 12. PHQ-9 depression scale

Mood questionnaires will be scored according to Table 13 below.

Table 13. Toxicity grading based on mood questionnaire scores

PHQ-9			GAD-7		
Score	**Severity**	**CTCAE grading**	**Score**	**Severity**	**CTCAE grading**
0-4	None	Normal	0-4	None	Normal
5-9	Mild	Grade 1	5-9	Mild	Grade 1
10-19	Moderate	Grade 2	10-14	Moderate	Grade 2
20-27	Severe	Grade 3	≥ 15	Severe	Grade 3

4.1.2.2 Hyperglycemia

In preclinical studies, insulin/glucose homeostasis was impacted in various species (mice, rats, dogs), as expected from the mode of action of buparlisib. In both rats and dogs, at the doses used in the 4-week studies, these effects were minimal. However, in mice treated at high doses (30 or 60 mg/kg/day) a clear induction of insulin resistance/ insensitivity was observed, without clear influence of the dose or the time point of testing.

Histopathologically, pancreas and liver showed changes which are in concordance with this activity.
Grade 4 Hyperglycemia was also observed in an ongoing phase 1a study of buparlisib in patients with solid tumors (CBKM120X2101). Therefore, no patients with uncontrolled diabetes mellitus will be enrolled in this study. In all patients, fasting plasma glucose will obtained at screening and will be monitored throughout the trial. For the treatment of glucose disturbances occurring under buparlisib treatment investigators are advised to adhere to the protocol guidelines outlined in Table 10 and as follows.

4.1.2.2.1 Management of Hyperglycemia

In addition to the dose modification and hyperglycemia treatment guidelines in Tables 9 and 10:

- Under the supervision of an endocrinologist, an insulin regimen should be initiated according to institutional standard of care or the Treat-To-Targ*et al*gorithm for Lantus® (Riddle, Rosenstock, and Gerich 2003).
- For any hyperglycemia ≥ Grade 1, the patient should continue to follow dietary guidelines provided by the American Diabetes Association (American Diabetes Association 2004).
- For each patient, a maximum of 2 dose reductions will be allowed after which the patient should be discontinued from the study. In addition, a patient must discontinue treatment with buparlisib, if after treatment is resumed at a lower dose, hyperglycemia recurs at a worse severity.

- ♦♦ For each patient, once a dose level reduction has occurred, the dose level may not be re-escalated in that patient during future treatment cycles with buparlisib.
- ♦♦ Based upon the results of preliminary clinical data and actual laboratory values (eg, glucose, insulin) generated, the treatment recommendations for study drug-induced hyperglycemia may be modified as needed.

4.1.2.3 Cardiac events

Cardiac safety studies, conducted in vitro and in vivo, did not indicate a prominent electrophysiological risk. The only effect considered relevant was a trend towards an increase in systolic and diastolic blood pressure, observed in two dog telemetry studies. As a precaution in the first-in man study with buparlisib no patients with a severe or unstable cardiac disease or cardiac disease requiring continuous treatment, and no patients with uncontrolled hypertension will be enrolled in early clinical studies. In addition, all patients will be assessed for cardiac diseases before start of treatment, while all patients enrolled in the trial will undergo regular cardiac monitoring throughout the conduct of the trial. For the treatment of acute cardiac events occurring under buparlisib treatment investigators are advised to adhere to the protocol guidelines. Vital signs, including pulse rate and blood pressure, will closely be followed during the early clinical studies.

4.1.2.3.1 Management of Cardiac events

At the screening visit a 12-lead electrocardiogram (ECG), will be performed to assess eligibility.

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

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

Patients should be informed about the possibility of developing mouth ulcers/ oral mucositis and instructed to report promptly any signs or symptoms to their physician, Patients should be educated about good oral hygiene, instructed to avoid spicy/ acidic/salty foods, and should follow the following guidelines:

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

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with buparlisib metabolism. Oral or systemic liver enzyme inhibitors such as topical antifungal creams are allowed.

4.1.2.3.3 Guidelines for the Treatment of Buparlisib-induced Psychiatric Disorders

Psychiatric adverse events will be closely monitored and evaluated at each planned visit until recovery to Grade ≤ 1 or baseline status. The grading of psychiatric adverse events/mood alterations must be based on the clinical interpretation of severity according to the NCI-CTCAE (v 4.03) guidelines.
For patients who experience new or worsening of existing psychiatric AEs of Grade ≥1, psychiatric consultation should be considered as described in
Table 10.
Patient self-reported mood questionnaires (GAD-7 and PHQ-9) will be used for screening and during the study treatment phase to aid the investigator in identifying new or worsening of events. For additional information regarding safety assessments based on patient self-reported mood questionnaires, please refer to Section Patient self rating mood questionnaires.
If question 9 in the PHQ-9 has a positive response (as indicated by selecting "1", "2", or "3"), omit treatment with buparlisib and refer the patient for psychiatric consultation for optimal management regardless of the total questionnaire score or CTCAE grading to confirm if study drug should be interrupted or permanently discontinued. In this specific case, the psychiatric advice can overrule the patient's PHQ-9 self-assessment. During the study, subjects will be monitored at regular scheduled visits (eg, Day 15 of Cycle 1, Day 1 and Day 15 of Cycles 2, Day 1 of each subsequent cycle, and at the End of Treatment visit) by the investigator/site staff through personal interaction and the two self reported questionnaires. Additional assessments may be done according to the clinical judgment of the investigator if desired.

4.1.2.3.4 Guidelines for the Treatment of Study Drug-induced Skin Toxicity

Skin toxicity is a class-effect observed with PI3Ki/mTORi agents. Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as adverse event. The most frequent skin adverse events reported are: maculopapular rash (only a minority present acneiform rash) (refer to Table 10 for clinical management); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate comedication and treatment interruption if needed.
Photographs of a skin rash event as well as skin biopsy are recommended, if possible.
According to the investigators discretion, a paired biopsy could be obtained (from both an affected and an unaffected skin area for local histopathology assessment) to further assess rash if clinical appropriate.
Recommended therapies for skin toxicity events (refer to Table 10 for specific guidance according to the type of skin toxicity):

- ♦♦ Topical steroids of moderate potency (face and folds): triamcinolone 0.025%; aclometasone 0.05% (< 8 weeks continuously), for mild and moderate rashes.
- ♦♦ Topical steroids of high potency (trunk/extremities): fluocinonide 0.05%; clobetasol 0.05% cream or spray (< 8 weeks continuously), for mild and moderate rashes.
- ♦♦ Oral antihistamines (sedating, evening): diphenhydramine 25 to 50mg TID; hydroxizine 25mg TID or QID;
- ♦♦ Oral antihistamines (non-sedating, day time): fexofenadine 180mg QD or 60mg TID (monitor the use of this class of drugs since skin toxicity has also been reported)

- ♦♦ Oral corticosteroids: prednisone 0.5mg/kg or equivalent up to 5 days of treatment
- ♦♦ In case of mild acneiform rashes topical antibiotics: clindamycin 1% to 2%; erythromycin 1% to 2% (gel or solution formulation can be used, ointments cannot be used); metronidazole 1%; silver sulphadiazine.
- ♦♦ For more severe acneiform rashes oral antibiotics: doxycycline 100mg BID; minocycline 100 mg BID; oxytetracycline 500mg BID for 6 weeks can be considered. If infection suspected (yellow crusts, purulent discharge, painful skin/nares), then switch to broad spectrum/gram negative antibiotics; consider skin swab for bacterial culture.
- ♦♦ Topical antipruritics (pramoxine 1%, doxepin 5% cream) applied twice daily
- ♦♦ For severe pruritus GABA Agonists: Gabapentin 300mg every 8 hours, or pregabalin 50 to 75 mg every 8 hours (to adjust of renal impairment) can be considered. Dose should be adjusted depending on patient's clinical condition be of potential and common side effects observed with GABA agonists such as: somnolence, dizziness (both drugs) and peripheral edema (Gabapentin) among others AEs.

Dry skin has been reported, it is recommended that patients with dry skin use mild and fragrance free soaps and detergents. According to the severity and BSA extension patients may apply mild moisturizers, ammonium lactate cream 12% or salicylic acid cream 6% BID.

Photosensitivity has been described in patients although preclinical experiments demonstrated that buparlisib has no potential phototoxic effect. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including regular use of sunscreen (factor 20 at least), wearing of sunglasses, using of hats, and protective clothes when outdoors.

4.1.2.3.5 Guidelines for the management of Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of PRES occurring under treatment with buparlisib. Signs and symptoms may include severe headache, confusion or seizures, altered consciousness, visual disturbances, with or without associated high blood pressure. Patients are instructed in the written patient information to inform their treating physician if they suspect such an event. Take appropriate measures in such cases to assess the signs and symptoms. If PRES is suspected based on the signs and symptoms, buparlisib should be interrupted and a brain MRI should be performed to confirm the diagnosis.

4.1.2.3.6 Management of Pneumonitis

Pneumonitis is a known side effect of rapamycin analogues. Based on the literature, the class of PI3K inhibitors has not previously been associated with the development of pneumonitis. Clinically significant pneumonitis typically accompanied by non-specific symptoms including dyspnea, nonproductive cough, fatigue, and fever. Diagnosis is generally suspected in individuals who develop these symptoms or in asymptomatic individuals in whom a routine chest CT scan reveals a new ground glass or alveolar infiltrate.

In ongoing clinical trials with buparlisib in the single agent setting two cases of Pneumonitis occurred. In the study BKM120X2101 one patient experienced pneumonitis

Grade 2 eight weeks after the first dose of buparlisib at 100mg which resolved in 7 days after antibiotic therapy and discontinuation of the study treatment due to fatigue. In the Japanese study BKM120X1101 one case of Pneumonitis occurred in a patient given 100 mg one month after the start of study medication with buparlisib. The patient experienced Pneumonitis with fatal outcome which was concomitant to progression of underlying malignancy including the progression of existing and the appearance of new lesions in combination with increasing pleural effusion (see Buparlisib Investigator Brochure).
All patients participating in clinical trials administering buparlisib will be routinely asked about the occurrence of adverse events which could include new or changed pulmonary symptoms (consistent with lung abnormalities). CT scans and pulmonary function test should be done, as clinically indicated, or if there are symptoms that indicate that the patient has developed Pneumonitis. In case of a documented pneumonitis, the guidelines (including dose modifications) in Table 14 should be followed. Consultation with a pulmonologist is highly recommended for any pneumonitis case identified during the study.

Table 14. Management of Pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Buparlisib Dose Adjustment
Grade 1	CT scans with lung windows. Repeat at least every 8 weeks until return to within normal limits.	No specific therapy is required	Administer 100% of buparlisib dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce buparlisib dose 50% (see Table 10) until recovery to ≤ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to ≤ Grade 1within 3 weeks.

Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment with buparlisib until recovery to ≤ Grade 1. May restart study treatment within 3 weeks at a 50% dose reduction if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment with buparlisib.

4.1.2.3.7 Management of Liver Toxicities

Monitoring Cycle 1 and 2: **every other week** (if visit schedule allows a more frequent monitoring this should be considered) or more frequently if clinically indicated especially for patients with borderline acceptable AST/ ALT/ bilirubin* values.
Monitoring Cycle 3 and more: **monthly** or more frequently if clinically indicated. In case of any occurrence of ALT/ AST/ bilirubin* increase **≥ Grade 2** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ Grade 1.**
In case of any occurrence of ALT/ AST/ bilirubin* increase **≥ Grade 3** the liver function tests must be monitored **weekly** or more frequently if clinically indicated **until resolved to ≤ Grade 1**; hereafter the 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).

4.1.2.4 **Study discontinuation**

All interruptions or changes to study drug administration must be recorded.
It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol violation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

4.2 Treatment Administration

4.2.1 Buparlisib Administration

The study drug buparlisib will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol. Buparlisib will be administered on a continuous once daily dosing schedule at a dose of **80mg daily**. Patients should be instructed to take the dose of buparlisib with Sonidegib (see below) daily in the morning, two hours after a light breakfast (morning meal) at approximately the same time each day. Buparlisib should be taken with a glass of water and consumed over as short a time as possible. Patients should swallow the capsules as a whole and not chew them. Do not crush capsule. Patients should continue to fast for 2 hours after the administration of each buparlisib dose.
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 during a treatment cycle must be noted as an adverse event. If the patient forgets to take her/his dose before 6:00 PM, then the dose should be withheld that day and buparlisib should be restarted the following day.
Patients must avoid consumption of St John's Wort, Seville oranges, grapefruit or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits from 7 days prior to the first dose of study medication and during the entire study treatment period due to potential CYP3A4 interaction with the study medication. Patients must avoid concomitant intake of strong and moderate CYP3A4/5 inhibitors and inducers. Orange juice is allowed.
All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. If a patient requires a buparlisib dose delay of > 21 days from the previous dose, the patient must be discontinued from treatment completely and will only require a 28-day follow up visit for study completion.
Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

4.2.2 Sonidegib Administration

The investigator needs to instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded in the dosage administration record CRF, as appropriately.

Sonidegib Treatment and Treatment Schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or regimen
Sonidegib	**Capsule or tablet for oral use**	**200 QD**	**daily**

Sonidegib will be administered orally with buparlisib, on a continuous once daily dosing schedule at a dose of 200 mg. Participating patients will receive flat doses on mg/ day basis and not according to their body weight or body surface area. Sonidegib is supplied as 200-mg hard gelatin capsules or tablets. Patients will receive 2 capsules or tablets. The shelf-life and storage conditions will be continually assessed based on accelerated and long term stability data Sonidegib. Medication labels will be in the local language (English) and comply with the legal requirements of USA.

Sonidegib should be taken as follows:

- ♦♦ Patients should be instructed to take their once-a day dose at approximately the same time each day
- ♦♦ Each daily dose of Sonidegib should be taken with a glass of water and consumed over as short a time as possible (eg, 1 capsule every 2 minutes)
- ♦♦ Patients should be instructed to swallow capsules whole and to not chew or open them
- ♦♦ Each daily dose of Sonidegib should be taken **2 hours after** a light breakfast (eg, consisting of juice, toast and jam). If breakfast was completed at 08:00 a.m., then study drug administration should occur at 10:00 a.m. Food intake should be avoided for at least 1 hour after study drug administration
- ♦♦ Patients must avoid grapefruit, pomegranate, star fruit and Seville (sour) oranges during the entire study. The juices and products containing these fruits may also be avoided.
- ♦♦ If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose
- ♦♦ If the patient forgets to take his/her daily morning dose, then he/she should take Sonidegib within 6 hours after the missed dose. If more than 6 hours have passed, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose. Patients should inform the investigational site staff of any missed or delayed dose. Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, 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 Novartis.

4.2.3 Concomitant therapy

All medications (excluding prior chemotherapy and biologic, immunologic or radiation therapy) taken within 4 weeks prior to the administration of buparlisib/sonidegib and all concomitant therapy administration during the study with reasons for therapy should be recorded. All prior chemotherapy; biologic, immunologic or radiation therapy; and surgery within 4 weeks prior to the administration of study drug, will be recorded.
Patients on chronic medications that can be given concomitantly with buparlisib/ sonidegib should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. 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 herbal medicines, physical therapy and blood transfusions) administered after the patient starts treatment with study drug, and any changes in dosing should be recorded.
In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted with the following exceptions described below in Section

4.2.3.1 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.
- ♦♦ *In vitro* metabolism studies suggest that oxidative metabolism of buparlisib is predominantly mediated by CYP3A4 (fm>0.9), with only minor contributions of CYP1A1. As buparlisib is a sensitive CYP3A4 substrate, co-administration of buparlisib with strong and moderate CYP3A4 inhibitors and CYP3A4 inducers is prohibited. Refer to Table 15 for a list of prohibited drugs. Please note this list may not be comprehensive.
- ♦♦ Based on in vitro studies, co-administration of buparlisib with CYP3A4 inducers is predicted to decrease the systemic exposure to buparlisib, thereby increasing the risk of exposing the patient to subtherapeutic drug levels. Refer to Table 15 for a list of prohibited CYP3A inducers. Please note that this list may not be comprehensive. Therapeutic doses of warfarin sodium (Coumadin®) or any other coumadin-derivative anticoagulants are not permitted.
- ♦♦ If a patient requires the concomitant use of any medication included in Table 16 entitled “List of Prohibited QT prolonging drugs” (ie, drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a risk of causing Torsades des de Pointes), study treatment administration must be interrupted as long as the patient requires therapy with the QT prolonging agent.
- ♦♦ Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to St. John’s wort, Kava, ephedra (ma huang), ginko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginsing. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

♦♦ Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective in this study.

Table 15. List of prohibited CYP3A Inhibitors and Inducers

CYP3A Inhibitors		CYP3A Inducers	
Strong	**Moderate**	**Strong**	**Moderate**
clarithromycin conivaptan grapefruit juice Indinavir itraconazole ketoconazole Lopinavir Mibefradil nefazodone Nelfinavir posaconazole Ritonavir Saquinavir telithromycin troleandomycin voriconazole	aprepitant atazanavir cimetidine ciprofloxacin darunavir diltiazem erythromycin fluconazole tofisopam verapamil amprenavir fosamprenavir elvitegravir tipranavir	avasimibe carbamazepine Phenobarbital (barbiturate) phenytoin rifabutin rifampin St John's Wort	bosentan efavirenz etravirine modafenil nafcillin ritonavir talviraline tipranavir

This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase buparlisib AUC > 5-fold, and moderate inhibitors are predicted to increase buparlisib AUC ≥ 2-fold but < 5-fold.
This database of CYP inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche *et al*. 2008).

All QT-prolonging drugs listed in Table 4-8 are prohibited for all patients from screening through permanent discontinuation of study treatment. Table 16 below lists drugs with a known risk for Torsades de Pointes (TdP) as well as sensitive CYP3A substrates (with narrow TI) with a possible or conditional risk for TdP.

Table 16. List of prohibited QT-prolonging drugs

Drug	QT risk(*)	Comment
Amiodarone	Known risk for TdP	Females > Males, TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females > Males.
Disopyramide	Known risk for TdP	Females > Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females > Males
Pentamidine	Known risk for TdP	Females > Males
Pimozide	Known risk for TdP	Females > Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females > Males
Sotalol	Known risk for TdP	Females > Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 sibstrate with narrow TI

Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Drug	**QT risk(*)**	**Comment**
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5fold or higher when co-administered with a potent inhibitor of the respective enzyme.		

4.2.3.2 Drugs to be used with caution

Preliminary in vitro metabolism studies suggest that buparlisib is a weak, reversible inhibitor CYP3A4/5 (Ki=13.6 μM, [I]/Ki= 0.4 where [I] is the average C_{max} at steady-state following 100 mg daily dose) and a weak reversible inhibitor of CYP2C8/2C9/2C19 (IC_{50}=34 μM, [I]/IC_{50}=0.15). Note: that with the data available, we are not able to confirm whether such interactions will occur in patients. Therefore, investigators, 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 potentiation of toxicity due to any individual concomitant medications, and may require dose titration or reduction of the drug substrate. Please refer to Table 17 for a list of CYP450 substrates and carefully consider their co-administration with buparlisib.

Particularly, caution is advised when buparlisib is coadministered with:

- ♦♦ Drugs which are substrates for CYP3A4, CYP2C8, CYP2C9 or CYP2C19 and which have a narrow therapeutic index.
- ♦♦ Oral anti-diabetics which are metabolized by CYP2C8 or CYP2C9 can possibly result in hypoglycemia. Patients who develop diabetes mellitus during the study should be treated according to the American Diabetes Association guidance. It is recommended that treatment start with metformin.
- ♦♦ If a patient, after study enrollment, requires the concomitant use of any QT prolonging medication with a possible or conditional risk for torsade de pointes then the investigators, at their discretion, may co-administer such medications. Patients receiving such medications must be monitored. Refer to Table 16 for a list of QT-prolonging medications to be used with caution.

Note: please refer also to Table 16 for a list of prohibited QT prolonging medication.

- ♦♦ Please refer to Table 17 for a list of CYP450 substrates and carefully consider their co-administration with buparlisib.
- ♦♦ Concomitant treatment with corticosteroids and buparlisib should be avoided, whenever possible, during this study. A short duration (< 2 weeks) of systemic corticosteroids is allowed (eg, for chronic obstructive pulmonary disease, or as an anti-emetic). Chronic dosing of corticosteriods is known to induce CYP3A enzymes, thereby increasing the risk or reducing buparlisib overall exposure to sub-therapeutic levels.

Table 17. List of CYP450 Substrates to be used with caution

CYP2C8	CYP2C9	CYP2C19	CYP3A**	
CYP2C8	CYP2C9	CYP2C19	CYP3A**	
amodiaquine cerivastatin pioglitazone repaglinide rosiglitazone torasemide troglitazone	celecoxib diclofenac flurbiprofen fluvastatin Glibenclamide (glyburide) gliclazide glimepiride glipizide indomethacin irbesartan ketobemidone lornoxicam losartan meloxicam naproxen nateglinide piroxicam rosiglitazone S-ibuprofen sulfamethoxazo le tenoxicam tolbutamide torasemide valdecoxib	amitriptyline citalopram clobazam clomipramine clopidogrel diazepam fluoxetine imipramine lansoprazole mephobarbital moclobemide omeprazole pantoprazole progesterone quazepam rabeprazole sertraline S-mephenytoin	Adinazolam alfentanil [1,2] Alpha- dihydroergocryptine 1 Alprazolam Amlodipine Aripiprazole Atorvastatin Brecanavir brotizolam [1] budesonide [1] buspirone [1] Capravirine Cerivastatin Chlorpheniramine cyclosporine [2] darifenacin [1] Diazepam diergotamine [2] ebastine [1] eletriptan [1] eplerenone [1] ergotamine [2] Estazolam everolimus [1]	felodipine [1] fentanyl [2] flunitrazepam fluticasone [1] lovastatin [1] maraviroc [1] midazolam [1] nifedipine nisoldipine nitrendipine perospirone [1] quinine sildenafil [1] simvastatin [1] sirolimus [1,2] tolvaptan trazodone triazolam [1]

Table 17. List of CYP450 Substrates to be used with caution (continued)

* This database of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table, and from (Zhou *et al*. 2009)

** CYP3A substrates were compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; and supplemented by the FDA's "Guidance for Industry, Drug Interaction Studies" and the University of Washington's Drug Interaction Database.

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

Table 18. List of QT prolonging drugs to be used with caution

Drug	QT risk	Comment
Alfuzosin	Possible risk for Torsades de Pointes	
Amantadine	Possible risk for Torsades de Pointes	
Amitriptyline	Conditional risk for Torsades de Pointes	
Azithromycin	Possible risk for Torsades de Pointes	
Chloral hydrate	Possible risk for Torsades de Pointes	
Citalopram	Conditional risk for Torsades de Pointes	
Clomipramine	Conditional risk for Torsades de Pointes	
Clozapine	Possible risk for Torsades de Pointes	
Desipramine	Conditional risk for Torsades de Pointes	
Diphenhydramine	Conditional risk for Torsades de Pointes	
Dolasetron	Possible risk for Torsades de Pointes	
Doxepin	Conditional risk for Torsades de Pointes	
Dronedarone	Possible risk for Torsades de Pointes	
Felbamate	Possible risk for Torsades de Pointes	
Flecainide	Possible risk for Torsades de Pointes	
Fluoxetine	Conditional risk for Torsades de Pointes	
Foscarnet	Possible risk for Torsades de Pointes	
Fosphenytoin	Possible risk for Torsades de Pointes	
Galantamine	Conditional risk for Torsades de Pointes	
Gatifloxacin	Possible risk for Torsades de Pointes	
Gemifloxacin	Possible risk for Torsades de Pointes	
Granisetron	Possible risk for Torsades de Pointes	
Imipramine	Conditional risk for Torsades de Pointes	
Indapamide	Possible risk for Torsades de Pointes	

Isradipine	Possible risk for Torsades de Pointes	
Levofloxacin	Possible risk for Torsades de Pointes	
Lithium	Possible risk for Torsades de Pointes	
Mexiletine	Conditional risk for Torsades de Pointes	
Drug	QT risk	Comment
Moexipril/HCTZ	Possible risk for Torsades de Pointes	
Moxifloxacin	Possible risk for Torsades de Pointes	
Nicardipine	Possible risk for Torsades de Pointes	
Nortriptyline	Conditional risk for Torsades de Pointes	
Drug	**QT risk**	**Comment**
Octreotide	Possible risk for Torsades de Pointes	
Ofloxacin	Possible risk for Torsades de Pointes	

Ondansetron	Possible risk for Torsades de Pointes	
Oxytocin	Possible risk for Torsades de Pointes	
Paliperidone	Possible risk for Torsades de Pointes	
Paroxetine	Conditional risk for Torsades de Pointes	
Perflutren lipid microspheres	Possible risk for Torsades de Pointes	
Protriptyline	Conditional risk for Torsades de Pointes	
Ranolazine	Possible risk for Torsades de Pointes	
Risperidone	Possible risk for Torsades de Pointes	
Roxithromycin*	Possible risk for Torsades de Pointes	*not available in the United States
Sertindole	Possible risk for Torsades de Pointes	
Sertraline	Conditional risk for Torsades de Pointes	
Solifenacin	Conditional risk for Torsades de Pointes	
Tizanidine	Possible risk for Torsades de Pointes	
Trazodone	Conditional risk for Torsades de Pointes	
Trimethoprim-Sulfa	Conditional risk for Torsades de Pointes	
Trimipramine	Conditional risk for Torsades de Pointes	
Venlafaxine	Possible risk for Torsades de Pointes	
Ziprasidone	Possible risk for Torsades de Pointes	
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

4.3 Visit schedule and assessments

4.3.1 Evaluation and Visit Schedule (Table 19)

Examination	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 to Cycle n**					
Day of Cycle	-21	1 (Baseline)	15	1	15	3	4	5	6	7	
Informed consent	X										
Medical History	X										
Inclusion/ exclusion criteria	X										
Serum pregnancy test (with 72 hours of 1st treatment for WOCBP)	As clinically indicated.										
Urinalysis	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Physical examination (including skin rash assessment)	X	X		X		X	X	X	X	X	X
Performance Status ECOG	X	X		X		X	X	X	X	X	X
Neuro-psychiatric assessment (self-rating mood questionnaire GAD and PHQ)	X	X	X	X	X	X	X	X	X	X	X
Examination	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 to Cycle n**					
Day of Cycle	-21	1 (Baseline)	15	1	15	3	4	5	6	7	
12-lead ECG*	X	As clinically indicated.									
Chest X-Ray (if locally advanced disease only)	X	Every 8 weeks from start of treatment until progression as per RECI									

Radiological tumor assessment/response assessment (CT or MERI Scans if no clinically visible)**	X					X		X		X	
Hematology*	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry*	X	X	X	X	X	X	X	X	X	X	
Coagulation Profile*	X			X			X		X		
Fasting plasma glucose*	X	X	X	X	X	X	X	X	X	X	
HgA1C*	X					X			X		
Tumor biopsy for biomarkers[3]	X					X			X		

* Can use screening if w/in 72 hours of baseline.

**Screening radiological assessments should be performed within 4 weeks of the first dose. Radiological tumor assessment should be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks, until progression of disease or end of treatment. If stable after cycle 4, then CT scan to be performed every 12 weeks instead. All assessments should be performed within ±7 days of the scheduled day of assessment. The assessment at the EOT visit is only to be performed if the prior assessment occurred ≥ 21 days before.

[3] Tissue samples at baseline, week 12 and 24 (or EOT, whichever occurs first) will be taken and sent for whole exome sequencing, gene expression profiling and immunohistochemistry if accessible to tumor biopsy.

4.3.2 Efficacy assessments

Efficacy will be assessed on the basis of clinical examination using calipers if the target tumor is visible on the skin. If it is not visible on the skin tumor imaging will be used to assess the single longest diameter for the basis of efficacy assessment. (see 4.3.1 Evaluation and Visit Schedule (Table 19). Tumor response by RECIST 1.1 criteria will be used for evaluation.

4.3.3 Safety assessments

Patients enrolled in this clinical trial will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study (see Study Calendar). Safety evaluations will consist of tumor assessments performed every 4 weeks, routine hematology, comprehensive metabolic profiles, EKGs and urinalysis.

To date, Sonidegib has been shown to be well-tolerated in early phase clinical studies with the most common side effects consisting of fatigue, nausea, vomiting, anorexia, muscle cramps, and dysgeusia (5). To date, the most common adverse events of patients on buparlisib (≥ 15%), regardless of grade and causality, reported in any treatment cycle were decreased appetite (45.5%), nausea (39.4%), constipation, diarrhea, fatigue (each 31.8%), rash (30.3%), hyperglycemia (27.3%), asthenia (25.8%), abdominal pain, vomiting (each 22.7%), anxiety (21.2%), depression (19.7%), mucosal inflammation, pruritus (each18.2%), dyspnea (16.7%), AST increase, dry skin, dyspepsia, pyrexia, and somnolence (each 15.2%), data provided by Novartis.
It is possible that the combination of the two medications, Sonidegib and buparlisib may lead to additive or synergistic side effects. Independently, both medications are known to cause frequent gastrointestinal side effects such as nausea and vomiting and the concomitant administration of both may compound these side effects.
All adverse events will be attributed to LB therapy unless they can be clearly attributed to progression or to another clearly identified etiology by the investigator. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0.
Intolerable toxicities are defined as new (not present at baseline) Grade 3 or 4 adverse events deemed to be related to LB therapy that are life threatening or irreversible, and when (in the opinion of the investigator) the risks outweighs the benefit of continued treatment.
Women of childbearing potential will be required to have a negative serum pregnancy test at screening, urine pregnancy test on Day 1 and every 4 weeks while on study. Women of childbearing potential or male patients with female partners of childbearing potential are required to use a highly reliable method of contraception, and for 12 weeks after discontinuation of LB therapy. Patients must agree not to donate bodily fluids for 12 months after discontinuation of LB therapy.
Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations. These assessments should be performed within ±2 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTC (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

4.3.4 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

4.3.4.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.
An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting

study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.
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 (mild, moderate, severe) or (Grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
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 constitutes a serious adverse event (SAE)

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, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.
Information about common side effects already known about the investigational drug can be found in the Investigators' Brochure. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

4.3.4.2 Serious adverse events

A serious adverse event is an undesirable sign, symptom or medical condition 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 the start of study drug
- ♦♦ 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, ie, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

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/participation
- ♦♦ after the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment
- ♦♦ after protocol-specified procedures begin (eg, placebo run-in, washout period, double-blind treatment, etc.) and until 4 weeks after the patient has stopped study treatment
- ♦♦ after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (eg, treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) 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 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.

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 in English, and send the completed, signed form by fax (877-778-9739) within 24 hours to the Novartis Drug Safety and Epidemiology Department. The original copy of the SAE
Report and the fax confirmation sheet must be kept within the Trial Master File 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 (if applicable), 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 Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.
Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

4.3.5 Novartis instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E). All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).
All events must be reported, by FAX (877-778-9739), to Novartis Pharmaceuticals DS&E

Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.
Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (eg, treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).
Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.
For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

4.3.5.1 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy 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 Study Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (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 treatment 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 any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.
The team needs to prepare information for the female partner of the male patient on required contraception. This information needs to be given to the male patient at the ICF signing for him to share it with his female partner. Information for female partners of male study participants
Your male partner is offered to participate in a clinical research study. As a prerequisite to participate in this study your partner must agree to use a condom during intercourse. This is important because test results of the study treatment in pregnant animals indicated that the medicine can harm an unborn baby through the sperm. At the same time it is also important that you do not become pregnant while your partner is taking the medication. Therefore, you should use a highly effective method of birth control (contraception) during the time your male partner receives the study treatment and thereafter for another 3 months.
Highly effective methods of contraception are those methods of birth control that have less than 1% of unwanted pregnancy during one year, if used appropriately according to the instructions of the manufacturer. Those methods are 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 contraception, injected or implanted hormonal methods are not allowed as buparlisib potentially decreases the effectiveness of hormonal contraceptives.
- ♦♦ Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, for 4 weeks (5 T1/2) after stopping treatment and for additional 12 weeks (16 weeks in total after study drug discontinuation) and should not father a child in this period.
- ♦♦ Female partner of male study subject should use highly effective contraception during dosing of any study agent and for 16 weeks after final dose of study therapy.

For details on the most appropriate contraception you may talk to your regular doctor or if your male partner agrees with the study doctor.
If you get pregnant despite taking the birth control precautions, please ask your partner to inform the study doctor as soon as possible. The study doctor will ask your permission to collect information about you, your pregnancy and your child.

4.3.5.2 Laboratory evaluations

Pregnancy Test

A serum pregnancy test (β-HCG) is required for all women of child-bearing potential at screening, within 72 hours prior to the first dose of buparlisib. 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. Additional pregnancy tests should be performed as clinically indicated. Will continue to check pregnancy tests once a month while in study.

Hematology

Hematology includes the following parameters: complete blood count (CBC) consisting of red blood cell (RBCs), a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin (Hgb); and platelet count.

Coagulation Profile

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

Serum chemistry

Biochemistry includes the following parameters: K+, Na+, Ca++, Mg++, LDH, ALT, AST, total bilirubin (direct and indirect), creatinine, creatinine kinase, amylase, GGT, lipase, alkaline phosphatase (fractionated if alkaline phosphatase is Grade 2 or higher), bicarbonate, phosphorus, uric acid, total cholesterol, HDL, LDL, triglycerides, glucose, urea or BUN, albumin, and total protein are required at every visit including baseline and end of treatment. Subsequent assessments always include K+, Na+, Ca++, ALT, AST, total bilirubin (direct and indirect), creatinine, creatinine kinase, alkaline phosphatase, bicarbonate, phosphorus, glucose, urea or BUN, albumin, and total protein BUT, lipase, total cholesterol, HDL, LDL, triglycerides should be obtained on the first day of odd numbered cycles only. C1D1 assessments may be performed up to 72 hours prior to the

scheduled visit. All other draws should occur within 24 hours of the intended visit. Because accurate serum glucose and lipid measurements are required, patients should be fasting at the time of the blood sampling.

Urinalysis

Urinalysis includes macroscopic (protein, glucose, ketones, blood, and specific gravity) and will be performed at screening visit and EOT visit. A microscopic (WBC/HPF, RBC/ HPF, and any additional findings) exam need only be performed if the urinalysis result is abnormal. This must be supplemented with laboratory quantification of any potentially relevant abnormalities.

4.3.5.3 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position as per the visit schedule.

4.3.5.4 Physical examination

Physical examination will be performed which must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system). Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded. Tumor exam will be done at each visit and will include measurements of single largest diameter of visible tumor or radiographic imaging for tumors that are not clinically visible.

4.3.5.5 Neuropsychiatric assessments

Patient self-rating mood questionnaires for anxiety and depression (PHQ-9, GAD-7) will be applied at:

- ♦♦ Screening
- ♦♦ Days 1 and 15 of Cycle 1
- ♦♦ Day 1 and 15 of Cycle 2
- ♦♦ Day 1 of Cycle 3 and subsequent cycles (only for patients who have not shown mood alterations during the first 2 cycles, patients who did should continue to fill out the questionnaire on a weekly base).
- ♦♦ End of Study treatment

Additional assessments may be done according to the clinical judgment of the Investigator. Symptomatic patients (≥ CTCAE Grade 1) must continue with questionnaires on a weekly basis while active on the treatment portion of the study.
Instructions on how to instruct the patient to complete the questionnaires as well as how to determine the scores will be provided together with each instrument. This will be done as an online HIPPA compliant survey tool through Stanford.

4.3.5.6 ECG/ECHO

A standard 12 lead ECG is to be performed at screening and as clinically indicated.
An echocardiogram (ECHO) or MUGA will be performed to assess eligibility. ECHO/MUGA will be repeated at Cycle 4 and then every 4_{th} cycle thereafter.

4.3.5.7 Performance status

Performance status will be assessed at screening and per the visit schedule. ECOG will be used for assessment (See Appendix A).

4.3.5.8 Special tests

Chest X-ray

Will be performed at baseline and every 8 weeks for monitoring per standard protocol.

CT scan

Will be performed at baseline, at 4 weeks and every 8 weeks thereafter for tumor assessment of non-visible tumors per RECIST 1.1 protocol. If CT scans show stability after cycle 4, then CT scan to be performed every 12 weeks instead.

Biomarkers

- ♦♦ Tissue samples at baseline, week 12 and 24 (or EOT, whichever occurs first) will be taken and sent for whole exome sequencing, gene expression profiling and immunohistochemistry. Whole exome sequence will include interrogation for DNA mutations in the tumor and peripheral blood. Gene expression analysis will identify increases or decreases in pathways including Hedgehog and PI3K. Immunohistochemistry to quantify protein levels of Gli 1,2, Ptch 1,2, PI3K in semi-quantitative fashion will be performed to confirm expression analysis results.
- ♦♦ Whole exome sequencing and gene expression analysis may identify novel resistance mechanisms in these BCCs that would be useful to inform future clinical trials

5 Investigational agent sampling and shipping information

Martha Hamilton, PharmD, or her designated associate will receive study medications at the Stanford Investigational Pharmacy, Redwood City, CA.

5.1 Investigational treatment

For this study, the terms “investigational drug”, “study drug” or “study treatment” refers to the combination of Sonidegib and buparlisib. If an individual drug is to be referenced the individual name will be present.

5.2 How supplied

buparlisib and Sonidegib will be dispensed at the start of every cycle, as needed.

5.2.1 Buparlisib

Novartis supplies buparlisib as 10-mg and 50-mg hard gelatin capsules. buparlisib will be administered orally once a day, as part of each 28-day cycle. Medication labels comply with the legal requirements of each country and will be printed in the local language. The storage conditions for study drug will be described on the medication label.

5.2.2 Sonidegib

Sonidegib will be supplied to the study investigators by Novartis. Sonidegib is formulated in capsules and tablets of 200-mg, strengths. The capsules are packaged in HDPE bottles with a child resistant closure. Sonidegib will be administered orally once a day, as part of each 28-day cycle.
Medication labels will conform to local legal requirements. Patient number will be added by the site pharmacist. The storage conditions for study drug will be described on the medication label. Sonidegib will be dispensed at the start of every cycle, as needed. Sonidegib will be administered orally once a day, as part of each 28-day cycle. The investigational site staff will inform each patient of their actual daily dose, and this will be recorded on the appropriate CRF.
When possible, individual doses will consist of the minimum number of capsules equaling the total dose given the available capsule sizes.
Doses for more than 7 days will be placed at 4_0 and patients will be informed of this at drug dispensing.

5.3 Storage and Preparation

The study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the pharmacist and designated assistants have access. Upon receipt, the investigational drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.
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/or at the completion of the study. All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the investigator must not destroy any drug labels, or any partly used or unused drug supply. Only after receiving written authorization by Novartis, the investigator will be instructed to either send all of the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction or to dispose of unused drug according to local regulations.

5.4 Disposal and destruction

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

6 Data management

6.1 Data collection

Investigators must record the information required by the protocol. The following analysis sets will be used for statistical analysis and data reporting.
The Full Analysis Set (FAS) consists of all patients who receive at least one (full or partial) dose of buparlisib and/or Sonidegib. Patients will be classified according to the assigned treatment.
Patients who are screened but never start treatment will be listed and will not be included in any of the summary tables.

The Safety Set consists of all patients who receive at least one (full or partial) dose of buparlisib and/or Sonidegib and have at least one valid post-baseline safety assessment. The statement that a patient has no adverse events (on the Adverse Event CRF) constitutes a valid safety assessment.
Patients will be classified according to treatment received, where treatment received for each drug is defined as (i) the treatment assigned if it was received at least once, or (ii) the first treatment received when starting study medication if assigned treatment is never received. Each patient will be classified into and analyzed consistently within one (and only one) treatment group.
The Dose-determining Set consists of all patients from the safety set who either meet the minimum exposure criterion and have sufficient safety evaluations (as determined by the investigators and Novartis), or have experienced a DLT during the first two cycles. This constitutes an evaluable patient for the determination of MTD.
A patient is considered to have met the minimum exposure criterion at a treatment group if a patient has been treated with at least 75% (ie, 42 days) of the planned 8 weeks (56 days) doses of buparlisib and Sonidegib and the patient has been observed for at least 8 weeks following the first dose, and has completed sufficient safety evaluations, as agreed by the investigators and the Sponsor, to determine whether a DLT has occurred or not.
The Biomarker Analysis Set (BAS) consists of all patients who receive at least one (full or partial) dose of buparlisib and LDE255 and provided at least one evaluable biomarker data.

6.1.1 Variables

- overall response rate (ORR) of LB therapy for patients with locally advanced or metastatic BCC in Smoothened inhibitor naive patients (Cohort 1) and those whose disease is refractory or relapsed on Smoothened inhibitor monotherapy (Cohort 2).
- median duration of response, on or after LB therapy
- frequency and severity of adverse events, including serious adverse events of LB therapy
- semi-quantitative evaluation of immunostaining for biomarkers including Gli 1, 2, PTCH, Sufu, Smoothened, PI3K markers and gene expression profiles at baseline and following 12 weeks of treatment

6.2 Analysis of the primary and key secondary variable(s)

Primary variables

♦♦ Overall Response Rate by RECIST criteria will be assessed for cohorts 1 and 2.

Secondary variables

♦♦ Median duration of response will be assessed for cohorts 1 and 2.
♦♦ Frequency of adverse events on LB therapy
♦♦ Changes in gene expression profiles of BCCs including Hedgehog pathway and PI3K pathways
♦♦ Correlation of particular gene expression profiles and response to LB therapy

7 Statistical methods

7.1 Statistical Methods

7.1.1 Statistical model, hypothesis, and method of analysis

This is an exploratory study to assess the Overall Response Rate (ORR) and median duration of response (DOR) for LB therapy after 12 weeks of treatment. Cohort 1 and 2 will not be compared directly but will be described separately, due to sample size limitations.
Effect on Progression Free Survival and Overall Survival is beyond the scope of this proposal due to sample size necessary for sufficient power would require multi-center studies.

7.1.2 Handling of missing values/censoring/discontinuations

Patients will not be replaced in this protocol. However, additional patients may be enrolled to ensure an adequate number of evaluable patients.
As of the date of data-cutoff for the purposes of reporting:

- ♦♦Patients continuing to receive study drug will have time-to-event data (eg, progression free survival, duration of response, etc.) censored at the date of last radiological disease assessment prior to the cut-off date.
- ♦♦Continuing events (eg, 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 in the core safety report and by dose-expansion part in the extension report

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9 APPENDICES

APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.

1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Participant Eligibility Checklist

Protocol Title:	An open-label pilot study to evaluate the efficacy and safety of a combination treatment of Sonidegib and buparlisib for the treatment of advanced basal cell carcinomas
Protocol Number:	IRB-29839
Principal Investigator:	Anne Lynn S Chang, MD

II. Subject Information:

Subject Name/ID:

Gender: Male Female

III. Inclusion/Exclusion Criteria

Inclusion Criteria	Yes	No	Supporting Documentation*

1. Age 18 years or older.			
2. Able to provide written informed consent obtained prior to any screening procedures			
3. Histologically documented diagnosis of basal cell carcinoma deemed to be locally advanced or metastatic			
4. ECOG performance status ≤ 2			
5. At least one measurable site of disease (as defined by Response Evaluation Criteria in Solid Tumors), or other disease specific response assessment criteria, as appropriate. State age restriction and/or gender/race-ethnic restrictions.			
6. Patients with adequate bone marrow, liver and renal function, as specified below:			
• Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L • Hemoglobin (Hgb) ≥ 9 g/dL • Platelets ≥ 80 x 10^9/L • Serum total bilirubin ≤ 1.5 x ULN (upper limit of normal) • AST and ALT ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases are present • Plasma creatinine phosphokinase (CK) < 1.5 x ULN • Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min ♦♦ CK > ULN			

Exclusion Criteria	**Yes**	**No**	**Supporting Documentation***

1. Cohort 1 only: prior therapy with non-Sonidegib Smo Inhibitor			
2. Patients who have received prior treatment with a P13K inhibitor			
3. Patients with a known hypersensitivity to buparlisib or to its excipients			
4. Metastatic CNS tumors may participate in this trial, if the patient is ≤ 4 weeks from therapy completion (incl. radiation and/or surgery), is clinically stable at the time of study entry and is not receiving corticosteroid therapy			
5. Patients who have had major surgery within 4 weeks of initiation of study medication.			
6. Patients with concurrent uncontrolled medical conditions that may interfere with their participation in the study or potentially affect the interpretation of the study data.			
7. Patients unable to take oral drugs or with lack of physical integrity of the upper gastrointestinal tract or known malabsorption syndromes. State exclusion requirements due to co-morbid disease or incurrent illness, as needed.			

8. Patients who have neuromuscular disorders (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil, and that cannot be discontinued at least 2 weeks prior to starting Sonidegib treatment. If it is essential that the patient stays on a statin to control hyperlididemia, only pravastatin may be used with extra caution.			
9. Patients who are planning on embarking on a new strenuous exercise regimen after initiation of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided whilst on sonidegib treatment			
10. Patients who have taken part in an experimental drug study within 4 weeks of initiating treatment with Sonidegib.			
11. Patients who are receiving other antineoplastic therapy (eg, chemotherapy, targeted therapy or radiotherapy) concurrently or within 2 weeks of starting treatment with sonidegib.			

12. Patients who are receiving treatment with medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with Sonidegib. Medications that are strong CYP3A4/5 inhibitors should be discontinued at least 7 days and strong CYP3A/5 inducers for at least 2 weeks prior to starting treatment with Sonidegib.			
13. Pregnant or nursing (lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).			
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method or a barrier method plus a hormonal method. Adequate barrier methods of contraception include: • Diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent. • Reliable contraception should be maintained throughout the study and for 3 months after study drug discontinuation.			

15. Uncontrolled medical medical problems including acute or chronic liver disease, renal disease or pancreatitis, diarrhea >CTCAE grade 2, active cardiac disease, uncontrolled diabetes, chronic steroids or other immunosuppressive agents			
16. Patients who have taken herbal medications and certain fruits within 7 days prior to starting study drug. Herbal medications include, but are not limited to St. John's Wort, Kava, ephedra (ma huang), dehydroepiandrosterone (DHEA), gingko biloba, yohimbe, saw palmetto, and ginseng. Fruits include the CYP3A inhibitors Seville oranges, grapefruit, pummelos, or exotic citrus fruits.			
17. Patients who are currently treated with drugs known to be moderate and strong inhibitors or inducers of isoenzyme CYP3A, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. Please refer to Table 15 for a list of prohibited inhibitors and inducers of CYP3A (Please note that co-treatment with weak inhibitors of CYP3A is allowed).			
18. Patients who have received any continuous or intermittent small molecule therapeutics (excluding monoclonal antibodies) ≤ 5 effective half lives prior to starting study drug or who have not recovered from side effects of such therapy			
19. Use of statin drugs or other medications known to associate with rhabdomyolysis. These drugs must be discontinued at enrollment			

20. Patients who have received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy			
21. Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.			
22. Patients who are currently taking therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulant. Low molecular weight heparin is allowed.			
23. Known diagnosis of human immunodeficiency virus (HIV) infection, Hepatitis B or Hepatitis C			
24. History of another malignancy within 3 years, except cured basal cell carcinoma of the skin, cured squamous cell carcinoma of the skin or excised carcinoma in situ of the cervix			
25. Patients with the following mood disorders as judged by the Investigator or a psychiatrist, or as a result of patient's mood assessment questionnaire: ♦♦ Medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal attempt or ideation, or homicidal ideation (immediate risk of doing harm to others) ♦♦ ≥ CTCAE Grade 3 anxiety ♦♦ Meets the cut-off score of ≥ 12 in the PHQ-9 or a cut-off of ≥ 15 in the GAD-7 mood scale, respectively, or selects a positive response of "1, 2, or 3" to question number 9 regarding potential for suicidal thoughts in the PHQ-9 (independent of the total score of the PHQ-9)			

26. Patients unwilling or unable to comply with the protocol.			

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

This subject is **eligible / ineligible** for participation in the study.

Signature :
Date:
Printed Name: