Study title:
Single-arm Study With Bimiralisib in Patients With HNSCC Harboring NOTCH1 Loss of Function Mutations

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Summary of Changes

Previous protocol version and date: version 4.0 dated 22-Jan-2020
New protocol version and date: version 5.0, see date of last approval on cover page

Substantial protocol changes		
Description of the substantial modification	**Protocol sections concerned**	**Rationale for the substantial modification**
Additional criterion for patient withdrawal has been added: a patient must be withdrawn from the study if he / she is unable to attend two or more protocol-specified study visits due to COVID-19	9.10 Patient withdrawal	COVID-19 situation. In line with FDA guidelines, the sponsor has assessed study protocol version 4.0 focusing on patient safety and data integrity in the context of the COVID-19. Specifically, for each visit described in the schedule of assessments (ToA – Table 2), the sponsor assessed if visits could be performed virtually (via either phone or videoconference) to reduce patients travelling to the study site. After thorough evaluation of assessments performed during scheduled visits and potential alternatives (such as use of a local laboratory), the sponsor concludes that physical patient visits to the site remain essential to adequately provide for patient safety and to appropriately evaluate tumor growth. While blood chemistry and hematology assessments could be performed at a local laboratory, efficacy assessments using imaging, safety assessments of ECOG, patient-reported questionnaires and vital signs cannot be assessed remotely. The sponsor acknowledges that patients who participate in this study do not have any standard curative or life prolonging therapy available (eligibility criterion #2). Weighing the COVID-19 risk against potential benefit for patients without life prolonging therapeutic options, the sponsor has decided to keep the study open with the visit schedule unchanged. However, a patient must be discontinued from the study if two (2) visits have been missed as essential safety assessments cannot be performed, nor can tumor growth be evaluated.

1 Protocol summary

1.1 Synopsis

Table 1: Study Synopsis

Title	Open-label, single arm, two-stage study, evaluating the efficacy and safety of bimiralisib (PQR309) in patients with recurrent or metastatic (r/m) head and neck squamous cell carcinomas (HNSCC) harboring *NOTCH1* loss of function (LOF) mutations
Sponsor and Clinical phase	PIQUR Therapeutics AG, phase II
Investigation type	Interventional clinical trial
Purpose and rationale	Preclinical *in vitro* and *in vivo* data suggest that HNSCC patients with *NOTCH1* LOF mutations may respond better to PI3K/mTOR inhibitors than those harboring *PIK3CA* mutations [1]. In the escalation part of clinical study PQR309-003 in advanced solid tumors, a patient with HNSCC harboring a *NOTCH1* LOF mutation achieved a durable partial response with over 80% reduction of her target lesions when treated with single agent bimiralisib. To further substantiate the clinical relevance of these data, study PQR309-009 has been designed to evaluate the potential benefit of bimiralisib in patients with r/m HNSCC harboring *NOTCH1* LOF mutations.
Primary objective	To determine the objective response rate (ORR) of patients with r/m HNSCC harboring *NOTCH1* LOF mutations to oral bimiralisib
Secondary objectives	• To evaluate the safety of bimiralisib in patients with HNSCC harboring *NOTCH1* LOF mutations • To evaluate additional clinical efficacy parameters of bimiralisib in patients with HNSCC harboring *NOTCH1* LOF mutations • To evaluate the pharmacokinetics of bimiralisib in patients with HNSCC harboring *NOTCH1* LOF mutations

Exploratory objectives	• ctDNA analyses
	  o Assess whether *NOTCH1* LOF mutation(s) can be detected in baseline ctDNA samples
	  o Explore potential mechanisms of resistance (ctDNA sample at progression)
	  o Correlate changes in ctDNA with radiological response assessment
	• To determine if bimiralisib affects the size and number of pre-cancerous keratinocytic lesions (actinic keratosis).
	• To assess NOTCH1 protein levels in archival tumor material
	• To explore how other mutations within tumor material may affect a patients' response to bimiralisib

Primary endpoint	Objective response rate (ORR): patients who achieved a confirmed partial or a confirmed complete response

Secondary endpoints	• **Safety:**
	  o Overall SAEs
	  o SAEs resulting in death
	  o SAEs resulting in discontinuation
	  o SAEs resulting in dose reduction or dose interruption
	  o Frequency, time to onset and severity of AEs
	  o Changes from baseline in safety parameters
	• **Additional Efficacy**: TTR, DOR, TTF and PFS, evaluated according to the response evaluation criteria in solid tumors (RECIST), version 1.1 [2, 3]
	• **Pharmacokinetics**:
	Bimiralisib plasma concentrations. To be reported separately.

Exploratory endpoints	• **ctDNA**:
	  o ctDNA sequences and levels in patient plasma
	• **Pre-cancerous keratinocytic skin lesions:**
	  o Number and size of index lesions
	• **NOTCH protein levels**
	  o Protein levels of cleaved NOTCH1 (NICD) as determined by immunohistochemistry (IHC)

Study design	This is an open-label, single arm, two-stage study to evaluate the efficacy and safety of bimiralisib in patients with r/m HNSCC containing *NOTCH1* LOF mutations. The study will be conducted in 1 – 4 centers. Patients will be treated with 140 mg bimiralisib p.o. once daily on two consecutive days followed by five days without treatment in consecutive 7-day treatment blocks. Patients will follow this iterative "2d on / 5d off" treatment scheme until unacceptable toxicity, tumor progression, patient's request for withdrawal, investigator judgment or death, whichever comes first. Stage 1 of the study will enroll 10 patients. Response evaluation of Stage 1 patients will be performed in an ongoing manner (ongoing analysis, OA). If two or more patients in stage 1 show a confirmed partial or confirmed complete response, stage 2 may enroll 19 patients. If less than two patients in stage 1 show a confirmed partial or confirmed complete response during the OA, a formal futility analysis will be performed once all 10 patients in Stage 1 have been assessed for their response to bimiralisib. If futility is confirmed as per defined criteria, the study will be stopped. The study will end when all patients have been treated for 6 months or have discontinued study participation for any reason, whichever comes first.
Patient population	Adult patients with recurrent or metastatic HNSCC with *NOTCH1* LOF mutations

Inclusion criteria	Patients may be included in the study if they meet all the below inclusion criteria: 1. ≥ 18 years of age. 2. Histologically or cytological confirmed diagnosis of HNSCC, for which no standard curative or life prolonging therapy is available. 3. Available CLIA-certified sequencing results of the *NOTCH1* gene in HNSCC tumor material. The tumor must harbor a *NOTCH1* LOF mutation as confirmed by central review (MD Anderson Cancer Center, MDACC). 4. ECOG performance status of ≤ 2 5. Adequate bone marrow, liver, and renal functions, defined as: • Platelet count ≥ 100 x 10^9/l, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, hemoglobin ≥ 9 g/dL. • ALT and AST ≤ 2.5 upper limit normal (ULN), or < 5 x ULN if liver metastases are present; serum total bilirubin ≤ ULN or 1.5 x ULN if liver metastases are present or total 3 x ULN with direct bilirubin ≤ ULN in patients with well-documented Gilbert syndrome. • Glomerular filtration rate (GFR) ≥ 30 ml/min (Cockcroft-Gault) 6. Fasting plasma glucose (FPG) ≤ 150 mg/dL. 7. Patient must understand the investigational nature of this study and sign an independent ethics committee/institutional review board approved written informed consent form prior to any study related procedure. 8. Measurable disease according to RECIST version 1.1 [2, 3] 9. The patient has already received standard platinum chemotherapy and immunotherapy. Patients who cannot tolerate platinum or immunotherapy or are ineligible for them, based on the judgement of the treating oncologist, will be eligible to enroll on this trial. 10. Patients of reproductive potential must agree to use effective contraception from screening until 90 days after discontinuing study treatment.

Exclusion criteria	Patients will be excluded from the study if they meet any of the below exclusion criteria: 1. Has an oncogenic *KRAS* mutation. 2. Has received any anti-cancer treatment including hormonal and investigational agents within 21 days prior to first dose of bimiralisib. 3. Patients who receive gamma knife radiosurgery for brain metastases or whole brain radiation are eligible if gamma knife radiosurgery was completed > 2 weeks before treatment is started or whole brain radiation was performed > 4 weeks before treatment is started, and are clinically stable. 4. Known hypersensitivity to any of the excipients of bimiralisib capsules. 5. Major surgery within 28 days prior to first dose of bimiralisib or persisting side effects that have not improved to NCI-CTCAE grade 1 or better. 6. Poorly controlled diabetes mellitus, steroid-induced diabetes mellitus, FPG > 150 mg/dL. 7. Concomitant treatment with medicinal products that increase the pH (i.e. reduce acidity) of the upper gastrointestinal tract, including, but not limited to, proton-pump inhibitors (e.g. Omeprazole), H2-antagonists (e.g. Ranitidine) and antacids is restricted. Patients may be enrolled in the study after a washout period sufficient to terminate their effect. 8. Active tobacco or e-cigarette smoking habit. Non-smoker status will be confirmed by cotinine test at screening in all patients with a history of smoking. Additional cotinine tests may be administered at the discretion of the treating investigator if current smoking is suspected. 9. Patients who are on (or will require) prolonged systemic corticosteroid treatment during the study (see section 8.2.3.2). 10. Use of oral herbal preparations or herbal medications during the study period. Patient should stop using oral herbal medications 7 days prior to the first dose of bimiralisib 11. Concurrent severe and/or uncontrolled medical conditions that would, in the investigator's judgment, contraindicate patient participation in the clinical study or require concomitant anti-cancer drugs (e.g., active or uncontrolled severe infection, chronic active hepatitis, immuno-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.). 12. Has other active malignancies that require systemic treatment.

	13. Has a known history of HIV infection (testing not mandatory). 14. Any of the following cardiac abnormalities: • History of, or current, documented congestive heart failure (New York heart association functional classification iii - iv), documented cardiomyopathy • Symptomatic (NYHA class II or higher) left ventricular ejection fraction (LVEF) < 40% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (echo) • Myocardial infarction ≤ 6 months prior to enrolment • Unstable angina pectoris • Serious uncontrolled cardiac arrhythmia • Symptomatic pericarditis 15. Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug. 16. Patient has a history of non-compliance to medical regimen or inability to grant consent. 17. Pregnant or nursing (lactating) women. 18. Medically documented history of an 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) or ≥ CTCAE grade 3 anxiety 19. History of interstitial pneumonitis or patients who require chronic oxygen supplementation.
Investigational therapy	140mg bimiralisib (capsules of 20mg and 80mg, supplier PIQUR Therapeutics AG, Basel, Switzerland) p.o. once daily on two consecutive days followed by five days without treatment in consecutive 7-day treatment blocks. Patients will follow this iterative “2d on / 5d off” treatment scheme until unacceptable toxicity, disease progression, patient’s request for withdrawal, investigator judgment or death, whichever comes first.
Efficacy assessments	Radiological tumor assessments will be performed by CT or MRI according to a standard protocol at baseline (BL), every 6 weeks, and at the end of treatment (EOT). PET scans are not permitted for efficacy assessment. All reasonable effort should be made for radiological tumor assessments at a study site to be performed by the same person. ORR, TTR, DOR, TTF and PFS will be determined according to RECIST version 1.1 [2, 3].

Safety assessments	Continuous serious adverse event (SAE) monitoring from date of consent until 30 days after the last dose of bimiralisib. Continuous adverse event (AE) monitoring (as per NCI-CTCAE classification, version 5.0) from first dose of bimiralisib until 30 days after the last dose of bimiralisib. Blood chemistry, hematology, vital signs, physical examination, ECG and HbA1c, Patient Health Questionnaire (PHQ)-9 and General Anxiety Disorder (GAD)-7 questionnaire. Pregnancy test as appropriate.
Other assessments	• ECOG • PK blood samples • Dermatological evaluation • ctDNA blood samples
Ongoing analysis (OA)	Stage 1 of the study will enroll 10 patients. Response evaluation as per RECIST 1.1 of Stage 1 patients will be performed in an ongoing manner (ongoing analysis, OA). If the OA reveals that two or more Stage 1 patients show a confirmed partial or confirmed complete response as per RECIST 1.1, Stage 2 may be opened for enrollment without a formal futility analysis.
Interim Analysis for futility	If less than two patients in stage 1 show a confirmed partial or confirmed complete response during the OA, a formal futility analysis will be performed once all 10 patients in Stage 1 have been assessed for their response to bimiralisib. If futility is confirmed as per defined criteria, the study will be stopped.
Analysis populations	**Safety set:** all patients who have received at least one dose of bimiralisib **Per protocol set:** all patients treated per protocol
Data analysis	**Primary endpoint:** Frequency and percentage of the ORR with a two-sided 95%-confidence interval **Secondary endpoints** (except pharmacokinetics): **Safety**: all safety data will be summarized in a descriptive manner **Additional efficacy parameters**: time to event data will be summarized using the Kaplan-Meier methodology. Other efficacy endpoints will be summarized descriptively **Pharmacokinetics (to be reported separately):** descriptive statistics for PK parameters (e.g., AUC, Cmax, t½, etc) **Exploratory endpoints (to be reported separately)**: descriptive statistics
Keywords	HNSCC, *NOTCH1* LOF, bimiralisib

1.2 Table of assessments (ToA)

The table of assessments (ToA) is shown below.

Table 2: Table of Assessments (ToA)

	Screening		On Treatment Visits									
	Day -28 to -1	**Day -1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 43**	**Day 64**	**Day 85**	**week 18 and subsequently every 6 weeks**	**End of Treatment**	**End of Study[6]**
Visit	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10 - n**	*within 7 days of decision to discontinue*	30 days after last dose (+/- 3 days)
Visit Window		**none**	**none**	**none**	**+/- 3 days**							
ASSESSMENT												
Signed ICF	X											
Confirm *NOTCH1* LOF mutation	X											
Medical history, other known mutations, previous and ongoing medications, demographics	X											
Cotinine test (urine based)	X		*at the discretion of the investigator (only for patients with a smoking history)*									
Vital Signs		X	X	X	X	X	X	X	X	X	X	
Height	X											
Weight		X		X	X	X	X	X	X	X	X	
Physical Examination	X										X	
ECOG performance status		X[3]			X	X	X	X	X	X	X	
Patient-reported questionnaires (GAD-7 and PHQ-9)	X			X	X	X	X	X	X	X	X	
Hematology	X		X	X		X	X	X	X	X	X	
Full Blood chemistry	X										X	
Limited Blood chemistry & Fasting Blood Glucose		X	X	X	X	X	X	X	X	X		
HbA1c	X										X	
Pregnancy test [1]	X[2a]						X[2b]	X[2b]	X[2b]	X[2b]	X[2a]	
Radiological tumor assessment	X						X		X	X	X	
Bimiralisib oral administration			*1h prior to breakfast[5] (fasted) on Day 1 and 2 of every week*									
Safety ECG	X										X	
PK sampling [4]			X	X		X	X	X				
ctDNA blood sampling	X						X				X	
Dermatologic evaluation[7]	X						X	X	X			
Collection of archival tissue (if available)	X											
Concomitant Medications			*Every visit after the first dose until 30 days after last dose*									
Adverse Event monitoring			*Every visit after the first dose until 30 days after last dose*									
Serious Adverse Event monitoring	*Continuous from signing of ICF until 30 days after last dose*											

Footnotes:

1: for women of childbearing potential only

2a: serum HCG

2b: serum HCG or urine test

3: ECOG may be collected anytime between day -2 and immediately prior to first dose on day 1

4: PK sampling:

- one **pre-**dose sample (prior to bimiralisib administration)

- one **post-**dose sample within 1 - 3 hours post bimiralisib administration *prior to food intake*

5: patients following the ranitidine mitigation strategy will take bimiralisib on an empty stomach in the early evening at least 1 hour before dinner

6: can be done via phone call; any bimiralisib-related ongoing adverse events have to be followed up until resolved to baseline or stabilized

7: Patients will have the option to undergo a standard of care (SOC) skin cancer screening exam by a collaborating, board-certified dermatologist during screening. If actinic keratosis (AK) or keratoacanthomas (KA) are identified, structured skin photography will be performed to map AK or KA lesions. Structured skin photography will subsequently be repeated every 6 weeks to document changes in lesion numbers and size. If no AK or KA lesions are identified, there will be no further dermatological evaluations on study.

2 Introduction

2.1 Indication: recurrent or metastatic HNSCC

More than 90% of tumors in the head and neck are squamous cell carcinomas (HNSCC) [4, 5]. Often, patients present with advanced disease that is incurable, or requires aggressive treatment, which leaves them functionally disabled. HNSCC is one of the most common cancers worldwide, with incidences of more than 30 per 100'000 population in India, France and Hong Kong. It constitutes about 4% of all cancers in the United States. Diagnosis is confirmed by biopsy of the primary site, and/or fine needle aspiration of any enlarged lymph nodes. A full pan endoscopy allows full assessment of the extent of the tumor and exclusion of tumors at other sites within the head and neck. Imaging is crucial in assessing the site, extent, and relationship of a histologically proved primary tumor, and to detect the presence of enlarged lymph nodes.

Following progression after first line chemotherapy, the standard of care for metastatic or recurrent HNSCC is anti-PD1 immunotherapy based on three pivotal studies. Although patients with higher PD-L1 tumor expression had higher response rates, currently there is no biomarker selection for immunotherapy in HNSCC. In the phase Ib keynote-012 study, patients with metastatic or recurrent HNSCC received pembrolizumab [6]. The overall response rate was 18% and six month PFS was 23%. In the single arm, phase II keynote-055 study patients with metastatic or recurrent HNSCC who were resistant to both platinum and cetuximab received pembrolizumab [7]. The overall response rate was 16% with an additional 19% of patients achieving stable disease. Overall 50% of patients had a reduction in the size of the target lesion. Six month PFS was 23%. In the phase III checkmate 144 study, patients with metastatic or recurrent HNSCC who had progressed after platinum-based chemotherapy were randomized to receive nivolumab or investigator's choice of methotrexate, docetaxel, or cetuximab [8, 9]. One year survival rates were higher in the nivolumab arm (36%) vs. the chemotherapy arm (17%) supporting the approval of nivolumab in this setting. Overall response rates to nivolumab were 13.3% which was higher than that of standard therapy (5.8%).

Although immunotherapy has had a striking effect in some patients with metastatic or recurrent HNSCC, the majority of patients still progress. Standard chemotherapy (methotrexate, docetaxel, others) or cetuximab beyond first line therapy benefits less than 15% of patients.

2.2 The PI3K/mTOR pathway

Dysregulation of PI3K/ mTOR signaling and their downstream effectors in cancer have been validated as important steps for the initiation and maintenance of the tumorigenic phenotype. In HNSCC, the PI3K/mTOR pathway is altered in 54% of patients including copy number alterations in *PIK3CA* (35%), *PTEN* (6%), *RICTOR* (7%), *AKT1* (3%), *PIK3R1* (2%), and *mTOR* (3%) [10]. In particular PIK3CA is the third most frequently altered gene (18%) in HNSCC with frequent hotspot mutations in the helical (E542K or E545K) and kinase (H1047R) domains in human papilloma virus (HPV)-negative HNSCC patients and mutations in the helical domain in HPV-positive HNSCC patients [11]. Clinical responses to PI3K/AKT/mTOR

pathway inhibitors have been modest and short-lived in most solid tumors [12, 13] and there are no biomarkers to guide patient selection [13]. Use of PIK3CA mutation as a biomarker is inconclusive, with studies showing both increased sensitivity [14, 15] and no differential response to PI3K/AKT/mTOR inhibitors in clinical trials [16-18]. Clinical responses of PIK3CA mutant tumors to pathway inhibitors are still modest [17, 19]. Consistent with the clinical findings, HNSCC cell lines and patient derived xenografts (PDXs) with PIK3CA mutations were more sensitive to PI3K/mTOR pathway inhibitors than PIK3CAwt HNSCC cells but these drugs led to only cell-cycle arrest with no apoptosis in the mutant cell lines [14, 18, 20].

2.3 Bimiralisib

Bimiralisib (PQR309) is best described as a selective pan-Class I PI3K inhibitor with a balanced activity against mTOR. The inhibition of the cellular PI3K/mTOR signaling pathways by bimiralisib translates into potent *in vitro* and *in vivo* anti-proliferative activity with the exception of cell lines expressing mutated *KRAS* [21-25].

Bimiralisib has been studied extensively in non-clinical models *in vivo* and is currently being evaluated in other clinical trials. Further information concerning the non-clinical and clinical properties of bimiralisib can be found in the current oral bimiralisib IB [26].

2.3.1 Non-clinical experience

2.3.1.1 Pharmacology

Bimiralisib, a small achiral molecule, inhibits the lipid kinase activity of all PI3K Class-I isoforms (including the mutant version of PI3Kα) as well as mTOR in biochemical assays in the 2-digit nanomolar range and showed no off-target activity *in vitro* when tested against the kinome (450 kinases), various ion channels, receptors and enzymes. Bimiralisib strongly inhibits the cellular phosphorylation of AKT (effector of PI3K) and S6 protein (effector of mTOR). The anti-proliferative effects of bimiralisib *in vitro* vary depending on the genotype of the cells but only the expression of KRAS cancer gene seemed to be associated with a decreased sensitivity [21, 22, 24, 25]

Bimiralisib showed *in vivo* antitumor activity against various tumors either alone or in combination with various targeted inhibitors, immune checkpoint inhibitors as well as chemotherapeutic agents either using once daily PO dosing or intermittent dosing [22, 23, 25]. Intermittent dosing (every second up to every fourth day revealed similar level on anti-tumor efficacy as once daily dosing but was better tolerated except for some hyperglycemia [27].

2.3.1.2 Pharmacodynamics

Preclinical *in vivo* studies in rodents indicate significant inhibition of phosphorylation of AKT (readout for PI3K activity) and S6 (read out for mTOR activity). PI3K is known to play a pivotal role in the regulation of glucose homeostasis, and preclinical studies suggest post-treatment induction of insulin insensitivity/resistance [21, 25, 27].

2.3.1.3 Non-clinical PK and metabolism

Bimiralisib showed dose proportional pharmacokinetics with good plasma and brain exposure. Bimiralisib is stable in mouse, rat, dog and human plasma and showed low potential of inhibiting CYP450 enzymes in *in vitro* enzymatic assays suggesting low probability of drug-drug interaction in humans. Bimiralisib was cleared rapidly after intravenous or oral administration in rats and dogs. *In vitro* metabolic stability data suggest bimiralisib rapid clearance was not caused by extensive metabolism in dogs, but by non-metabolic clearance such as biliary excretion [21].

Bimiralisib, passes the blood brain barrier and showed good oral bioavailability in both rodents as well as non-rodents predicting good oral bioavailability also in humans [21, 27]. Toxicokinetic during the 4-week GLP studies in dogs and rats showed rapid absorption with C_{max} at 0.5 to 2 hrs and dose-proportional exposure with exception of a 2-fold accumulation in female dogs. There was a higher exposure of female compared to male rats which was less pronounced in dogs (4.8 – 16.0 hrs in female rats compared to 3.3 – 5.1 hrs in male rats). In dogs the terminal $t_{1/2}$ for both genders was between 5.9 to 9.3 hrs [21, 27, 28].

2.3.1.4 Safety pharmacology and toxicology

Bimiralisib shows the expected mild toxicity in the hemato-lymphoid system, the reproductive system and salivary glands with high potential for recovery. Body weight changes and lack of appetite were found to be dose-limiting.

Adverse effects similar to those observed with other molecules targeting the PI3K and/or mTOR pathways were seen in rats and/or dogs and included diarrhea and vomiting.

Bimiralisib demonstrated a gender difference in rats with respect to tolerability, which is mainly due to an increased exposure of female compared to male.

2.3.1.5 Genotoxicity status and metabolites

Bimiralisib is not mutagenic in the bacterial reverse mutation assay (Ames test) for DNA base substitution, frameshift mutations and DNA strand breaks.

2.3.2 Clinical experience

More than 228 patients received at least one dose of bimiralisib in a clinical study sponsored by PIQUR, in various cancer indications. A dedicated clinical pharmacology study dosed 39 healthy volunteers with bimiralisib.

Six clinical studies with bimiralisib have recruited more than 228 patients with various malignant diseases (PCNSL, GBM, systemic lymphoma, TNBC and solid tumors). Across all studies, 11 dose levels have been evaluated (10, 15, 30, 40, 50, 60, 80, 90, 100, 120 and 150 mg) in a continuous once daily dosing regimen. In addition, intermittent dosing schedules have been evaluated, where patients were dosed on two days out of seven, either on days 1 and 2 or days 1 and 4. The following bimiralisib dose levels were evaluated on the intermittent dosing schedules: 80mg, 100mg, 120mg, 140mg, 160mg, and 200mg. Additionally, in the combination study with eribulin (study PQR309-007) patients receiving 120mg intermittently have been

exposed. A dedicated clinical pharmacology study (PQR309-008) enrolled 39 healthy volunteers who received three single doses of bimiralisib. Dosing was either p.o. (80mg) or i.v. (20mg).

For further details on clinical experience, please refer to the latest version of the current IB.

2.3.3 Clinical pharmacokinetics

The pharmacokinetics of bimiralisib in humans are dose proportional and linear with time. The compound is rapidly absorbed with a t_{max} of about 1 to 2h after dosing. The oral bioavailability is on average 72%. The elimination half-life ($t_{1/2}$) is approximately 40h. Bimiralisib accumulates after daily administration and plasma concentrations reach a steady state in about 10 days. The accumulation ratio is 3.5 for continuous daily dosing.

2.3.4 Potential for drug-drug interactions

2.3.4.1 Effect of acid reducing agents on the PK of bimiralisib

Bimiralisib is a weak base and its solubility is pH dependent. Under fasting conditions, bimiralisib is dissolved quickly at the low pH in the stomach and reaches the upper GI tract in a super- saturated solution which fosters a quick absorption and sharp plasma Cmax (Absorption modeling using Gastroplus™, data on file). Increases in gastric pH limits the dissolution of bimiralisib and affects absorption.

Study PQR309-008 investigated the effect of concomitant use of the H2-antagonist ranitidine on the PK of bimiralisib [29](PQR309-008CSR 2018)(PQR309-008CSR 2018) . A group of healthy male volunteers received the following three treatments in randomized order with a 2 week washout between treatment days:

- Treatment A: Single dose of 80 mg bimiralisib p.o. alone,
- Treatment B: a single dose 80 mg bimiralisib given 2h after ranitidine (300mg) and
- Treatment C a single dose of bimiralisib 80 mg given 10h after and 2h before ranitidine (150mg).

Two hours after ranitidine 300 mg the gastric effect of the drug is strong and the gastric pH is elevated. When bimiralisib is administered at that time, there is a clear delay in the absorption and Cmax is reduced on average by 65% . The overall exposure is also affected and the AUC_{24h} is reduced by 47%. As expected, there is no significant effect on the elimination of bimiralisib and $t_{1/2}$ remains unchanged.

Staggered administration of bimiralisib 10h after and 2h before ranitidine 150mg was explored as potential mitigation strategy to give guidance for the use of H2-antagomist in combination with bimiralisib. This strategy was only partially effective: compared to bimiralisib alone, the Cmax is still reduced by 46% and the AUC_{24h} is approximately 18% lower.

A second mitigation strategy was therefore explored where ranitidine is given at bedtime and bimiralisib 22h later in the late afternoon 2h before dinner. This mitigation strategy successfully avoids the impact of ranitidine on bimiralisib pharmacokinetics. The parameters are similar for both treatments and the average concentration time curves are superimposable [29].

Based on these data, the mitigation strategy of 300mg ranitidine given in the evening 22 hours prior to bimiralisib administration can be proposed to patients who require pharmacological intervention to increase the pH of their GI tract. In this setting, bimiralisib intake is to occur in the early evening on an empty stomach at least 1 hour prior to dinner. See also section 8.2.3.3.2.

2.3.4.2 Effect of cigarette smoking on the pharmacokinetics of bimiralisib

In vitro experiments had identified CYP1A2 as metabolic pathway for bimiralisib[26] In order to assess the relevance of this metabolic pathway for the elimination of the compound, the PK profile after 80mg p.o. and 20mg i.v. was studied in a group of healthy male smokers (PQR309-008). If CYP1A2 was an important elimination pathway for bimiralisib in humans, smokers would eliminate the compound faster than non-smokers as CYP1A2 is induced by cigarette smoking.

Results from the PQR309-008 study fully confirmed this hypothesis [29]. Faster elimination of bimiralisib in smokers is reflected by a considerably shorter half-life of approx. 18 to 19h and the faster clearance (2 to 2.5-fold compared with non-smokers). These findings were further substantiated by concomitant administration of the CYP1A2 inhibitor fluvoxamine with bimiralisib at a separated occasion. In this setting, the half-life of bimiralisib is prolonged and the clearance substantially reduced. Taken together, these data indicate that CYP1A2 is indeed an important metabolic pathway for bimiralisib in humans leading to lower average plasma concentrations in smokers compared to non-smokers given the same [29] dose, warranting the exclusion of active smokers from the present study. Smoking status will be assessed via cotinine testing at screening. Additional cotinine tests may be administered at the discretion of the treating investigator if current smoking is suspected.

3 Study purpose, objectives and endpoints

The main purpose of this study is to determine the objective response rate (ORR) of patients with r/m HNSCC harboring *NOTCH1* LOF mutations to oral bimiralisib. The ORR comprises patients with confirmed partial response (PR) or confirmed complete response (CR) as per RECIST version 1.1 [2, 3].

The study objectives and related endpoints are summarized in Table 3.

Table 3: Objectives and related endpoints

Objective(s)	Endpoint(s)	Assessment Description
Primary		
To determine the objective response rate (ORR) of patients with r/m HNSCC harboring *NOTCH1* LOF mutations to oral bimiralisib	ORR: comprised of all patients who achieved a confirmed partial or a confirmed complete response	Section 9.3
Secondary		
To evaluate the safety of bimiralisib in patients with r/m HNSCC harboring *NOTCH1* LOF mutations	○ Overall SAEs ○ SAEs resulting in death ○ SAEs resulting in discontinuation ○ SAEs resulting in dose reduction or dose interruption ○ Frequency, time to onset and severity of AEs ○ Changes from baseline in: ▪ body weight, ▪ vital signs, ▪ ECOG performance status, ▪ ECG, ▪ hematology, ▪ biochemistry and ▪ Patient Health Questionnaire (PHQ)-9 and General Anxiety Disorder (GAD)-7 mood scale score	Section 9.4

Objective(s)	Endpoint(s)	Assessment Description
To evaluate additional clinical efficacy parameters of bimiralisib in patients with r/m HNSCC harboring *NOTCH1* LOF mutations	TTR, DOR, TTF and PFS, evaluated according to RECIST version 1.1 [2, 3].	Section 9.3
To evaluate the pharmacokinetics of bimiralisib in patients with r/m HNSCC harboring *NOTCH1* LOF mutations	Bimiralisib plasma concentrations. To be reported separately.	Section 9.6
Exploratory		
To determine if bimiralisib affects the size and number of pre-cancerous keratinocytic lesions (actinic keratosis)	Number and size of index lesions	Section 9.7.1
ctDNA analyses o Assess whether *NOTCH1* LOF mutation(s) can be detected in baseline ctDNA samples o Explore potential mechanisms of resistance (ctDNA sample at progression) o Correlate changes in ctDNA with radiological response assessment	ctDNA sequences and levels in patient plasma	*Will be performed only if at least 6 of the 29 patients experience at least a confirmed partial response.* *Analyses will be performed as per current standard at the time of analysis.* *Results will be reported separately* Section 9.7.2
To assess NOTCH1 protein levels in archival tumor material (optional)	Protein levels of cleaved NOTCH1 (NICD) as determined by immunohistochemistry (IHC)	Section 9.7.3
To explore how other mutations within tumor material may affect a patients' response to bimiralisib	Presence / absence of additional mutations in tumor material	Section 9.7.4

4 Study design

4.1 Overall design

This is an open-label, single arm, two-stage study to evaluate the efficacy and safety of bimiralisib in patients with r/m HNSCC containing *NOTCH1* LOF mutations. The study will be conducted in 1 – 4 centers.

Patients will be treated with 140 mg bimiralisib p.o. once daily on two consecutive days followed by 5 days without treatment in consecutive 7-day treatment blocks. Patients will continue this iterative "2d on / 5d off" treatment scheme until unacceptable toxicity, tumor progression, patient's request for withdrawal, investigator judgment or death, whichever comes first. The bimiralisib dose may be decreased to 100 mg p.o. administered on the same dosing schedule in order to manage safety and/or tolerability (see section on dose interruptions and modifications, section 7.2). Changes in dosing schedule are not allowed.

Stage 1 of the study will enroll 10 patients. Response evaluation of Stage 1 patients will be performed in an ongoing manner (ongoing analysis, OA). If two or more patients in stage 1 show a confirmed partial or confirmed complete response, Stage 2 may enroll 19 patients. Conversely, Stage 2 may not start if only one or no patients in Stage 1 have shown a confirmed partial or confirmed complete response.

If patients withdraw consent or drop out for other reasons unrelated to safety or disease progression, they may be replaced. This includes patients who start smoking (as evidenced by cotinine test) within the first 12 weeks on bimiralisib treatment, because smoking is known to severely compromise bimiralisib exposure due to induction of CYP1A2, the main metabolizing enzyme of bimiralisib. These patients may remain on treatment but will be replaced. Patients for whom IHC analyses indicated high protein levels of NICD which are deemed incompatible with NOTCH1 loss-of-function may be replaced. In total, we anticipate up to 20% of patients to drop out, resulting in enrollment of up to 35 patients in total.

The study will end when all patients have been treated for at least 6 months or have discontinued study participation for any reason, whichever comes first.

4.2 Scientific rationale for the study design

The spectrum of truncating and missense mutations, along with published [30] and preliminary data, demonstrate that many *NOTCH1* mutations in HNSCC tumors lead to loss of function (LOF). Two HNSCC patient derived xenograft (PDX) mouse models with *NOTCH1* LOF mutations were sensitive to a PI3K inhibitor *in vivo* [31]. Moreover, drug screening in 59 HNSCC cell lines showed a strong association of sensitivity to PI3K/mTOR/AKT pathway inhibitors, including bimiralisib, with *NOTCH1* LOF mutations. Treatment with bimiralisib led to increased apoptosis, cell cycle arrest, and decreased colony formation in vitro in *NOTCH1* mutant lines but not in *NOTCH1* wild-type (wt) lines. These data suggest that this genomic subtype of HNSCC may be addicted to the PI3K pathway [1, 32, 33]. Additional preclinical *in*

vitro and *in vivo* data suggest that HNSCC patients with *NOTCH1* LOF mutations may respond even better to PI3K/mTOR inhibitors than those harboring *PIK3CA* mutations. In support of this, treatment of orthotopically transplanted HNSCC tumors harboring *NOTCH1*-LOF mutations resulted in tumor shrinkage when animals were treated with bimiralisib [1, 32, 33] .

In the escalation part of clinical study PQR309-003 in advanced solid tumors, one patient with a HNSCC harboring a *NOTCH1* LOF mutation achieved a durable partial response of more than 6 months, with over 80% reduction of her target lesions. Prior to starting treatment with bimiralisib on an intermittent dosing schedule, this patient, a 53-year old female, had undergone numerous tumor-directed resections, radiotherapy, several lines of chemotherapy, two EGFR-targeted therapies as well as an immune-checkpoint inhibitor.

In order to further substantiate the clinical relevance of these data, the current study PQR309-009 has been designed to evaluate the potential benefit of bimiralisib in patients with HNSCC with *NOTCH1* LOF.

4.3 Rationale for patient selection

In advanced centers, patients with recurrent or metastatic (r/m) HNSCC routinely undergo next generation sequencing (NGS) to increase treatment options. All common NGS platforms, including foundation one and MD Anderson's Oncomine, include the *NOTCH1* gene [34]. MD Anderson has developed an algorithm to determine whether an identified *NOTCH1* mutation is likely to be LOF, which might be specifically sensitive to bimiralisib treatment (Figure 1). Patients with *NOTCH1* mutations in regions associated with activation including TAD/PEST domains or mutations in LNR and HD domains that are not truncating will be excluded. Splice mutations in Exon 33 or 34 would also be excluded, but patients with *NOTCH1* mutation in all other regions will be eligible for the PQR309-009 study.

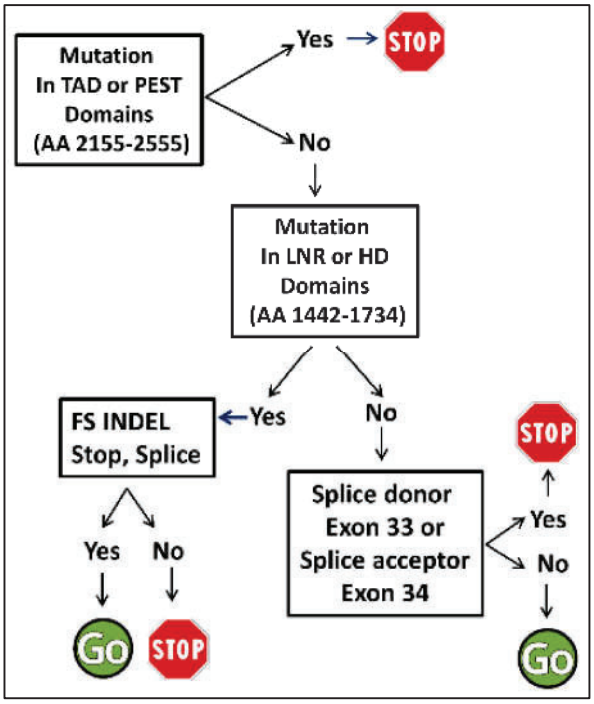

Figure 1: Algorithm to screen patients for eligibility

4.4 Dose justification

Results of an open label Phase 1 study of bimiralisib in 25 patients with advanced solid tumors identified the MTD and recommended Phase 2 dose of bimiralisib as 80mg given continuously once daily [35]. Analysis of bimiralisib pharmacokinetics in humans has shown that the drug has an elimination half-life of about 40 hours and accumulates upon repeated administration. Intermittent dosing with consecutive "2 days on / 5 days off" bimiralisib treatment blocks takes advantage of the PK as drug exposure is expected to build up during the two consecutive days of dosing to reach levels that strongly inhibit the signaling pathway. During the 5 days without bimiralisib intake, drug levels will decline giving the patient a chance to recover and thereby reducing the probability of adverse events. Following preliminary results of other clinical studies with bimiralisib, the biologically active dose of bimiralisib is 140mg given once daily for 2 days, followed by 5 days in consecutive 7-day treatment blocks (2d on / 5d off).

4.5 Benefits and risks

4.5.1 Potential benefit for participants

Treatment with bimiralisib may result in clinical benefit in patients with HNSCC with *NOTCH1* LOF. Based on preclinical and preliminary clinical data, treatment with bimiralisib is expected to be well tolerated and to reduce tumor burden.

4.5.2 Potential risks to clinical trial participants

Patients in this study will be carefully monitored for key toxicities that have been observed with bimiralisib. Safety assessments are presented in detail in section 9.4. Risk will be further minimized by adherence to inclusion/exclusion selection criteria, avoidance of prohibited medication, close safety monitoring and dose adjustment guidelines. PK sampling will be conducted in patients to assess plasma concentration of the study drug that may help to evaluate potential drug interaction. If the patient agrees to providing a skin biopsy sample (see section 9.7.4), this might result in pain despite local anesthesia and the potential risk of infection of the biopsy site.

4.5.2.1 Anemia

Anemia is an identified risk. As anemia is a well-known event and well manageable and serious cases of anemia are currently not expected as none of the events was reported as serious, this risk currently is not considered an important identified risk.

4.5.2.2 Body weight decreased

There is only preclinical evidence that bimiralisib may induce body weight decrease. There is currently no clinical evidence for a causal relation between bimiralisib and the event of weight decrease, and thus weight decrease is considered an important potential risk.

4.5.2.3 Depression & suicidality

The currently available evidence supports that it is possible that bimiralisib might be causally related to depression. Depression is to be considered an important identified risk. One case of suicide attempt has been reported, but apart from the fact that the patient had been exposed to bimiralisib, there is no further evidence that supports a causal relationship. Therefore, there is currently insufficient evidence that bimiralisib is causally related to suicide.

4.5.2.4 Fatigue

It is possible that bimiralisib is related to fatigue and asthenia, making this an identified risk. As most events were reported as not-serious, and were well manageable, and as no other complications of fatigue or asthenia were observed in any of the cases, the topic of fatigue is not considered an important identified risk.

4.5.2.5 Gastro-intestinal toxicity

Diarrhea is a known AE associated with PI3K and mTOR inhibitors. Diarrhea has also been reported in patients treated with bimiralisib. The currently available evidence supports that there is a causal relationship between bimiralisib and events of nausea, diarrhea, vomiting, abdominal pain, and dyspepsia. Thus, GI symptoms are considered an identified risk. However, even though these signs and symptoms occur commonly to very commonly, these events are well manageable and only very rarely do they result in discontinuation. Therefore, this is not considered an important identified risk.

4.5.2.6 Hepatotoxicity

There is no known MoA for bimiralisib to increase liver function tests (LFTs), and reversible increases in transaminases are common events in advanced cancer patients. Elevations of transaminases (ALT and AST) have been reported in patients treated with PI3K and mTOR inhibitors including bimiralisib. It is possible that bimiralisib may increase ALT and/or AST, up to G3 or G4 in patients exposed to bimiralisib.

So far, no noteworthy hepatotoxicity cases have been observed, and no actual events of hepatotoxicity, liver injury, or liver failure have been reported, there is currently no evidence to support that bimiralisib may induce liver injury. However, as stated above, as bimiralisib may induce ALT increase and AST increase, hepatotoxicity will remain an important potential risk.

4.5.2.7 Pneumonitis

There is a potential class effect as pneumonitis is an identified risk for many mTOR inhibitors (Sirolimus, Everolimus) and PI3K inhibitors (Idelalisib, Copanlisib, Duvelisib). A few serious pneumonitis cases have been reported in patients after exposure to bimiralisib. For two serious pneumonitis cases, important confounding factors were identified, making a causal relationship with bimiralisib less likely. For two other serious pneumonitis cases, no confounding factors were identified, making it plausible that there may be a causal relationship with bimiralisib and the reported events. Therefore, taking all available information into account, bimiralisib may be causally related to pneumonitis.

4.5.2.8 Hyperglycemia

The PI3K/AKT pathway is important in regulating glucose metabolism, particularly by regulating glucose transport into adipocytes and muscle tissue. Therefore, hyperglycemia is considered to be an “on-target” effect of bimiralisib. Hyperglycemia was reported in almost 50% of patients exposed to bimiralisib.

Based on the available information, hyperglycaemia is confirmed as an important identified risk.

4.5.2.9 Neutropenia

There is no MoA or PCS evidence for bimiralisib to induce neutropenia.

It is important to note that most neutropenia cases were reported in a study where patients are concomitantly using eribulin, which is known to induce neutropenia in 80% of treated patients with a similar disease. However, neutropenia and febrile neutropenia events have also been reported in studies 002 and 005.

This supports that there is a causal relationship between bimiralisib and events of neutropenia and febrile neutropenia, and neutropenia is considered an important identified risk. There is no causal relationship between bimiralisib and the occurrence of infection events, including but not limited to sepsis. There is no causal relationship between bimiralisib and any fatal outcomes of infection events related to neutropenia.

4.5.2.10 Skin toxicity

Currently, no known MoA and no preclinical evidence are available to support a causal relation between rash / pruritus and bimiralisib specifically. However, skin rashes are known AEs associated with PI3K and mTOR inhibitors. It is possible that bimiralisib may be causally related to rash and pruritus. Skin rashes seen in patients treated with bimiralisib have no typical location or distribution pattern, are mainly maculo-papular sometimes associated with pruritus.

4.5.3 Benefit-risk evaluation

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, recommendations for concomitant medications, guidance for prohibited medications, and the dose adjustments. There may be unforeseen risks with bimiralisib.

Based on key anticipated benefits and potential risks, the benefit-risk evaluation is anticipated to be positive for the target population of this trial.

5 Study population

The investigator or designee must ensure that only patients who satisfy all eligibility criteria are offered treatment in the study. Patients are not permitted to participate in additional parallel investigational drug or device studies.

5.1 Inclusion criteria

Written informed consent must be obtained prior to any screening procedures. Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. ≥ 18 years of age.
2. Histologically or cytological confirmed diagnosis of HNSCC, for which no standard curative or life prolonging therapy is available.

3. Available CLIA-certified sequencing results of the *NOTCH1* gene in HNSCC tumor material. The tumor must harbor a *NOTCH1* LOF mutation as confirmed by central review (MD Anderson Cancer Center, MDACC).
4. ECOG performance status of ≤ 2
5. Adequate bone marrow, liver, and renal functions, defined as:
   - Platelet count ≥ 100 x 10^9/l, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l, hemoglobin ≥ 9 g/dL.
   - ALT and AST ≤ 2.5 upper limit normal (ULN), or < 5 x ULN if liver metastases are present; serum total bilirubin ≤ ULN or 1.5 x ULN if liver metastases are present or total 3 x ULN with direct bilirubin ≤ ULN in patients with well-documented Gilbert syndrome.
   - Glomerular filtration rate (GFR) ≥ 30 ml/min (Cockcroft-Gault)
6. Fasting plasma glucose (FPG) ≤ 150 mg/dL.
7. Patient must understand the investigational nature of this study and sign an independent ethics committee/institutional review board approved written informed consent form prior to any study related procedure.
8. Measurable disease according to RECIST version 1.1 [2, 3]
9. The patient has already received standard platinum chemotherapy and immunotherapy. Patients who cannot tolerate platinum or immunotherapy or are ineligible for them, based on the judgement of the treating oncologist, will be eligible to enroll on this trial.
10. Patients of reproductive potential must agree to use effective contraception from screening until 90 days after discontinuing study treatment.

5.2 Exclusion criteria

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

1. Has an oncogenic *KRAS* mutation.
2. Has received any anti-cancer treatment including hormonal and investigational agents within 21 days prior to first dose of bimiralisib.
3. Patients who receive gamma knife radiosurgery for brain metastases or whole brain radiation are eligible if gamma knife radiosurgery was performed > 2 weeks before treatment is started or whole brain radiation was performed > 4 weeks before treatment is started, and are clinically stable.
4. Known hypersensitivity to any of the excipients of bimiralisib capsules.
5. Major surgery within 28 days prior to first dose of bimiralisib or persisting side effects that have not improved to NCI-CTCAE grade 1 or better.
6. Poorly controlled diabetes mellitus, steroid-induced diabetes mellitus, FPG > 150 mg/dl.
7. Concomitant treatment with medicinal products that increase the pH (i.e. reduce acidity) of the upper gastrointestinal tract, including, but not limited to, proton-pump inhibitors (e.g. Omeprazole), H2-antagonists (e.g. Ranitidine) and antacids is restricted. Patients may be enrolled in the study after a washout period sufficient to terminate their effect.
8. Active tobacco or e-cigarette smoking habit.. Non-smoker status will be confirmed by cotinine test at screening in patients with a history of smoking. Additional cotinine tests may be administered at the discretion of the treating investigator if current smoking is suspected.
9. Patients who are on (or will require) prolonged systemic corticosteroid treatment during the study (see section 11.1.4).
10. Use of oral herbal preparations or medications during the study period. Patient should stop using oral herbal medications 7 days prior to the first dose of bimiralisib
11. Concurrent severe and/or uncontrolled medical conditions that would, in the investigator's judgment, contraindicate patient participation in the clinical study or require concomitant anti-cancer drugs (e.g., active or uncontrolled severe infection, chronic active hepatitis, immuno-compromised, acute or chronic pancreatitis, uncontrolled high blood pressure, interstitial lung disease, etc.).
12. Has other active malignancies that require systemic treatment.
13. Has a known history of HIV infection (testing not mandatory).
14. Any of the following cardiac abnormalities:
    - History of, or current, documented congestive heart failure (New York heart association functional classification iii - iv), documented cardiomyopathy
    - Symptomatic (NYHA class II or higher) left ventricular ejection fraction (LVEF) < 40% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (echo)
    - Myocardial infarction ≤ 6 months prior to enrolment
    - Unstable angina pectoris
    - Serious uncontrolled cardiac arrhythmia
    - Symptomatic pericarditis

15. Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug.
16. Patient has a history of non-compliance to medical regimen or inability to grant consent.
17. Pregnant or nursing (lactating) women.
18. 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) or ≥ CTCAE grade 3 anxiety
19. History of interstitial pneumonitis or patients who require chronic oxygen supplementation.

6 IMP supply and handling

6.1 Study treatment

Bimiralisib is the investigational medicinal product (IMP) for this trial.

Bimiralisib is manufactured according to current good manufacturing practices (cGMP). Bimiralisib is provided in capsules for oral administration by PIQUR Therapeutics AG, Basel. Each capsule contains 20 or 80 mg of the active study drug substance.

6.2 Supply of bimiralisib

PIQUR will order an initial stock of medication for each participating site upon receipt of health authority, local EC and hospital approvals. The distribution will be managed by an authorized distributor.

6.3 Packaging and shipment of bimiralisib

The capsules are packaged in bottles with a sealed and child-resistant closure, and should be stored at room temperature (15°C to 25°). The shelf-life and storage conditions will be continually assessed based on accelerated and long-term stability data.

6.4 Handling of bimiralisib

The study pharmacist, or a delegated person at the site, will be responsible for handling study drug, preparation of the appropriate doses to be administered, and completion of trial-specific drug accountability logs. However, the investigator will finally be responsible for the accountability of all used and unused clinical trial supplies.

Study drug must be handled strictly in accordance with the protocol and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Study drug should be administered only to patients participating in the study.

6.5 Dispensing and accountability of bimiralisib

The site must maintain an overall drug accountability log for the study, as well as individual accountability records for each patient. The dose, amount dispensed, amount received, and amount remaining unused must be recorded in the source document. Drug accountability will be verified by the monitor during site visits and the completion of the study for each individual patient

In order to facilitate drug accountability and monitor compliance, the patient will complete a diary on the intake of bimiralisib which will be brought to the site at each visit. At each visit, the site will make a photocopy of the diary which will be dated and stored with the patient's source data.

6.6 Unused bimiralisib

Partly unused or expired medication can only be destroyed at the site after drug accountability has been performed by the monitor and authorization has been given by the sponsor. The destruction should be documented using the drug inventory log.

7 IMP administration

7.1 IMP dosing instructions

Patients will be treated with 140 mg bimiralisib p.o. once daily on two consecutive days followed by five days without treatment in consecutive 7-day treatment blocks. Patients will follow this iterative "2d on / 5d off" treatment scheme until unacceptable toxicity, tumor progression, patient's request for withdrawal, investigator judgment or death, whichever comes first.

Bimiralisib should be taken in the morning at the same time on an empty stomach at least 1 hour before breakfast with a full glass of non-carbonated, non-flavored water (~7 ounces or 200ml).

For patients who are unable to swallow bimiralisib capsules, capsule content is to be suspended in non-carbonated, non-flavored water. As for oral capsule administration, bimiralisib suspension is to be administered in the morning on an empty stomach. Bimiralisib suspension may be administered by mouth or through a gastric feeding tube as applicable following standard local practice, including rinsing of the tube with water. Feeding tubes that bypass the stomach (e.g. J tubes) cannot be used for bimiralisib administration. In total, suspension and rinsing volume – by tube or by mouth – should be equivalent to about 7 ounces.

Exception: patients who follow the ranitidine mitigation strategy will take bimiralisib in the evening on an empty stomach at least 1 hour before dinner. Patients should be instructed not to

bite or chew on the capsules. In case of breakage of the capsules in the oral cavity, additional water should be taken as a rinse.

Re-dosing is not allowed if the patient vomits after bimiralisib intake.

Should a patient miss drug intake at the scheduled time, the planned dose of bimiralisib may be administered within 12h of delay in the following manner: at least 2 hours after the previous meal and 1 hour before the next meal. In case of longer delay the dose is to be omitted and bimiralisib dosing is to be resumed at the next scheduled day.

At specified clinic visits (Table 2), the study drug will be administered in the clinic with dosing appropriately timed relative to blood sampling for bimiralisib pharmacokinetics. On these days the patient comes to the clinic fasted and should refrain from taking food until the collection of the post-dose PK sample.

7.2 Treatment interruptions and bimiralisib dose reductions

For patients who do not tolerate the protocol-specified dose, dose adjustments are permitted in order to allow the patient to continue bimiralisib treatment. Changes in dosing schedule are not allowed. Any changes in bimiralisib administration must be recorded on the CRF. Whenever possible, any dose adjustment of bimiralisib should be discussed between the investigator and the study sponsor prior to implementation.

As a first step to manage bimiralisib-related toxicities, bimiralisib treatment should be temporarily interrupted.

All treatment interruptions, discontinuations and dose reductions must be based on the worst preceding AE as graded by the NCI common terminology criteria for AE (NCI-CTCAE version 5.0). Once the bimiralisib dose has been reduced, re-escalation is not permitted.

Guidelines for treatment interruptions and bimiralisib dose reductions are described in Table 4.

Table 4: Treatment interruptions and dose reductions for adverse events (*except hyperglycaemia)* considered related to bimiralisib by the treating physician

Reason	Treatment change
Non-haematological AE Grade 4	Stop bimiralisib treatment permanently.
Haematological AE Grade 4	Interrupt bimiralisib treatment. If AE resolves to baseline or CTCAE grade 1 within 7 days, patients may resume treatment at the reduced dose of 100mg. If AE resolves within 8 to 14 days, patient may resume treatment at the reduced dose of 100mg if agreed between investigator and sponsor. If AE does not resolve to baseline or CTCAE grade 1 within 14 days, bimiralisib treatment must be discontinued permanently.
Grade 3 AE	Interrupt bimiralisib treatment. If AE resolves to baseline or CTCAE grade 1 within 7 days, patient may resume treatment at 140mg. If AE resolves to CTCAE grade 1 within 8 to 14 days, patient may resume treatment at the reduced dose of 100mg. If AE does not resolve to baseline or CTCAE grade 1 within 14 days, bimiralisib treatment must be discontinued permanently.
Any non-haematological AE grade 2	Continue bimiralisib treatment. Dose reduction at the discretion of the treating physician

Patients who after dose interruption do not tolerate bimiralisib treatment at 100 mg must be permanently discontinued. If during the first three months on study, a patient cannot restart at the 100 mg dose level within 14 days, this patient is not evaluable for the primary endpoint, and the investigator must discuss the individual benefit-risk evaluation of this patient with the sponsor before restarting dosing. These patients may be replaced.

7.3 Follow-up for toxicities

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

8 Concomitant therapy

8.1 Permitted concomitant therapy

Medications required to treat adverse events, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed, except if specifically prohibited (see section 8.3).

The patient must be instructed to notify the investigational site about any new medications she/he takes after signing of the informed consent. All medications (other than study drug) and significant non-drug therapies (including complementary and alternative treatments, vitamins, physical therapy and blood transfusions) administered within the screening period and up to 30 days after last study drug intake must be listed on the concomitant medications/significant non-drug therapies CRF.

Medications include not only physician prescribed medications, but also all over-the-counter medications, oral herbal medications (prohibited, see section 8.3) and food or vitamin supplements.

8.2 Concomitant (permitted) therapies that may require caution

8.2.1 Effect on other drugs metabolized by CYP enzymes

Bimiralisib has a low potential to cause clinically relevant drug-drug interactions by inhibiting cytochrome P450 isoenzymes. However, the induction potential could not be assessed yet and a potential enzyme induction for CYP2B6 and 3A4 could not be ruled out. It is therefore advised to monitor the efficacy of concomitant medications that are pre-dominantly metabolized by these enzymes to ensure that the patients are not underexposed during concomitant treatment with bimiralisib.

8.2.2 Effect of other drugs to affect the metabolism of bimiralisib

The major route of bimiralisib excretion is metabolism via CYP1A2/1 as identified *in vitro* and confirmed by clinical data in healthy volunteers and patients. Concomitant administration of the CYP1A2 inhibitor fluvoxamine causes a two-fold decrease in bimiralisib clearance and a respective prolongation of the elimination half-life. Consequently, caution should be exercised if strong or moderate inhibitors (e.g. ciprofloxacin, enoxacin, fluvoxamine zafirlukast, methoxsalen, mexiletine, oral contraceptives) or inducers (phenytoin, rifampin, ritonavi, teriflunomide) of CYP1A2/1 enzymes are concomitantly given with bimiralisib. For an updated list of compounds known to cause clinically relevant interactions refer to http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm

8.2.3 Oral contraceptives and hormone replacement therapy

Several human studies have shown that gonadal steroids contained in oral contraceptive pills (OCPs) or hormone replacement therapy (HRT) agents have a significant effect on CYP enzymes, generally inhibiting enzymatic activity including CYP1A2 [36]. Therefore, patients receiving OCP or HRT should be monitored more closely for bimiralisib related adverse events and patients should be advised to inform their physician if their treatment with OCP or HRT is changing as cessation can lead to a drop in bimiralisib concentrations.

8.2.3.1 Drugs with a known risk to induce torsades de pointes (TdP)

Drugs with a known risk of TdP should be used with caution. Lists of drugs that can prolong QT and induce TdP can be accessed at https://www.crediblemeds.org/index.php/login/dlcheck

8.2.3.2 Systemic corticosteroid treatment

Corticosteroid treatment during the study is limited to the following:

- If receiving corticosteroids prior to enrollment, patients must have been on a stable or decreasing dose of corticosteroids and no more than 8 mg dexamethasone (or equivalent) for at least 5 days prior to date of enrollment.
- If treated with steroids at the time of first bimiralisib dose, the steroids should be tapered and then eventually discontinued as soon as possible. Maintenance steroids to prevent adrenal insufficiency and pituitary insufficiency due to hypophysitis are allowed. Permanent steroids use for the treatment of hypophysitis is allowed.
- **Local applications** for treatment of e.g. rash, inhaled sprays for treatment of e.g. obstructive airways diseases, eye drops or local injections (e.g. intra-articular)
- A **short duration of systemic corticosteroids for symptomatic reasons** (e.g. of chronic obstructive pulmonary disease, etc.) corresponding at maximum to the anti-inflammatory potency of 4 mg dexamethasone per day

8.2.3.3 Gastric protection agents

Bimiralisib is characterized by a pH-dependent solubility. Medicinal products that increase the pH of the upper gastrointestinal (GI) tract may alter the solubility of bimiralisib and consequently its absorption. These agents include, but are not limited to, proton-pump inhibitors (e.g. Omeprazole), H2-antagonists (e.g. Ranitidine) and antacids. These agents are restricted during the bimiralisib treatment.

8.2.3.3.1 Appropriate washout of gastric protection agents

Bimiralisib can only be administered after the interruption of these medicinal products sufficient to terminate their effect. The time i.e. washout period, after the last day of intake of acid-reducing agents (ARAs) before treatment with bimiralisib can start, depends on the class of the ARA. H2 receptor antagonists (e.g. ranitidine, famotidine, cimetidine, nizatidine, roxatidine, lafutidine) and direct acting antacids (e.g. maalox, tums, mylox, rolaids), are short acting and 3 days is recommended as the sufficient washout period prior to bimiralisib therapy. Proton-pump inhibitors e.g. omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole, are longer acting and the half-life for recovery of acid secretion is up to 46 hours after treatment discontinuation. It is advisable to wait at least 5 half-lives for the full recovery of gastric acid secretion and therefore the recommended washout period of at least 10 days is recommended for the proton-pump inhibitors before bimiralisib therapy can start. Due to their long term action, use of PPIs is prohibited until the end of bimiralisib treatment.

8.2.3.3.2 Ranitidine-based mitigation strategy

If patients who are receiving bimiralisib require treatment to increase the pH of the upper GI tract, they can be treated with 300mg ranitidine given once daily at bed-time. Importantly, in this case patients will take bimiralisib on an empty stomach approximately 4 hours after lunch and remain fasted for at least 1 hour prior to an evening meal. If ranitidine is not acceptable for the patient, other H2 antagonists may be proposed at the equivalent dose [37].

8.3 Prohibited concomitant therapy

8.3.1 Other anticancer therapies (exception: surgical treatment of skin cancer)

Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than bimiralisib must not be given to patients while the patient is enrolled in the trial. If such treatments are required for a patient, then the patient must be permanently discontinued from the study.

Refer to section 9.7.1 for the exception of surgical treatment of skin cancer.

8.3.2 Other investigational therapies

Other investigational therapies must not be used while the patient is on the study.

8.3.3 Herbal medications

In general, oral herbal preparations/medications are not allowed throughout the study, because data on their DDI potential are limited. These herbal medications include: St. John's wort, kava, ephedra (ma huang), gingko biloba, yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications at least 7 days prior to first dose of study treatment.

Herbal medications not listed here can be considered for concomitant use during the study, but only after discussion with and approval from the sponsor.

8.3.4 Hallucinogens

The use of hallucinogens is prohibited throughout the study.

8.4 Prohibited concurrent procedures

Unless for emergencies, major surgical procedures (excluding biopsies) are not permitted during the trial treatment phase.

9 Study assessments and procedures

Planned time points for all study assessments and procedures are provided in the table of assessments (ToA) Table 2.

Screening / Baseline evaluations must be performed within 28 days prior to first administration of bimiralisib.

During the course of the study, test procedures should occur on schedule whenever possible. Screening and baseline assessments should occur within the indicated windows. Assessments scheduled for Day -1, Day 1 and Day 8 should be performed on this day unless specified otherwise. At all subsequent visits, associated assessments that occur +/- 3 days from the scheduled visit date will not constitute protocol deviations. Tumor assessments (except at baseline) may occur within +/- 3 days from the scheduled date.

9.1 Patient Enrollment

Prior to consenting a patient for the study, the investigator contacts the sponsor / CRO to obtain a patient number. The sponsor / CRO assigns a patient numbers as described in section 9.1.1.

Upon reception of the patient number, the investigator performs the following steps:

- Obtain written informed consent from the patient prior to any protocol-specific procedure
- Check eligibility criteria
- Complete “Patient Enrollment Form” (ERF, provided as separate document).

Upon completion, the site emails the completed, dated and signed “Enrollment Form” to the sponsor / CRO. Importantly, a Patient Enrollment Form should also be completed and send to the sponsor / CRO if the patient is NOT eligible. The sponsor will then inactivate the corresponding patient number. For patients how are NOT eligible, the serious adverse event (SAE) reporting period will end on the date when the site provides the ERF confirming non-eligibility of the patient.

If the patient is eligible, the sponsor / CRO will provide the “date of enrollment” in writing to the study site by email.

9.1.1 Patient numbering

Upon request by an investigator, the sponsor / CRO assigns a 5-digit patient number (XX-XXX) to the patient under consideration for participation in the study. The patient number will serve from consent signature onwards as unique identifier of the patient in the study. If the patient is eligible and enrolled into the study, the patient number is retained as the unique identifier for the patient throughout his/her entire participation in the trial. The patient number consists of the two-digit center number (assigned by the sponsor / CRO to the investigative site) followed by a sequential 3-digit incremental number for all patients included into this study (XX-XXX), so that each patient is numbered uniquely within the study.

9.2 Screening and baseline assessments

After ICF signature, screening assessments will be performed within 28 days prior to first administration of bimiralisib. Refer to the schedule of assessments for details (Table 2).

Re-screening of patients is allowed once per patient and only if the patient was not previously enrolled.

9.2.1 Patient demographics and other baseline characteristics

Patient information and material to be collected at screening include:

- Demography (year of birth, sex and race (where permitted)).
- Medical history (e.g. relevant medical and allergic conditions and surgical procedures which could have an impact on the patient's evaluation; this includes the smoking history of a patient) and current medical conditions present at the time of signing informed consent. Ongoing medical conditions, symptoms and disease which are recorded on the Medical History CRF should be graded by NCI-CTCAE version 5.0.
- HNSCC diagnosis (including histology and sites of disease at study entry) determined radiologically according to local practice
- Mutational landscape of the HNSCC: CLIA-certified evidence of a *NOTCH1* LOF mutation; if information on additional mutations is available, this will be collected as well
- All prior antineoplastic treatment regimens including surgical interventions.
- All medications and significant non-drug therapies (including physical therapy, oxygen and blood transfusions) received within 28 days prior to the first administration of bimiralisib
- Physical Examination (Section 9.4.1)
- Vital signs (Section 9.4.2)
- Height, weight
- ECG (Section 9.4.3)
- Laboratory evaluations (e.g. haematology, blood chemistry, HbA1c, cotinine) (Section 9.4.4)
- Patient self-reported mood questionnaires (Section 9.4.5)
- Dermatologic evaluation (Section 9.7.1)
- ctDNA baseline sample collection (Section 9.7.2)
- if available: five unstained sections of most recent available archival tumor material (FFPE, 4um thick, mounted on standard glass slides)
- Pregnancy test (Section 9.4.4)

9.3 Efficacy assessments

Radiological tumor assessments will be performed by CT or MRI according to a standard protocol at baseline (BL), every 6 weeks (± 3 days) until disease progression, starting of another anti-neoplastic treatment, or death whichever occurs first.

Response evaluation criteria in solid tumors (RECIST), version 1.1, will serve to evaluate responses to bimiralisib treatment.

For the futility analysis, only a confirmed partial response (PR) or confirmed complete response (CR) are considered a response to treatment.

Confirmation of a treatment response requires at least two on-treatment response assessments. As per protocol, the first two on-treatment response assessments are scheduled for day 43 (+/- 3 days) and day 85 (+/- 3 days), respectively. If a treatment response in a patient does not meet the RECIST criteria for a partial response at the first response assessment, confirmation of a potential response might occur only at subsequent later on-treatment response assessments

PET scans are not permitted for efficacy assessment. If a patient has undergone radiological tumor assessment prior to consenting to the study, the data may be used as the baseline assessment if the imaging protocol is in line with the standard imaging protocol of the study and if the assessment was performed within 28 days of receiving the first dose of bimiralisib.

All reasonable effort should be made for radiological imaging used for tumor assessments to be read by one dedicated local radiologist at each study center. Results must be reported in the CRF. ORR, TTR, DOR, TTF and PFS will be determined according to the response evaluation criteria in solid tumors (RECIST), version 1.1 [2].

9.4 Safety assessments

Safety will be monitored by physical examination and assessments of vital signs, performance status evaluation, ECG and laboratory evaluations (hematology and biochemistry). Adverse events will be collected at every visit. For details on adverse event collection and reporting, refer to section 9.5 and appendix 12.2.

9.4.1 Physical examinations

Physical examination is to be performed according to the visit schedule as outlined in the table of assessments (Table 2).

The physical examination comprises a complete body examination that should include: weight, general appearance, skin, eyes, oral cavity, lungs, heart, abdomen, lymph-nodes, extremities, and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site.

Relevant findings that were present prior to first bimiralisib intake must be included in the medical history page in the CRF. Relevant new findings that begin or worsen after the first bimiralisib intake must be recorded on the adverse event page of the CRF.

9.4.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) will be monitored as per the visit schedule (Table 2).

Blood pressure (systolic and diastolic) and pulse should be measured in sitting position. Clinically significant findings that were present prior to first bimiralisib intake must be included in the relevant medical history/current medical conditions page on the CRF. Relevant new findings that begin or worsen after first bimiralisib intake and meet the definition of an AE must be recorded on the adverse event page of the CRF.

9.4.3 ECGs

A standard 12-lead ECG will be performed at the time points as outlined in the table of assessments (Table 2).

The following ECG data will be collected and recorded in the CRF: time of assessment, ventricular rate, PQ or PR interval, QRS duration, QT interval (uncorrected), QTcF (calculated by the ECG machine), and overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormality, which need to be specified further). ECG findings that fulfill adverse event (AE) criteria must be recorded on the relevant CRF page(s).

9.4.4 Clinical safety laboratory assessments

Blood-based clinical laboratory analyses (hematology, blood chemistry, HbA1c and pregnancy test) are to be performed by a certified local laboratory according to the table of assessment (Table 2).

The cotinine test and serum HCG test or urine-based pregnancy tests may be administered by the site.

Table 5: Laboratory Tests

Test category	Test name
Hematology panel	Haematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with automatic differential count (for neutrophils, lymphocytes, monocytes, eosinophils and basophils), platelets
Full blood chemistry panel	Fasting plasma glucose (FPG), electrolytes (sodium, potassium, calcium), serum creatinine, alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), alkaline phosphatase (AP), total bilirubin, total

Test category	Test name
	protein (albumin), lipids (total cholesterol, triglyceride, LDL, HDL), pancreas (amylase), enzymes (LDH, CPK), and CRP Total bilirubin: in case of high level of total bilirubin, fractionated (direct and indirect) bilirubin will be collected
Limited blood chemistry panel	Fasting plasma glucose (FPG), serum creatinine, alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), alkaline phosphatase (AP), total bilirubin) and enzymes (CPK) Total bilirubin: in case of high level of total bilirubin, fractionated (direct and indirect) bilirubin will be collected
HbA1c	HbA1c (glycated Haemoglobin)
Pregnancy test	Serum HCG or Urine HCG
Smoking test	Cotinine (urine based)

The sponsor / CRO must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the CRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

Abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), will be recorded on the adverse events CRF page, if available in the form of the underlying diagnosis. Several laboratory abnormalities may be summarized by the unifying, underlying AE diagnosis. Laboratory data will be graded using the common terminology criteria for adverse events (CTCAE) version 5.0.

The investigator may choose to repeat any test that yielded an abnormal result **once** in order to rule out laboratory error, within 24 hours after the initial assessment. An abnormal lab result that within 24h has been assessed by the investigator to be highly likely to be a laboratory error is flagged with "lab error", together with the results of the repeated assessment.

"NCS" will be entered on the original laboratory sheet to the right of all laboratory values that are outside the reference range, but are judged "not clinically significant". The physician making the assessments shall date and initial each form. A copy of each lab report must be available in the patient's source data file. Only valid laboratory results should be recorded in the CRF.

Any clinically relevant laboratory abnormality must be followed-up with repeated evaluations until normalization (i.e., return to baseline or Grade 1 or 0) or until the change is no longer clinically relevant.

9.4.5 Patient Self-reported Mood Questionnaires

Psychiatric AEs including mood alterations have been reported with the treatment of BKM120 [38], a pan-class PI3K inhibitor, and may reflect effects of PI3K inhibition in the CNS, given that this compound crosses the blood–brain barrier. They were reversible upon dose-reduction, dose-hold, and appeared to be responsive to treatment with selective serotonin reuptake inhibitors and anxiolytics.

The Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) will be administered at specified study visits (see table of assessment, Table 2) to aid in the identification and monitoring of potential mood alterations. The PHQ-9 and GAD-7 are validated patient self-administered questionnaires developed for use in clinical practices.

The PHQ-9 (Appendix 5, Table 4: PHQ-9 Depression Scale) consists of 9 questions that assess anhedonia, depressed mood, sleep, energy, appetite, guilt and worthlessness, concentration, feeling slowed down or restlessness, and suicidal thoughts. For each of these questions, patients are asked to rate how much over the past 2 weeks they have been bothered by the symptom. Scoring of the PHQ-9 is based on a Likert-type scale from 0 to 3 (0 indicates not at all; 1, several days; 2, more than half the days; 3, nearly every day). The sum of all nine responses constitutes the total PHQ-9 score ranging from 0 to 27. The GAD-7 (Appendix 5, Table 5: GAD-7 Anxiety Scale) is a one-dimensional questionnaire consisting of 7 questions. Patients are asked to indicate how often, over the past 2 weeks, they have been bothered by each of the seven core symptoms of generalized anxiety disorder as referenced in the “Diagnostic and Statistical Manual of Mental Disorders, 4th Edition” (DSM IV). Response options are ‘‘not at all’’, ‘‘several days’’, ‘‘more than half the days’’ and ‘‘nearly every day’’, scored as 0, 1, 2, and 3, respectively. The sum of all seven responses constitutes the total GAD-7 score which can range from 0 to 21. Additional psychiatric assessments may be performed according to the clinical judgment of the investigator.

On specified study visits (see table of assessments, Table 2), PHQ-9 and GAD-7 questionnaires are given by the site to the patient in the patient’s local language and reviewed for completeness and possible adverse events. Patients should complete the questionnaires after they have eaten (fed state).

For any clinically relevant change in questionnaire scores (as evaluated by the investigator), and for any psychiatric adverse events (as per SOC), the patient must be referred to a psychiatrist for consultation. Investigator and psychiatrist should evaluate the need for bimiralisib treatment interruption.

9.5 Adverse events and serious adverse events

Definitions of the terms “adverse event” (AE) and ”serious adverse event” (SAE) are provided in Appendix 2: Adverse Events: definitions, assessment, follow-up, and reporting.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, assessing, and documenting events that meet the definition of any AE.

9.5.1 Time period and frequency for collecting AE and SAE information

SAEs will be collected from the signing of the informed consent form (ICF) until 30 days after the last dose of study drug.

AEs will be collected from the first dose of bimiralisib until 30 days after the last dose of bimiralisib.

Medically relevant occurrences that begin after obtaining informed consent but before the first dose of bimiralisib will be recorded on the medical history section of the CRF, not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately (within 24 hours of awareness), as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of awareness.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has discontinued from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

9.5.2 Method of detecting AEs and SAEs

The method of detecting, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.5.3 Follow-up of AEs and SAEs

All SAEs and bimiralisib-related AEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in section 9.12.2).

9.5.4 Regulatory reporting requirements for SAEs

Prompt (i.e. within 24 hours of awareness) reporting of an SAE by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has the legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study medication under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRB)/independent ethics committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.5.5 Pregnancy

To ensure patient safety, any pregnancy occurring while the patient is on study treatment must be reported to PIQUR within 24 hours of learning of its occurrence. The pregnancy should be followed up until end of 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 dedicated pregnancy form and reported by the investigator to the sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the PIQUR study treatment of any pregnancy outcome. Any serious adverse event experienced during pregnancy must be reported following standard SAE reporting requirements.

If a female partner of a male patient participating in this study becomes pregnant within 90 days of the last bimiralisib dose taken by the male patient, pregnancy outcomes must be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.5.6 Reporting and treatment of overdose

For this study, any dose of bimiralisib greater than the assigned daily dose within a 24-hour time period [+/- 2 hours] OR greater than the assigned weekly dose will be considered an overdose.

If an overdose results in adverse event(s), the term "overdose" and the actual event must be recorded as separate AEs.

The sponsor does not recommend specific treatment for an overdose.

Decisions regarding bimiralisib dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

9.6 Pharmacokinetics (PK)

Two blood samples for PK analyses will be collected on the following study days:

- Day 1
- Day 8

- Day 22
- Day 43
- Day 64

The first sample will be a *pre-dose* sample, which will be collected prior to bimiralisib administration. The second sample will be collected within 1 – 3 hours post bimiralisib administration prior to food intake.

Procedural details for collection, processing, storing and shipping of samples are provided in a separate manual. Materials for PK sampling will be provided by PIQUR.

9.7 Exploratory Assessments - optional

9.7.1 Dermatologic Evaluations

Several studies indicate that PI3K/mTOR signalling plays a critical role in non-melanoma skin cancer, including actinic keratosis (AK) [39]. Analysis of human epidermal tumors showed that mTOR itself, as well as its downstream effectors 4EBP1, S6K, and AKTSer473 are phosphorylated at much higher levels in AK and squamous cell carcinoma (SCC) compared to normal skin [40, 41]. Moreover, reverse phase protein microarray analysis of SCC and AK revealed aberrantly activated mTOR pathways in the pre-cancerous and transformed tissues compared to normal skin [42]. Significant up-regulation of the PI3K/AKT/mTOR pathway was not only found in SCC and SCC *in situ*, but also in AK when compared to normal, healthy skin. Increased PI3K/mTOR pathway activity is observed after a short term UV-R and persistently detected in sun-damaged skin lesions [40, 43, 44].

In the present study, patients will have the option to undergo a standard of care (SOC) skin cancer screening exam by a collaborating, board-certified dermatologist during screening. If actinic keratosis (AK) or keratoacanthomas (KA) are identified, structured skin photography will be performed to map AK or KA lesions. Structured skin photography will subsequently be repeated every 6 weeks to document changes in lesion numbers and size.

These assessments will not impact or interfere with SOC clinical management of the lesions. Resulting data will be reported separately.

Minor surgical procedures are permitted while on bimiralisib. Concomitant systemic anti-cancer therapy is not permitted while on bimiralisib.

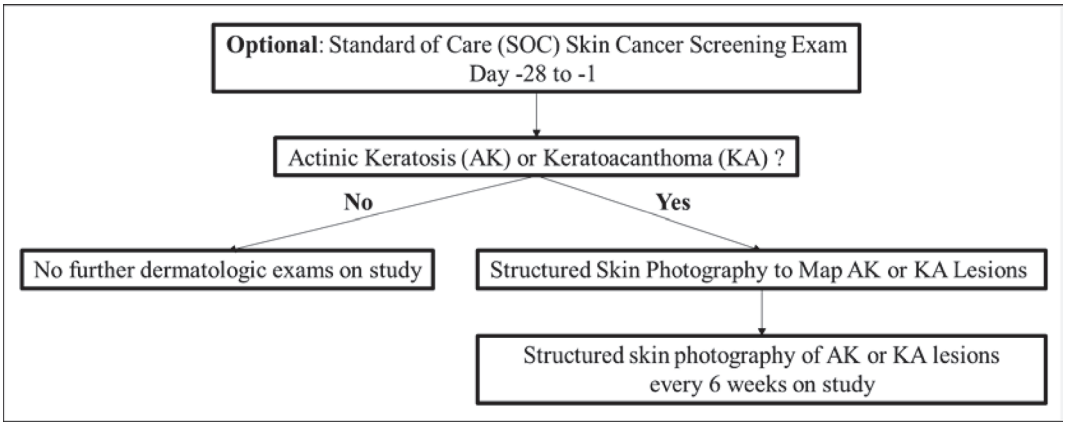

Figure 2: Dermatologic Evaluations during the PQR309-009 study

AK: actinic keratosis; KA: keratoacanthoma; SOC: standard of care;

9.7.2 Circulating tumor DNA (ctDNA)

Circulating tumor DNA will be collected to

- assess whether *NOTCH1* LOF mutation(s) can be detected in baseline ctDNA samples
- explore potential mechanisms of resistance (ctDNA sample at progression)
- correlate changes in ctDNA with radiological response assessment

To that end, 20 ml of whole blood will be collected at the indicated timepoints and processed to plasma (see separate lab manual for safety and ctDNA samples). Materials for collection of ctDNA samples will be provided centrally.

Samples will only by analyzed if at least 6 of the 29 patients experience at least a confirmed partial response. If available, matching archival tumor material may be sequenced to guide ctDNA analyses. Resulting data will be reported separately.

9.7.3 Assessment of cleaved NOTCH1 protein levels in archival tumor material

If available, archival tumor material (FFPE sections) may be analyzed by immunohistochemistry to assess protein levels of cleaved NOTCH1 protein. Analyses will be performed centrally. Resulting data will be reported separately.

9.7.4 Evaluation of additional mutations

Information about additional mutations in tumor material will be collected if available. While patient eligibility is conditional to the *NOTCH1* loss-of-function status of their disease, other

mutations may be present which could alter response to bimiralisib. Based upon TCGA data, we expect several other alterations detectable by the Foundation One platform to occur with *NOTCH1* mutations at a reasonable prevalence, including mutations in TP53, FAT1, CDKN2A, PIK3CA, KMT2D, and Cyclin D amplifications. However, based upon their frequency of co-occurrence and power calculations, we do not expect to have sufficient power to detect their effects unless either the mutated or wild type groups have response rates approaching 70%, with response rates < 20% in the opposite group. Still, we will analyze the data for exploratory purpose and trends could be tested in future clinical trials. Resulting data will be reported separately.

9.8 Treatment period

Patients will receive bimiralisib until unacceptable AE, disease progression (radiologically documented as per RECIST version 1.1 [2, 3]), patient's request for withdrawal, investigator judgement or death – whichever comes first.

9.9 End of treatment (EOT)

Patients who discontinue bimiralisib should be scheduled for an End of Treatment (EOT) visit within 7 days of the decision of study discontinuation. For details of EOT assessments, refer to the table of assessments (Table 2). If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT.

9.10 Patient withdrawal

Patients may voluntarily withdraw from the study or be removed from it at the discretion of the investigator at any time. Premature patient withdrawal refers to the point/time when the patient voluntarily discontinues study treatment. At the time of withdrawal, all study procedures outlined for the End of Treatment visit should be completed. Should a patient request or decide to withdraw, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

All information should be reported on the applicable CRFs. The investigator (or designee) must notify PIQUR of the patient's treatment discontinuation.

Patient must be withdrawn from the study treatment if any of the following occur:

- Pregnancy
- Progressive disease
- Unacceptable adverse event
- Lost to follow-up
- Physician decision

- Study terminated by sponsor
- Patient decision
- Patient unable to attend two (2) or more protocol-specified study visits due to COVID-19

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

- Non-compliance with study treatment
- Protocol deviation

9.11 Patient Replacement

If patients withdraw consent or drop out for other reasons unrelated to safety or disease progression, they may be replaced. This includes patients who start smoking (as evidenced by cotinine test) within the first 12 weeks on bimiralisib treatment. These patients may remain on treatment but will be replaced. Patients who start smoking after the first 12 weeks on bimiralisib treatment will not be replaced. Patients for whom IHC analyses indicate high protein levels of NICD which are deemed incompatible with NOTCH1 loss-of-function may be replaced.

In total, we anticipate up to 20% of patients to drop out, resulting in enrollment of up to 35 patients in total.

9.12 Follow up period

9.12.1 Safety follow-up

All patients will be followed up for safety up to 30 days after last dose of PQR309. The end of this period is defined as the “end of study” (EOS). At EOS, the investigator should contact the patient to inquire about any AE observed/concomitant medication taken during this period. This maybe done via a phone call. Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first. This will include all study assessments appropriate to monitor the event.

9.12.2 Loss to follow-up

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

10 Statistical considerations

The data will be analyzed by PIQUR and/or a designated CRO. Any data analysis carried out independently by an investigator should be submitted to PIQUR before publication or presentation. The data from all centers that participate in this study will be combined in the final safety and efficacy analysis.

10.1 Statistical hypotheses

This is an open-label, single arm, two-stage study evaluating clinical efficacy, safety and pharmacokinetics of bimiralisib in patients with recurrent or metastatic HNSCC harboring *NOTCH1* LOF mutations. The primary goal of the clinical trial is to determine the objective response rate (ORR, including confirmed complete and partial responses) in patients with r/m HNSCC harboring *NOTCH1* to oral bimiralisib. An ORR of 10% or less is considered to be uninteresting and therefore this study has been designed with a reasonable power to detect a response rate of 30%.

10.2 Sample size determination

To minimize accrual if bimiralisib is ineffective, a Simon's optimal two-stage design is used. In order to have 80% power to detect a response rate of 30%, (one-sided α=0.05 and β=0.20) up to 10 patients will be enrolled in the first stage. If 1 or 0 patient respond to the treatment, the trial will be closed due to futility and the treatment is considered ineffective. If two or more patients have an objective response, the study will enroll an additional 19 patients in the second stage. The null hypothesis (H0: ORR $\leq$ 10%) will be rejected if the number of responses is $\geq$ 6 in 29 patients.

If patients withdraw consent or drop out for other reasons unrelated to safety or disease progression, they may be replaced (see section 9.11). We anticipate up to 20% of patients to drop out, resulting in enrollment of up to 35 patients in total.

This sample size is also reasonable to evaluate the pharmacokinetic and other correlative science endpoints; yet, no explicit sample size justification is made for these exploratory endpoints.

10.3 Populations for analyses

10.3.1 Safety set

The safety set includes all patients who received at least one dose of bimiralisib.

10.3.2 Per-protocol set

The per-protocol set (PPS) consists of a subset of the safety set who are compliant with requirements of the clinical study protocol. All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the data handling plan and statistical analysis plan.

10.3.3 Pharmacokinetic analysis set

The PK analysis set (PAS) will consist of all patients who receive at least one dose of bimiralisib and have at least one evaluable concentration measurement. PK data will be reported separately.

10.4 Statistical analyses

Detailed data handling methods will be addressed in the statistical analysis plan.

10.4.1 Efficacy analyses

All efficacy analyses will be performed on the PPS.

ORR including confirmed complete response (CR), and confirmed partial response (PR) is the primary endpoint.

Frequency and percentage of the ORR with a two-sided 95%-confidence interval will be determined.

Secondary endpoints include additional clinical efficacy assessment by time to response (TTR), duration of response (DOR), time to treatment failure (TTF) and progression-free survival (PFS).

Time to event data will be summarized using the Kaplan-Meier methodology.

Time to response (TTR) is defined as the time from first study drug administration to the first documentation of response (complete or partial).

Duration of response (DOR) is defined as the time from the date of the first confirmed response to the first documentation of disease progression, whichever occurs first

Progression- free survival (PFS) is defined as the time from first study drug administration to disease progression or death due to any cause.

Time to treatment failure (TTF) is defined as the time from first study drug administration to any treatment failure including disease progression or discontinuation of treatment for any reason (e.g., disease progression, AE, patient withdrawal of consent, initiation of new treatment without documented progression, death)

10.4.2 Safety analyses

10.4.2.1 Analysis set and grouping for the analyses

For primary safety analyses, the safety set will be used.

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

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of ICF signature to the day before first dose of bimiralisib

2. On-treatment period: from day of first dose of bimiralisib to 30 days after last dose of bimiralisib
3. Post-treatment period: starting at day 31 after last dose of bimiralisib

10.4.2.2 Adverse events (AEs)

Summary tables for adverse events will include only adverse events that started or worsened during the on-treatment period, i.e. ***treatment-emergent*** adverse events.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE version 5.0 grades), type of adverse event, relation to study treatment by treatment arm. Deaths reportable as serious adverse events and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment arm.

Serious adverse events and non-serious adverse events during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

10.4.2.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 5.0, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges. All low or high results must be accompanied by a designation of "NCS" in case the result is not clinically significant, or "CS" if the result is clinically significant. Clinically significant result must be reported as (S)AE – if available, the underlying diagnosis should be reported.

The following by-treatment summaries will be generated separately for hematology and biochemistry laboratory tests:

- Number and percentage of patients with worst post-baseline CTCAE grade (regardless of the baseline status)
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades, the classifications relative to the laboratory normal ranges, and the "NCS" or "CS" designation.
- Listing of all notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities)

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the statistical analysis plan.

Laboratory values collected later than 30 days after last dose of bimiralisib will be flagged in the listings.

10.4.2.4 ECG and other safety data

Summary statistics for data from other tests will be provided, notable values will be flagged, and any other information collected will be listed as appropriate.

Summary statistics will be provided for:

- ECGs: changes from baseline
- Vital signs: number and percentage of patients with at least one post-baseline vital sign abnormality

Listings with flagged notable values and any other information collected will be provided as appropriate.

10.4.2.5 Tolerability

Tolerability will be studied in terms of dose reductions and drug interruptions due to AE. Reasons for dose reductions and interruptions will be listed and summarized by treatment.

10.4.3 Other analyses

10.4.3.1 Pharmacokinetics

Bimiralisib concentrations in plasma will be determined by a validated HPLC method.

No formal statistical analysis beyond descriptive statistics is planned. For each PK parameter, individual and mean data and summary statistics will be presented.

Data will be reported separately.

10.4.3.2 Exploratory Analyses

Exploratory analyses will be reported separately.

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12 Supporting documentation and operational considerations

12.1 Appendix 1: Regulatory, ethical, and study oversight

12.1.1 Regulatory and ethical considerations

This clinical study was designed, shall be implemented and reported in accordance with the ICH harmonized tripartite guidelines for good clinical practice, with applicable local regulations (including US Code of Federal Regulations title 21), and with the ethical principles laid down in the declaration of Helsinki.

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted institutional review board/independent ethics committee (IRB/IEC) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to PIQUR monitors, auditors, PIQUR clinical quality assurance representatives, designated agents of PIQUR, IRB/IEC and regulatory authorities as required.

12.1.2 Quality control and quality assurance

Several procedures ensure the quality of the trial in compliance with applicable regulatory requirements, GCP and the protocol:

- Written standard operating procedures are implemented
- Personnel involved in conducting the trial is qualified by education, training and experience
- An updated authorization list must be kept at the site
- Use of validated computerized systems to manage the clinical trial (e.g. pharmacovigilance, clinical database, CRF, statistical analysis, TMF
- On-site monitoring (SDV, verification of informed consent etc.) by personnel designated by the sponsor
- Data captured online will be validated in real-time, yielding errors (for inacceptable data) and warnings (for possibly inconsistent data – these warnings may be overruled by the user)
- Audit trail of changes
- Safety monitoring
- Accountability of PQR309.

12.1.3 Financial disclosure

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12.1.4 Informed consent process

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's informed consent was obtained will be recorded in the CRF.

PIQUR will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP E6 (R2) guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by PIQUR before submission to the IRC/IEC, and a copy of the approved version must be provided to the PIQUR monitor after IRC/IEC approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study up to 90 days after last intake of bimiralisib. If there is any question that the patient will not reliably comply, they should not be entered in the study.

12.1.5 Data protection

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

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

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

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

Year of birth will be solicited (in the place of exact date of birth) to establish that the patient satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

12.1.6 Source documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with section 4.9 of the ICH GCP E6 (R2), and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a PIQUR-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site principal investigator. The study CRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in essential documents for the conduct of a clinical trial (ICH GCP E6 (R2) section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the clinical trial unless sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

12.1.7 Monitoring and Auditing

All source data must be accessible for auditing and monitoring. Monitors and auditors will maintain patient confidentiality.

Monitoring will be periodically performed during the study, to ensure that GCP and all aspects of the protocol are followed. The monitoring frequency will be adapted to patient accrual of trial sites. As further defined in the monitoring plan, monitoring of trial data can be done either on-site or by central review of anonymous source data. The investigators/ their institutions guarantee access to source documents by the monitor and appropriate regulatory agencies.

Patient source documents are the physician's patient records maintained at the study site. Generally, source documentation will be the hospital's or the physician's chart. In these cases, the information collected on the case report form must match source documentation.

The trial site may also be subject to quality assurance audit by PIQUR as well as inspection by appropriate regulatory agencies.

It is important that the investigator and the relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

Authorities have the right to perform inspections, and the sponsor has the right to perform on-site auditing during working hours upon reasonable prior notice.

12.1.8 Ongoing review of data

As this is an open label single-arm study, and as the currently known risks to trial participants are relatively well manageable, a formal independent Data Monitoring Committee is considered not needed. However, ongoing review of safety and efficacy data will be performed at regular intervals (at least once every 2 months) by the principal investigator, representatives of the sponsor (Chief Medical Officer and Drug Safety Officer), and an experienced physician not directly involved in the conduct of the trial. Data to be reviewed will include adverse events reported, laboratory abnormalities, answers to the patient questionnaires, as well as tumor response data. Reviewed data and meeting minutes will be stored in the TMF.

12.1.9 Study and site closure

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

12.1.10 Publication policy

PIQUR is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. PIQUR assures that the key design elements of this protocol will be posted in a publicly accessible database, e.g. such as www.clinicaltrials.gov, before

study start. Within 1 year of upon study completion (i.e., last patient last visit) and finalization of the study report, the results of this study will be submitted for publication by PIQUR.

Authors will not receive remuneration for their writing of a publication, either directly from PIQUR or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, PIQUR supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

12.2 Appendix 2: Adverse Events: definitions, assessment, follow-up, and reporting

12.2.1 AE Definition

An AE is any untoward medical occurrence in a patient, temporally associated with the use of an investigational medicinal product (IMP, bimiralisib), whether or not considered related to the IMP.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.

12.2.1.1 Events meeting the AE definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. IMP overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se is not considered an AE. Such instances will be captured in the efficacy assessments. However, symptomatic disease progression (signs, symptoms, and/or clinical sequelae resulting from lack of efficacy) will be reported as AE if they fulfil the definition of an AE.

12.2.1.2 Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- Asymptomatic disease progression
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.2.2 SAE Definition

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.2.3 Assessment, documentation and follow-up of AE

When an AE occurs, it is the responsibility of the investigator to review all available relevant documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE and recorded in the CRF.

12.2.3.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and assign it to one of the following categories, and where appropriate, in accordance with the CTCAE criteria version 5.0:

Grade 1 (Mild): An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

Grade 2 (Moderate): An event that causes sufficient discomfort and interferes with normal everyday activities.

Grade 3 (Severe): An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

12.2.3.2 Assessment of Causality

The investigator is obligated to assess the relationship between IMP and each occurrence of each AE. The assessment will be either “related” or “unrelated”.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

For each AE, the investigator must document in the medical notes that he/she has reviewed the AE and has provided an assessment of causality.

12.2.4 Reporting of SAEs

Safety information is to be reported to **Precision Safety** until 31 January 2020 at 23:59 CET.

Safety information is to be reported to **PRA Health Sciences** from 01 February 2020 at 00:00 CET onwards.

Initial Reporting: Within 24 hours of becoming aware of a serious adverse event (SAE):

- Complete the AE eCRF indicating the event is serious
- Complete the eCRFs for the patient (Demographics, Medical History, Concomitant Medications)
- E-mail de-identified available source documentation (i.e., discharge summary) to Precision Safety or PRA Health Sciences (see above), ensuring patient number and protocol number are included on all documents
- Submit the SAE notification to your local IRB, as required

Only if the EDC system is unavailable, immediately:

- Fax the following documents to Precision Safety or PRA Health Sciences
  - Completed back-up paper *SAE Report Form.*
    The following fields must be completed before sending: "Patient identification," "Site identification," "Event term," "Relationship to study drug," and "Serious criteria"
- Enter the SAE into EDC system within 24 hours of the system becoming available

Important Contact Information:

Until 31 January 2020, at 23:59 CET
Precision Safety email: PIQUR-PQR309-009@precisionformedicine.com
Precision Safety fax: (760) 683-6635

From 01 February 2020, at 00:00 CET
PRA Health Sciences email: MHGSafety@prahs.com
PRA Health Sciences Fax: +44 1792 525 720

Initial notification via telephone or email does not replace the need for the investigator to provide a completed SAE report form within the designated reporting time frames.

There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the sponsor.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

12.2.5 Follow-up of SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.

The investigator will submit any updated SAE data to the sponsor within 24 hours of awareness. The investigator will re-assess causality whenever submitting SAE follow-up information.

Follow-up Reporting:

- Update EDC within 24 hours of receipt of new information and fax or email available source documents to Precision Safety or PRA Health Sciences
    - If EDC is unavailable, complete the back-up paper *SAE Report Form* and fax or email to Precision Safety or PRA Health Sciences

12.3 Appendix 3: Criteria for definition of women with childbearing potential and guidance on contraception methods

12.3.1 Female patients with childbearing potential are defined as follows:

- Patients with regular menses
- Patients, after menarche with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who underwent tubal ligation 1 year or more prior to consent signature

12.3.2 Female patients may be considered to NOT be of childbearing potential for the following reasons:

- The patient has undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy or bilateral oophorectomy
- The patient is medically confirmed to be menopausal (no menstrual period) for 24 consecutive months

12.3.3 Guidance on contraception methods

(adapted from the '*Recommendations related to contraception and pregnancy testing in clinical trials*', Clinical Trials Facilitation Group, 15 September 2014) for women of childbearing potential

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Patients should use a highly effective contraceptive measure from the list below. This requirement is valid for female patients with childbearing potential, as well as female partners with childbearing potential of male patients.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1] :
  - o oral
  - o intravaginal
  - o transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation [1] :
  - o oral
  - o injectable
  - o implantable [2]
- Intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]

- bilateral tubal occlusion [2]
- vasectomised partner [2,3]
- sexual abstinence. [4]

[1]Hormonal contraception may be susceptible to interaction with the IMP, and can thus NOT be used alone as method of contraception

[2]Contraception methods that are considered to have low user dependency.

[3]Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Unacceptable methods of contraception for women of childbearing potential:

Birth control pills without oestrogen

Intrauterine device progesterone T

Female condom

Natural family planning (i.e., rhythm method) or breastfeeding

Fertility awareness

Withdrawal

Cervical shield.

12.4 Appendix 4: ECOG performance status

SCORE

0 Able to carry out all normal activity without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out light work.

2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

12.5 Appendix 5: Patient Reported Questionnaires

Table 4: PHQ-9 Depression Scale

Over **the last 2 weeks**, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	**0**	**1**	**2**	**3**
2. Feeling down, depressed, or hopeless	**0**	**1**	**2**	**3**
3. Trouble falling or staying asleep, or sleeping too much	**0**	**1**	**2**	**3**
4. Feeling tired or having little energy	**0**	**1**	**2**	**3**
5. Poor appetite or overeating	**0**	**1**	**2**	**3**
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	**0**	**1**	**2**	**3**
7. Trouble concentrating on things, such as reading the newspaper or watching television	**0**	**1**	**2**	**3**
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	**0**	**1**	**2**	**3**
9. Thoughts that you would be better off dead or of hurting yourself in some way	**0**	**1**	**2**	**3**
For Office Coding	**0 + + + = 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

For information purposes only

Table 5: 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**
(For office coding: Total Score T	_____ = _____+ _____ + _____)			

For information purposes only

12.6 Appendix 6: recommendations for the management of specific safety events

12.6.1 Recommendations for management of hyperglycemia

The PI3K/AKT pathway is important in regulating glucose metabolism, particularly by regulating glucose transport into adipocytes and muscle tissue. Therefore, hyperglycaemia is considered to be an "on-target" effect of bimiralisib, and it has been commonly observed in patients treated with bimiralisib so far. Contrary to regular type 2 diabetes, bimiralisib-induced hyperglycemia may present with a rapid onset on high fasting plasma glucose (FPG) peaks.

In order to mitigate the risk of developing uncontrolled hyperglycaemia on PQR309 treatment, only patients with FPG ≤ 150 mg/dL are eligible for study entry. In addition, vigilant monitoring of patients is recommended including: regular monitoring of FPG to identify hyperglycaemia at an early stage and prevent acute/sub-acute complications. Particular caution is warranted if a patient presents any of the following:

- (family) with history of diabetes mellitus
- borderline fasting glucose (126 mg/dL or higher)
- impaired fasting glucose
- obesity
- patient receiving corticosteroids
- other severe medical conditions (e.g. infections).

For patients concerned by any of the above, it may be necessary to measure FPG more frequently than indicated in the "Schedule of Assessments" (Table 4), e.g. daily, or as clinically indicated. In addition, a home glucometer may be provided to patients to monitor blood glucose levels at home in between study visits.

Hyperglycemia management guidance should also include dietetic measures: patients should be advised about appropriate diet to minimize risk and facilitate management of hyperglycemia.

If a patient develops hyperglycaemia with FPG levels above the "upper limit of normal" (ULN), FPG must be monitored more frequently, e.g. daily with a home glucometer, or as clinically indicated until resolved to < ULN. Importantly any FPG value used for treatment-relevant decisions has to be confirmed by two consecutive measurements performed by a certified laboratory. Once hyperglycemia has resolved, FPG monitoring should be continued as clinically indicated.

If FPG levels rise above ULN, it is advised to initiate or intensify therapy preferably with oral medication. Inhibitors of the Sodium-glucose linked –transporter -2 (SGLT2) (e.g. canagliflozin

(InvokanaTM) are recommended, as they generally show effect within 1-2 days. Patients treated with SGLT2 inhibitors should closely be monitored for signs or symptoms of ketoacidosis.

If SGLT2 inhibitors are not available or contra-indicated (e.g. in patients with renal impairment), metformin should be used. Sulfonylureas should be avoided because of their mechanism of action.

If FPG levels cannot be reduced to < 13.9 mmol/L (250 mg/dL) with adequate anti-diabetic treatment within two consecutive days, treatment with insulin should be initiated or intensified. It is advised to use long-acting insulin, e.g. Tresiba™, starting with 8 units and increasing every 3 days by 2 units if necessary. If target glucose control is not reached continue escalation after 3 day evaluations.

If a patient interrupts or discontinues PQR309 treatment while on anti-diabetic medication, he/she has to be monitored vigilantly for signs or symptoms of **hypo**glycaemia.

PQR309 treatment should be continued as long as hyperglycaemia is controlled. If hyperglycaemia is not controlled (defined as FPG > 13.9 mmol/L (250 mg/dL) for more than two consecutive days) despite adequate intervention, therapy with PQR309 should be interrupted. Re-start of PQR309 treatment can be considered once FPG levels are controlled and maintained at < 9.0 mmol/L (160 mg/dL) with adequate medication. Conditions for PQR309 treatment restart including dosing are provided in Section 12.6.1.1.

A graphical representation of these guidelines is shown in Figure 3.

Figure 3: General Treatment Guidelines for Hyperglycaemia

Fasting Glucose (FPG): *analyses to be performed by certified laboratory; hyperglycemia has to be confirmed by two consecutive measurements*

G1/2	• **dietary advice** • **start with or intensify oral anti-diabetics** *SGLT2 inhibitors recommended** • **increase frequency of FPG monitoring – home glucometer** • **continue with PQR309 treatment at the same dose**
> ULN - < 13.9 mmol/L **> ULN - < 250 mg/dL**	

G3/4	**Interrupt PQR309 treatment** **Initiate or intensify insulin therapy** *(long-acting insulin is recommended)*
≥ 13.9 mmol/L **≥ 250 mg/dL** *for > 2 days*	

Re-starting PQR309: *PQR309 may be restarted if FPG controlled below 9 mmol/L (160 mg/dL) for two consecutive days; additional conditions and PQR309 dose restrictions apply for restart (see section 10.8.2)*

* If not available or counter-indicated (e.g. for patients with renal impairment), metformin should be used. Sulfonylureas should not be used because of their mechanism of action.

12.6.1.1 Treatment Guidelines for High-Grade (G3/4) Hyperglycaemia G3 (> 250-500 mg/dL; > 13.9-27.8 mmol/L)

First occurrence

- Improved to G1 (< 160 mg/dL; 8.9 mmol/L) within 14 days on adequate anti-diabetic treatment: patient may restart the same dose
- Improved to G1 within 21 days on adequate anti-diabetic treatment: patient may restart at reduced dose level
- Not improved to G1 within 21 days on adequate anti-diabetic treatment: discontinue* patient from study
- G3 persisting for more than 14 days despite adequate anti-diabetic treatment: discontinue* patient from study.

G4 (> 500 mg/dL; > 27.8 mmol/L)

First occurrence

- Improved to G1 (< 160 mg/dL; 8.9 mmol/L) within 21 days on adequate treatment: patient may restart at reduced dose level
- Not improved to G1 within 21 days on adequate treatment: discontinue* patient from study
- G4 persisting for more than 14 days despite adequate anti-diabetic treatment: discontinue* patient from study.

Second or subsequent occurrences of G3 or G4: re-start options to be discussed with the sponsor

* if, in the opinion of the principal investigator, a patient might benefit from re-starting PQR309 treatment, this can be considered but needs to be discussed with the sponsor.

12.7 Appendix 7: Country-specific requirements

Not applicable – US-only.

12.8 Appendix 8: List of abbreviations

AE	Adverse Event
AKT	Protein Kinase B
ALT	Alanine Aminotransferase
ANC	absolute neutrophil count
AST	Aspartate Aminotransferase
AUC	Area Under The Plasma Drug Concentration Versus Time Curve
BID	Bis In Die / Twice A Day
cGMP	Current Good Manufacturing Practices
C_{max}	Maximum Observed Plasma Drug Concentration
CPK	Creatine Phosphokinase
CR	Complete Response
CRF (eCRF)	Case Report Form (Electronic Case Report Form)
CT	Computerized Tomography
CTCAE	Common Terminology Criteria For Adverse Events
CYP3A4	Human Cytochrome P450 3A4
DDI	Drug-drug interaction
DOR	Duration of Response
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EC	Ethics Committee
ECG	Electrocardiography, Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
EOS	End of Study
FDA	US Food and Drug Administration
FPG	Fasting Plasma Glucose
GAD-7	Generalized Anxiety Disorder 7-item scale
GCP	Good Clinical Practices
Hb	Haemoglobin

HbA1c	Glycated Haemoglobin
HDL	High Density Lipoprotein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional review board
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
mg	Milligram
MRI	Magnetic Resonance Imaging
mTOR	mammalian Target Of Rapamycin
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
PAS	PK analysis set
PET	Positron Emission Tomography
PD	Progressive Disease
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire 9
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetics
p.o.	Per Os / Oral
PFS	Progression free survival
PR	Partial Response
PS	Performance Status
PTEN	Phosphatase And Tensin Homolog
PPS	Per protocol set
QD	Quaque Die / Every Day
RBC	Red Blood Cell
SAE	Serious Adverse Event

SD	Stable Disease
SDV	Source Document Verification
SOC	Standard of care
$t_{½}$	Elimination Half-Life
t_{max}	Time To Maximum Observed Drug Concentration
TMF	Trial Masterfile
TTF	Time to treatment failure
TTR	Time to Response
ULN	Upper Limit Of The Normal Range
WBC	White Blood Count / White Blood Cells

12.9 Appendix 9: Protocol amendment history

Version	Version date	Changes
5.0	Refer to date of last approval on signature page	Refer to Summary of Changes in Version 5.0
4.0	22 January 2020	Refer to Summary of Changes in Version 4.0
3.0	16 August 2019	Refer to Summary of Changes in Version 3.0
2.0	14 February 2019	Refer to Summary of Changes in Version 2.0
1.0	Date of last approval	Not Applicable

12.10 Appendix 10: Investigator Agreement

A signed copy of this page must be sent to PIQUR, before patient enrolment under this protocol amendment.

As investigator for this study, I understand that this protocol contains information that is confidential and proprietary to PIQUR. I have received and read the above mentioned protocol and agree that it contains all necessary details for carrying out the study as described; I will conduct this protocol as outlined therein.

I will provide copies of this protocol and access to all information furnished by PIQUR to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study. I agree to keep accurate records on all patient information (source documents and Patients' informed consent statement) and all other information collected during the study for a minimum period of 15 years.

I agree to perform the clinical trial according to the international good clinical practice principles (ICH-GCP E6 (R2)), the Declaration of Helsinki and national and local requirements.

I will provide adequate resources at my Institution to conduct the trial according to protocol and submit data in a timely fashion.

Approval from the relevant Ethics Committee will be obtained before the start of the study and the first patient will be included only after the regulatory authority approval. PIQUR will be informed in case the Ethics Committee withdraws approval of the trial.

I agree to use the trial material, including medication, only as specified in the protocol.

The patients will be properly informed about the trial, including risks, possible adverse drug reactions and means to reduce/treat side effects. Informed consent will be obtained and signed from each patient prior to registration and prior to application of any trial-specific procedure.

Any violation of the protocol may lead to early termination of the trial at the institution.

Any clinical adverse event that is serious (SAE), whether considered treatment-related or not will be reported within the international timelines as per ICH-GCP E6 (R2).

I will ensure direct access to examine, analyse, verify and reproduce source data / documents, and reports from all trial related sites for the purpose of monitoring and auditing, and inspection by domestic and foreign regulatory authorities while respecting the Data Protection defined in this protocol.

I will take care that all members of the local trial team will comply with the content of this protocol.

I agree not to publish any results of the study carried out under this protocol, without the prior review of PIQUR.

…….... .....
Investigator (printed name) Signature Date

Institution, Address, Phone Number .....

…….... .....
PIQUR Representative Signature Date