DRUP – Drug specific study manual for ALPELISIB (Piqray)

1. Drug specific in- and exclusion criteria

Alpelisib specific criteria are highlighted in light grey.

Inclusion criteria	Yes	No	n.a.
1. Patients must be ≥18 years of age.			
2. Histologically-proven locally advanced or metastatic solid tumor, multiple myeloma or non-Hodgkin lymphoma, with symptomatic disease progression or progression according to RECIST-criteria after standard anti-cancer therapy, or for whom no such treatment is available or indicated.			
a. *For patients with a primary brain tumor: histologically confirmed recurrent or de novo primary brain tumor, with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.*			
3. Presence of a oncogenic mutation that can potentially be targeted by alpelisib (please refer to the list of drugs and acceptable profiles for further definitions). A complete sequencing report, confirming the actionable mutation has to be submitted for patient enrollment.			
4. ECOG performance status 0-2			
5. Patients must have normal organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:			
a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L			
b. Hemoglobin > 5.6 mmol/l			
c. Platelet count > 100 x 10^9/L			
d. Total bilirubin < 2 x ULN (any elevated bilirubin should be asymptomatic at enrollment) except for subjects with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN			
e. AST (SGOT) and ALT (SGPT) < 3 x institutional ULN (or ≤ 5 x ULN in patients with known hepatic metastases, elevated AST or AST values must be stable for 2 weeks, without evidence of biliary obstruction by imaging)			
f. Fasting serum amylase ≤ 2x ULN and fasting serum lipase within normal limits			
g. Calculated or measured creatinine clearance ≥ 35 mL/min/1.73 m^2			
h. Fasting plasma glucose ≤ 7.7 mmol/l and HbA1c ≤ 6.4% (both criteria have to be met)			
i. Potassium within normal limits, or corrected with supplements.			
j. Magnesium and calcium (corrected for serum albumin) within normal limits or ≤ grade 1 according to NCI-CTCAE version 4.03 if judged clinically not significant by the Treating Physician, or corrected with supplements			
6. Objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma, glioblastoma or ovarian cancer in case of CA125-based evaluation).			

Inclusion criteria	Yes	No	n.a.
7. Patient has no pre-existing pulmonary conditions (e.g. pneumonitis, interstitial lung disease). A baseline chest CT-scan should be performed for confirmation.			
8. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made: a) An exception is made for patients with a primary brain tumor, only if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained: i. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression) ii. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure. b) In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP. c) An exception is made for patients that underwent an allogeneic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample			
9. Ability to understand and the willingness to sign a written informed consent document.			
10. For orally administered drugs, the patient must be able to swallow and tolerate oral medication and must have no known malabsorption syndrome.			
11. Women of child-bearing potential and men must agree to use adequate contraception for the duration of study participation, and for four months following completion of study therapy. For women of childbearing potential: negative serum pregnancy test. For men: mandatory use of a condom during intercourse.			

Exclusion criteria	Yes	No	n.a.
1. Patients that are eligible for on-label treatment with alpelisib or for ongoing phase 2 / 3 trials with alpelisib are excluded from treatment with alpelisib within the DRUP trial.			
2. Patients who received prior treatment with any PI3K, mTOR or AKT inhibitor.			
3. Known hypersensitivity to the active substance or to any of the excipients. For patients with a known medical history of hypersensitivity, such as seasonal allergy, allergic asthma and drug-induced exanthema, oral antihistaminics should be used as prophylaxis.			
4. Patients with a history of Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme (EM) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are not eligible.			
5. Patients with a history of acute pancreatitis within 1 year of study entry and patients with a history of chronic pancreatitis are not eligible.			
6. Patient with established diagnosis of diabetes mellitus type I or uncontrolled type II (based on fasting plasma glucose and HbA1c)			
7. Patient has a known history of Human Immunodeficiency Virus (HIV) infection			
8. Patient has had surgery within 14 days prior to starting program drug or has not recovered from major side effects.			
9. Patient has a concurrent malignancy or malignancy within 3 years of start of study treatment, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer.			
10. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of alpelisib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection) based on investigator discretion.			
11. Patients with Child Pugh score B or C.			
12. Patient is currently receiving any of the following medications and cannot be discontinued 7 days prior to the start of the treatment: • Strong inducers of CYP3A4 • Inhibitors of BCRP (excluding proton-pump inhibitors)			
13. Patients with unresolved osteonecrosis of the jaw.			
14. Ongoing toxicity > grade 2, other than alopecia.			
15. Patient is receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least two weeks. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.			
16. Patient is pregnant or nursing.			
17. Patients with known active progressive brain metastases. Patients with previously treated brain metastases are eligible, provided that the patient has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to registration. All patients with previously treated brain metastases must be stable for at least 1 month after completion of treatment and off steroid treatment prior to study enrollment.			

Exclusion criteria	Yes	No	n.a.
a. *<u>For patients with a primary brain tumor</u>: (I) Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization. (II) No radiotherapy within the three months prior to the diagnosis of progression. (III) No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.*			
18. Subject has clinically significant, uncontrolled heart disease and/or recent cardiac events including any of the following: • History of angina pectoris, coronary artery bypass graft (CABG), symptomatic pericarditis, or myocardial infarction within 6 months prior to the start of study treatment • History of documented congestive heart failure (New York Heart Association functional classification III-IV) • Documented cardiomyopathy • Patient has a previously determined Left Ventricular Ejection Fraction (LVEF) < 50%. • Clinically significant cardiac arrhythmias, (e.g., ventricular tachycardia), complete left bundle branch block, high grade AV block (e.g. bifascicular block, Mobitz type II and third degree AV block without pacemaker in place), supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months. • Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening. • Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or Fredericia QT correction formula (QTcF) > 470msec at screening, or any of the following: • Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia • Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication • Bradycardia (heart rate < 50 at rest), by ECG or pulse. • On screening, inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or corrected QT (QTcF) >450 msec for males and >460 msec for females (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs).			

Exclusion criteria	Yes	No	n.a.
19. If patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or did not fully recover from side effects of such treatment. An exception is made for patients receiving corticosteroids as suppletion therapy, **if** fasting glucose and HBA1c (as measured during screening) are within normal ranges. For these patients, daily fasting glucose monitoring is mandatory during the first two treatment cycles, and weekly thereafter. Note: The following uses of corticosteroids are always permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).			
20. Participation in a prior investigational study within 30 days prior to the start of study treatment or within 5 half-lives of the investigational product, whichever is longer.			
21. Patients with stroke (including TIA) or acute myocardial infarction within 2 months before the first dose of study treatment are not eligible.			
22. Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness/social situations.			

NB Please note that official prescription instructions, as outlined in the Investigators Brochure and / or any other official documents concerning this drug, will always take precedence over this manual. This manual is provided for practical support; treatment can be performed according to local standard-of-care protocols.

2. Treatment schedule

	Screening (≤28 days before treatment start)	After screening, before start	D1 of every treatment cycle (1 cycle = 28 days)	At the end of every 2nd treatment cycle	After end of treatment (≤ 30 days after stop)
Concurrent meds	x		x		
Adverse events			x		
Physical exam	x		x[1,]		
Vital signs	x		x[1,2]		
Performance Status	x		x[1]		
Neutrophil count, platelets	x[3]		x[1]		
Hemoglobin and hematocrit	x[3]		x[3]		
Serum chemistry	x		x[1]		
Renal function, ALT, AST, bilirubin, amylase, lipase, calcium and magnesium	x[4]		x[4]		
Blood glucose levels	x[5]		x[5]		
ECG	x				
Radiological imaging	x[8]				
Alpelisib			x (continuous dosing)		
Tumor biopsy		x[7]			x[7]
Response evaluation	x[6]			x[6]	

1. According to local standard clinical practice, or as clinically indicated.
2. Monitor for hypertension and treat as needed.
3. Before initiation of, and periodically throughout, treatment with alpelisib.
4. Before initiation of, and periodically throughout, treatment with alpelisib.
5. See table 1 below.
6. A baseline scan should be performed <28 days before start of treatment. Tumor assessments will initially be repeated every 8 weeks after treatment initiation. If the patient continues study treatment beyond 3 response evaluations (i.e., 24 weeks), response evaluation will thereafter be performed at the end of every 3rd treatment cycle (i.e., every 12 weeks).
7. Tumor biopsy: after screening is positive, a mandatory DRUP pre-treatment biopsy should be taken. After termination of DRUP treatment, a post-treatment biopsy can be taken. The post-treatment biopsy is optional.
8. This should include a chest CT-scan to confirm no pre-existing pulmonary conditions are present.

Table 1 Schedule of fasting glucose monitoring

<table>
<tr><th></th><th>Recommended schedule for the monitoring of fasting glucose and HbA1c levels in all patients treated with alpelisib</th><th>Recommended schedule of monitoring of fasting glucose and HbA1c levels in patients with diabetes, pre-diabetes, BMI ≥30 or age ≥75 years treated with alpelisib</th></tr>
<tr><td>At screening, before initiating treatment with alpelisib</td><td colspan="2">Test for fasting plasma glucose (FPG), HbA1c, and optimise the patient's level of blood glucose (see figure 1).</td></tr>
<tr><td rowspan="3">After initiating treatment with alpelisib</td><td colspan="2">Monitor FPG at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter.</td></tr>
<tr><td>Monitor/self-monitor fasting glucose regularly, more frequently in the first 4 weeks and especially within the first 2 weeks of treatment, according to the instructions of a healthcare professional*.</td><td>Monitor/self-monitor fasting glucose daily for the first 2 weeks of treatment. Then continue to monitor fasting glucose as frequently as needed to manage hyperglycaemia according to the instructions of a healthcare professional*.</td></tr>
<tr><td colspan="2">HbA1c should be monitored after 4 weeks of treatment and every 3 months thereafter.</td></tr>
<tr><td rowspan="2">If hyperglycaemia develops after initiating treatment with alpelisib</td><td colspan="2">Monitor fasting glucose regularly, as per local standard of care and at least until fasting glucose decreases to normal levels.</td></tr>
<tr><td colspan="2">During treatment with antidiabetic medication, continue monitoring fasting glucose at least once a week for 8 weeks, followed by once every 2 weeks, and monitor fasting glucose according to the instructions of a healthcare professional with expertise in the treatment of hyperglycaemia.</td></tr>
<tr><td colspan="3">* All glucose monitoring should be performed at the physician's discretion as clinically indicated.</td></tr>
</table>

3. Administration and starting dosage

The recommended dose of alpelisib is 300 mg (2x150mg tablets) daily taken after a meal, preferably every day at same time. Alpelisib should be swallowed whole with a glass of water.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs that cannot be managed by concomitant medicinal products or dose adjustments. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

4. Considerations before starting alpelisib

Prior to initiation of alpelisib treatment:

- Assess and optimize fasting plasma glucose and HbA1c levels (see Figure 1 below for guidance)
- Consider rash prophylaxis with nonsedating oral antihistamines at start of therapy
    - Use of prophylactic antirash medication was associated with a lower frequency of rash (26.7% vs 64.1%) in patients taking alpelisib plus fulvestrant
- Assess concomitant medications
- Avoid coadministration of alpelisib with strong CYP3A4 inducers or BCRP inhibitors
- Evaluate past medical history
    - Do NOT initiate alpelisib if past history includes Stevens Johnson Syndrome (SJS), Erythema Multiforme (EM), or Toxic Epidermal Necrolysis (TEN)

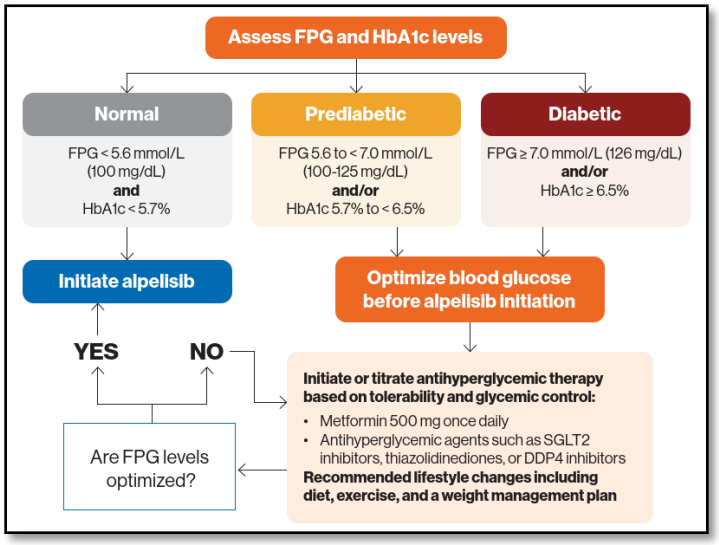

Figure 1: assessment of fasting plasma glucose and HbA1c levels before treatment initiation

5. How supplied

Alpelisib is supplied as 50mg, 150mg and 200mg film-coated tablets. Drugs can be (re-)ordered by filling in the required fields in the eCRF. Drugs will be shipped to the site's pharmacy. Per shipment, sufficient drug can be ordered to treat the patient until the next response evaluation (and 1 cycle beyond for the first order, to cover the period in between response evaluation and re-supply).

6. Dose modifications for toxicity

Please refer to Summary of Product Characteristics (SmPC).

Patients who experience adverse events of Grade 3 or higher severity (except hyperglycemia) or do not tolerate the dosing schedule recommended in the Treatment Plan should permanently discontinue treatment. Guidelines for the suggested management of selected toxicities are described below.

Table 4-2 Dose reduction sequential steps for alpelisib

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

6.1 Guidelines for the treatment of alpelisib induced skin toxicity

Skin toxicity is a class-effect adverse event observed with PI3Ki/mTORi agents.

Close monitoring of potential skin reactions should be performed at each planned visit. The most frequent skin adverse events reported are: maculopapular rash (only a minority present acneiform rash); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate co-medication and treatment interruption if needed. Skin reactions may fade slowly over 10 days or more and may not require ongoing concomitant therapy. Detailed guidelines for management of alpelisib induced skin toxicity is provided in Table 4.3.

Table 4.3: Criteria for interruption and re-initiation of alpelisib treatment due to skin toxicity

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib
Skin and subcutaneous tissue disorders *Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. (see also Section4.2 and table 3 in SPC). Dermatologist consultation is mandated for serious cutaneous reactions (i.e. fulfilling seriousness criteria for AE Reporting) and for severe cutaneous reactions like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).*	
Grade 1 (<10% body surface area (BSA) with active skin toxicity*)	**Maintain dose level** Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are Triamcinolone, Betamethasone as long as skin toxicity is active, during maximum 28 days If active rash is not resolved within 28 days of appropriate treatment, add low dose systemic corticosteroid (20-40 mg/d), such as prednisone 10 mg 3x/day. For subjects with symptoms like burning and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night
Grade 2 (10-30% BSA with active skin toxicity*)	**Maintain dose level.** Initiate or intensify topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone as long as skin toxicity is active, up to max. 28 days Consider adding Add systemic corticosteroids 20-

Worst toxicity-CTCAE Grade (value)	**Dose Modifications for alpelisib**
	40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued For subjects with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine such as cetirizine once daily during daytime and, consider adding a sedating anti-histamine such as diphenhydramine once daily at night
Grade 3 (>30% BSA with active skin toxicity*)	**Omit alpelisib** dose until rash /skin toxicity is improved to Grade 1 or resolved, consider recommend documentation by photography and consider performing a skin biopsy. Initiate topical corticosteroids 3-4x daily, preferred compounds to use are Triamcinolone or Betamethasone for at least 28 days Add systemic corticosteroids 20-40mg/d If rash resolves to ≤ G1 within 10 days systemic corticosteroid may be discontinued For subjects with symptoms like burning, stinging and/or pruritus add non-sedating anti-histamine during day time, consider adding a sedating anti-histamine at night Re-start alpelisib dose once rash /skin toxicity is fading but no longer active but fading (G1): - at a reduced dose in case of first occurrence, at reduced dose level in case of second occurrence - If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with alpelisib/placebo; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued • For subjects with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night. Antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib.
Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	**Permanently discontinue** subject from alpelisib • Consult a dermatologist, ensure documentation by photography, and obtain a skin biopsy for central assessment • Treatment may follow guidelines for Grade 3 above with the exception of rechallenge. • Additional measures may be taken as per local treatment guidance

Worst toxicity-CTCAE Grade (value)	**Dose Modifications for alpelisib**
Any Grade of Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis or other SJS/TEN-like severe skin reactions	**Permanently discontinue** subject from alpelisib • Consult dermatologist, ensure documentation by photography and obtain skin biopsy for central assessment • Follow local treatment guidelines for SJS/TEN/DRESS
** "Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.*	

6.2 Guidelines for the treatment of alpelisib induced hyperglycemia

Alpelisib, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy 2012). Alpelisib induced hyperglycemia is generally manageable with adequate antidiabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Patients with pre-diabetes (i.e. FPG 100 – 125 mg/dl; 5.6 - 6.9 mmol/L) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing an early detection and prompt management of increases in FPG or RBG while on alpelisib treatment. However all patients, even those with blood glucose levels within normal limits prior to starting treatment with alpelisib, may develop alpelisib induced hyperglycemia. Detailed guidelines for management of alpelisib induced hyperglycemia is provided in Table 4.4 on the next page of this document.

Table 4.4: Dose modification and management for hyperglycaemia[1]Fasting glucose (FG) values[1]	**Recommendation**
Dose modification and management should only be based on <u>fasting</u> glucose (plasma/blood) values.	
>ULN-160 mg/dl or >ULN-8.9 mmol/l	No Piqray dose adjustment required. Initiate or intensify oral antidiabetic treatment[2].
>160-250 mg/dl or >8.9-13.9 mmol/l	No Piqray dose adjustment required. Initiate or intensify oral antidiabetic treatment[2]. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days with appropriate oral antidiabetic treatment[2,3], reduce Piqray dose by 1 dose level and follow FG-value-specific recommendations.
>250-500 mg/dl or >13.9-27.8 mmol/l	Interrupt Piqray. Initiate or intensify oral antidiabetic treatment[2] and consider additional antidiabetic medicinal products such as insulin[3] for 1-2 days until hyperglycaemia resolves, as clinically indicated. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances). If FG decreases to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, resume Piqray at next lower dose level. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 3 to 5 days under appropriate antidiabetic treatment, consultation with a healthcare professional with expertise in the treatment of hyperglycaemia is recommended. If FG does not decrease to ≤160 mg/dl or 8.9 mmol/l within 21 days following appropriate antidiabetic treatment[2,3], permanently discontinue Piqray treatment.

>500 mg/dl or ≥27.8 mmol/l	Interrupt Piqray. Initiate or intensify appropriate antidiabetic treatment[2,3] (administer intravenous hydration and consider appropriate treatment [e.g. intervention for electrolyte / ketoacidosis / hyperosmolar disturbances]), re-check within 24 hours and as clinically indicated. If FG decreases to ≤500 mg/dl or ≤27.8 mmol/l, then follow FG-value-specific recommendations for <500 mg/dl. If FG is confirmed at >500 mg/dl or ≥27.8 mmol/l after 24 hours, permanently discontinue Piqray treatment.

[1] Fasting glucose levels reflect hyperglycaemia grading according to CTCAE Version 4.03 CTCAE = Common Terminology Criteria for Adverse Events.

[2] Applicable antidiabetic medicinal products, such as metformin, SGLT2 inhibitors or insulin sensitisers (such as thiazolidinediones or dipeptidyl peptidase-4 inhibitors), should be initiated and the respective prescribing information should be reviewed for dosing and dose titration recommendations, including local diabetic treatment guidelines. Metformin was recommended in the phase III clinical study with the following guidance: Metformin should be initiated at 500 mg once daily. Based on tolerability, the metformin dose may be increased to 500 mg twice daily, followed by 500 mg with breakfast, and 1000 mg with the evening meal, followed by further increase to 1000 mg twice daily if needed (see section 4.4).

[3] As recommended in the phase III clinical study, insulin may be used for 1-2 days until hyperglycaemia resolves. However, this may not be necessary in the majority of cases of alpelisib-induced hyperglycaemia, given the short half-life of alpelisib and the expectation that glucose levels will normalise following interruption of Piqray.

6.3 Guidelines for the treatment of alpelisib induced pneumonitis

Table 4.5: Management of pneumonitis related to alpelisib

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

6.4 Guidelines for the treatment of alpelisib induced diarrhea or colitis

Mild to moderate diarrhea has been reported within the ongoing studies of single-agent alpelisib. In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as well as proper management of diarrhea is mandatory. The following section outlines the recommended algorithm for management and treatment of alpelisib-induced diarrhea (Benson et al 2004; Kornblau et al 2000; Wadler et al 1998).

The algorithm for treatment for diarrhea management is based on (Wadler et al 1998; Kornblau et al 2000).

Table 4.6: Criteria for interruption and re-initiation of alpelisib treatment due to diarrhea or colitis

Worst toxicity-CTCAE Grade (value)	Dose Modifications for alpelisib
Grade 1	Maintain dose level
Grade 2	Omit dose until resolved to ≤ Grade 1, then restart at same dose
Grade 3	Omit dose until resolved to ≤ Grade 1, then resume at the next lower dose level
Grade 4	Permanently discontinue alpelisib

Patient history of diarrhea

- Prior start of program treatment, the patient's history of diarrhea should be reviewed and the patient should be appropriately informed of potential alpelisib-induced diarrhea and its management
- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions
- Stop all diarrheogenic agents, otherwise exclude from program
- Instruct patients regarding risk of developing diarrhea
- Perform baseline clinical/laboratory studies (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp.,Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients)
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading.

First report of diarrhea:

- Obtain history of onset and duration of diarrhea
- Description of number of stools and stool composition (e.g. watery, blood, mucus in stool)
- Assess patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)

- Proactively look for occurrence of diarrhea. If no problems occur, instruct the patient to call when a problem does arise

Management of diarrhea

General Recommendation

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (e.g. Metamucil®) and stool softeners (e.g. docusate sodium, Colace®)
- Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g. bananas, rice, apple sauce, toast)
- It is recommended that patients are treated with loperamide tablets. Patients should be instructed on the use of loperamide in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each visit and the Treating Physician should ensure that the patient understands the instruction. At each visit, patients should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the Treating Physician should question the patient regarding the actions taken for these symptoms.
- Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea.
- Loperamide is the first-line treatment of diarrhea (any Grade) in this recommended algorithm. Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms. Another first-line treatment for diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide, however it is important to note that loperamide and diphenoxylate hydrochloride/atropine sulfate must not be used in conjunction with one another due to the risk of developing paralytic ileus. Upon treatment with any antidiarrheal agents, the patient's response to treatment should be observed and appropriately documented.

Treatment of diarrhea CTCAE Grade 1 or 2

Diarrhea CTCAE Grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) or after each unformed stool).

12-24 hours later:

- Diarrhea resolved
    - Continue instructions for dietary modification
    - Gradually add solid foods to diet
    - Discontinue loperamide after 12 hours diarrhea-free interval
- Diarrhea unresolved
    - Persisting diarrhea CTCAE Grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of patients condition to rule out dehydration, sepsis, ileus, medical check and selected workup if patient does not need hospitalization (see section Diarrhea workup below). Observe patient for response to antidiarrheal treatment.
    - Persisting diarrhea CTCAE Grade 3 or 4 may be treated with hospitalization, high dose

loperamide (initial 4 mg, then 2 mg every 2 hours) and addition of opium tincture (DTO) or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe patient for response.

After 12-24 hours:

- Diarrhea resolved
    - Continue instructions for dietary modification
    - Gradually add solid foods to diet
    - Discontinue loperamide and/or other treatment after 12 hrs diarrhea-free interval
- Diarrhea unresolved
    - If diarrhea still persisting (CTCAE Grades 1 and 2), after 2 x 24 hrs with high dose loperamide and opiates then admit to hospital and employ measures as for CTCAE grade 3 and 4 until diarrhea resolved.
    - If diarrhea still persisting and progressed to CTCAE Grades 3 and 4, employ measures described below.
    - Treatment of diarrhea CTCAE Grade 3 or 4
    - Severe diarrhea CTCAE Grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section Diarrhea workup below).
    - Observe patient for response.

After 12-24 hours:

- If diarrhea is persisting administer s.c. Sandostatin/octreotide (100-500 µgtid)
- Continue IV fluids and antibiotics as needed
- If diarrhea CTCAE Grade 3 or 4 still persists patients should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea CTCAE Grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg TID) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Program treatment should be continued only when diarrhea resolves.

Diarrhea workup

- Perform appropriate tests (Fine et al 1999).
- Spot stool analysis
- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)
- Endoscopic examinations
    - Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be

exercised in undertaking these invasive procedures:

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis

Table 4.7: NCI CTCAE version 4.03 grading of diarrhea for patients without Colostomy

Toxicity	0	1	2	3	4
Diarrhea	None	Increase of < 4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements.					

6.5. Guidelines for the treatment of alpelisib induced thrombocytopenia

Investigations	
Thrombocytopenia	
Grade 1 (Platelets (PLT)< LLN - 75 x 109/L) Grade 2 (PLT < 75 - 50 x 109/L)	Maintain dose level.
Grade 3 (PLT < 50-25 x 109/L)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level. If resolved in > 7 days, then decrease 1 dose level
Grade 4 (PLT < 25 x 109/L)	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level.

6.6. Guidelines for the treatment of alpelisib induced renal impairment

Investigations (renal)	
Serum Creatinine	
< 2 x ULN	Maintain dose level
2-3X ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level. If resolved in > 7 days, then decrease 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN)	Permanently discontinue subject from alpelisib/placebo.
Grade 4 (> 6.0 x ULN)	Permanently discontinue subject from alpelisib/placebo.

6.7 Guidelines for the treatment of alpelisib induced hepatic impairment

Investigations (Hepatic)	
Isolated total Bilirubin elevation	
Grade 1 (>ULN - 1.5 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 1.5 - 3.0 x ULN)	Interrupt dose until recovery to Grade ≤ 1 and resume at the same dose if resolved in ≤ 14 days or resume at the next lower dose level if resolved in > 14 days.
Grade 3 (>3.0 - 10.0 x ULN)	Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (>10.0 x ULN)	Permanently discontinue.
Isolated AST or ALT elevation	
Grade 1 (>ULN - 3.0 x ULN) Grade 2 (>3.0 - 5.0 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 (>5.0 - 20.0 x ULN)	Interrupt dose until recovery to Grade ≤ 1, then resume at the next lower dose level.
Grade 4 (>20.0 x ULN)	Permanently discontinue.
Combined ALT/AST and TBIL elevation	Please see specific instructions below[1]

1. Participants with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

   In general, any increase of serum aminotransferases to > 3 x ULN should be followed by repeat testing within 48 to 72 hours.

   If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required.

   The threshold for potential DILI may depend on the participant's baseline AST/ALT and TBIL value; participants meeting any of the following criteria will require further follow-up as outlined below:

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

   As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.
   A detailed history, including relevant information such as Medical review needs to ensure that liver test elevations of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

   Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT, GLDH, prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion - e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (ultrasound or MRI, ERCP) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis is defined as an ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of the-specific ALP isoenzyme in participants with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury (livertox.nih.gov/rucam.html).

If DILI confirmed: permanently discontinue study treatment.

If DILI is unlikely - interrupt treatment. Treat identified cause according to institutional guidelines. If resolved, reduce by one dose level. Re-administration of study treatment should be considered only if the investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drug/s and dose regimen should be discussed with the Novartis medical safety team.

6.8. Guidelines for the treatment of alpelisib induced pancreatitis

Investigations (Pancreatic)	
Pancreatitis	
Grade 2 (enzymatic elevation or radiologic findings only)	Omit dose until resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. If toxicity recurs, permanently discontinue patient from alpelisib/placebo
Grade 3 For subjects deriving clinical benefit upon investigator's judgement: For other subjects:	 Omit dose until complete resolution of symptoms and lipase resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed. If recovery to ≤ Grade 1 is greater than 28 days, the subject ,must be discontinued from the study. If toxicity reoccurs, permanently discontinue subject from alpelisib/placebo Permanently discontinue subject from alpelisib/placebo
Grade 4	Permanently discontinue subject from alpelisib/placebo

6.9. Guidelines for the treatment of alpelisib induced stomatitis/oral mucositis

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

6.10. Guidelines for the treatment of alpelisib induced amylase/lipase elevation

Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥ 3 (> 2.0 x ULN)	Omit dose until resolved to baseline, then If resolved in ≤ 14 days, maintain dose level If resolved in > 14 days, then ↓ 1 dose level. Note: In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase) as specified in

6.11: Guidelines for the treatment of other alpelisib induced events

Investigations (any other)	
Other adverse events	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Permanently discontinue subject from alpelisib/alpelisib matching-placebo Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)

6.12: Warnings and precautions

Hypersensitivity (including anaphylactic reaction)

Serious hypersensitivity reactions (including anaphylactic reaction, anaphylactic shock and angioedema), manifested by symptoms including, but not limited to, dyspnoea, flushing, rash, fever or tachycardia, were reported in patients treated with alpelisib (see section 4.8). Alpelisib should be permanently discontinued and should not be re-introduced in patients with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

Severe cutaneous reactions

Severe cutaneous reactions have been reported with alpelisib. In the phase III clinical study, Stevens Johnson syndrome (SJS) and erythema multiforme (EM) were reported in 1 (0.4%) and 3 (1.1%) patients, respectively. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post marketing setting (see section 4.8).

alpelisib treatment should not be initiated in patients with a history of severe cutaneous reactions.

Patients should be advised of the signs and symptoms of severe cutaneous reactions (e.g. a prodrome of fever, flu like symptoms, mucosal lesions or progressive skin rash). If signs or symptoms of severe cutaneous reactions are present, alpelisib should be interrupted until the aetiology of the reaction has been determined. A consultation with a dermatologist is recommended.

If a severe cutaneous reaction is confirmed, alpelisib should be permanently discontinued. Alpelisib should not be re-introduced in patients who have experienced previous severe cutaneous reactions. If a severe cutaneous reaction is not confirmed, alpelisib may require treatment interruption, dose reduction or treatment discontinuation as described.

Hyperglycaemia

Severe hyperglycemia, including ketoacidosis, has been reported in patients treated with alpelisib.

In the phase III clinical study, hyperglycaemia occurred more frequently in patients who were diabetic (0 out of 12 patients [0%] with grade 1 2, and 10 out of 12 patients [83.3%] with grade 3 4), pre diabetic (42 out of 159 patients [26.4%] with grade 1 2, and 77 out of 159 patients [48.4%] with grade 3 4), had BMI ≥30 at screening (13 out of 74 patients [17.6%] with grade 1 2, and 38 out of 74 patients [51.4%] with grade 3 4) or ≥75 years of age (6 out of 34 patients [17.6%] with grade 1 2, and 19 out of 34 patients [55.9%] with grade 3 4).

As hyperglycaemia may occur with a rapid onset after starting treatment, it is recommended to self monitor frequently in the first 4 weeks and especially within the first 2 weeks of treatment, as clinically indicated. A specific schedule for fasting glucose monitoring is recommended in Table 1.

In the phase III clinical study, patients with a history of diabetes mellitus intensified use of antidiabetic medicinal products while on treatment with alpelisib.

All patients should be instructed on lifestyle changes that may reduce hyperglycaemia (e.g. dietary restrictions).

Patients should be advised of the signs and symptoms of hyperglycaemia (e.g. excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with weight loss).

In the 190 patients with hyperglycaemia, 87.4% (166/190) were managed with antidiabetic medication, and 75.8% (144/190) reported use of metformin as single agent or in combination with other antidiabetic medication (e.g. insulin, dipeptidyl peptidase 4 (DPP 4) inhibitors, SGLT2 inhibitors and sulfonylureas).

Oral antidiabetic medication was used in 154 patients. Out of these 154 patients, 17 (11.0%) discontinued study treatment due to hyperglycaemia. Concomitant insulin medication was used in 54 patients; of these 13 (24.1%) discontinued study treatment due to hyperglycaemia.

Out of 162 patients with grade ≥2 hyperglycaemia, 155 had at least 1 grade improvement, median time to improvement from the first event was 8 days (95% CI: 8 to 10 days).

Of the patients with elevated FPG who continued fulvestrant treatment after discontinuing alpelisib (n=58), 98.3% (n=57) had FPG levels that returned to baseline.

The safety of alpelisib in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from the phase III clinical study. Patients with a medical history of Type 2 diabetes were included. Patients with a history of diabetes mellitus may require intensified diabetic

treatment and should be closely monitored.
Based on the severity of the hyperglycaemia, alpelisib may require dose interruption, reduction or discontinuation as described. Drug reaction with Hyperglycemic Hyperosmolar Non-Ketotic Syndrome (HHNKS) has been reported in the post marketing setting (see section 4.4 of SmPC).

Pneumonitis
Pneumonitis, including serious cases of pneumonitis/acute interstitial lung disease, have been reported in alpelisib treated patients in clinical studies. Patients should be advised to report promptly any new or worsening respiratory symptoms. In patients who have new or worsening respiratory symptoms or are suspected to have developed pneumonitis, alpelisib treatment should be interrupted immediately and the patient should be evaluated for pneumonitis. A diagnosis of non infectious pneumonitis should be considered in patients presenting with non specific respiratory signs and symptoms such as hypoxia, cough, dyspnoea, or interstitial infiltrates on radiological examination and in whom infectious, neoplastic and other causes have been excluded by means of appropriate investigations. alpelisib should be permanently discontinued in all patients with confirmed pneumonitis.

Diarrhea or colitis
Patients should be monitored for diarrhoea and other symptoms of colitis, such as abdominal pain and mucus or blood in stools.

Severe diarrhoea and clinical consequences, such as dehydration and acute kidney injury, have been reported during treatment with Piqray and resolved with appropriate intervention. 59.5% of patients (n=169) experienced diarrhoea during treatment with Piqray. Grade 3 diarrhoea occurred in 7% (n=20) of patients with no reported cases of grade 4. Among patients with grade 2 or 3 diarrhoea (n=76), the median time to onset was 50 days (range: 1 to 954 days).

Dose reductions of Piqray were required in 5.6% of patients and 2.8% of patients discontinued Piqray due to diarrhoea. In the 169 patients who experienced diarrhoea, antidiarrhoeal medications (e.g. loperamide) were required to manage symptoms in 64.5% (109/169).

Based on the severity of the diarrhoea or colitis, Piqray may require dose interruption, reduction or discontinuation as described in Table 4.6 of this manual.

Patients should be advised to start antidiarrhoeal treatment, increase oral fluids and notify their physician if diarrhoea or other symptoms of colitis occur while taking Piqray. In case of colitis, additional treatment, such as steroids, may be considered as clinically indicated.

Osteonecrosis of the jaw
Caution should be exercised when alpelisib and bisphosphonates or denosumab are used either simultaneously or sequentially. alpelisib treatment should not be initiated in patients with ongoing osteonecrosis of the jaw from previous or concurrent treatment with bisphosphonates/denosumab. Patients should be advised to promptly report any new or worsening oral symptoms (such as dental mobility, pain or swelling, non healing of mouth sores, or discharge) during treatment with alpelisib. In patients who develop osteonecrosis of the jaw, standard medical management should be initiated.

Symptomatic visceral disease
The efficacy and safety of this medicinal product have not been studied in patients with symptomatic visceral disease.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film coated tablet, that is to say essentially 'sodium free'.

Arterial hypertension has been observed in patients treated with alpelisib. Regular blood pressure monitoring during the treatment is recommended.

Cardiac events: although no clinically-significant associated cardiac signs and/or symptoms were observed in patients treated with alpelisib, it is recommended that ECG and LVEF are monitored regularly during the study treatment.

Concomitant medication:
Medicinal products that may increase alpelisib plasma concentrations

BCRP inhibitors
Alpelisib is a substrate for BCRP in vitro. BCRP is involved in the hepatobiliary export and intestinal secretion of alpelisib, therefore inhibition of BCRP in the liver and in the intestine during elimination may lead to an increase in systemic exposure of alpelisib. Therefore, caution and monitoring for toxicity are advised during concomitant treatment with inhibitors of BCRP (e.g. eltrombopag, lapatinib, pantoprazole).

Medicinal products that may decrease alpelisib plasma concentrations

Acid reducing agents
Population pharmacokinetic analysis showed no significant effect of co administration of acid reducing agents, including proton pump inhibitors, H2 receptor antagonists and antacids, on the pharmacokinetics of alpelisib. Therefore, alpelisib can be co administered with acid reducing agents, provided alpelisib is taken immediately after food.

Medicinal products whose plasma concentrations may be altered by alpelisib
Based on the results of metabolic in vitro induction and inhibition studies, alpelisib may induce the metabolic clearance of co administered medicinal products metabolised by CYP2B6, CYP2C9 and CYP3A and may inhibit the metabolic clearance of co administered medicinal products metabolised by CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (time dependent inhibition) if sufficiently high concentrations are achieved in vivo.

CYP3A4 substrates
No dose adjustment is required when co administering alpelisib with CYP3A4 substrates (e.g. everolimus, midazolam). Caution is recommended when alpelisib is used in combination with CYP3A4 substrates that also possess an additional time dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. rifampicin, ribociclib, encorafenib).

CYP2C9 substrates with narrow therapeutic index
In the absence of clinical data on CYP2C9, caution is recommended. In vitro evaluations indicated that the pharmacological activity of CYP2C9 substrates with a narrow therapeutic index such as warfarin may be reduced by the CYP2C9 induction effects of alpelisib.

CYP2B6 sensitive substrates with narrow therapeutic index
Sensitive CYP2B6 substrates (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib, as alpelisib may reduce the clinical activity of such medicinal products.

Substances that are substrates of transporters
In vitro evaluations indicated that alpelisib (and/or its metabolite BZG791) has a potential to inhibit the activities of OAT3 drug transporters and intestinal BCRP and P-gp. Alpelisib should be used with caution in combination with sensitive substrates of these transporters which exhibit a narrow therapeutic index because alpelisib may increase the systemic exposure of these substrates.

Hormonal contraceptives
No clinical studies were conducted assessing the drug drug interaction potential between alpelisib and hormonal contraceptives.

Contraception and pregnancy: based on in vivo non-clinical studies, alpelisib is embryofetotoxic and teratogenic. Women of childbearing potential and men who are treated with alpelisib must therefore agree to use effective contraception from the moment they start alpelisib treatment, until 1 week after discontinuation of the treatment. Sexually active male participants should always use a condom, also if they had a vasectomy, to prevent delivery of the drug via seminal fluid. Women are not allowed to breastfeed during and / or 1 week after the last dose of alpelisib treatment.