NOVARTIS

Department: Novartis Research and Development Department

Non-Interventional Post-Authorization Safety Study (PASS)

CBYL719C2404

Title	Alpelisib (Piqray®) Post-Authorization Safety Study (PASS): a non-interventional study of alpelisib in combination with fulvestrant in postmenopausal women, and men, with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), locally advanced or metastatic breast cancer with a phosphatidylinositol-3-kinase catalytic subunit alpha (PIK3CA) mutation, in the real-world setting
Protocol version identifier	v00
Date of last version of protocol	23-March-2021
EU PAS register number	Study not yet registered
Active substance	Alpelisib (BYL719)
Medicinal product	Piqray®
Product reference	EU/1/20/1455/001-009
Procedure number	EMEA/H/C/004804
Name of marketing authorization holder(s)	Novartis Europharm Limited
Joint PASS	No

Research question and objectives	Primary objective: To assess the incidence of hyperglycemia (adverse event of special interest, AESI) observed during follow-up of patients treated with alpelisib in combination with fulvestrant. Secondary objectives: To assess the risk factors of hyperglycemia; To estimate the incidence of complications of a non-compensated hyperglycemic state, such as ketoacidosis and hyperglycemic hyperosmolar non-ketotic syndrome (HHNKS); To assess the incidence of osteonecrosis of the jaw (ONJ), and the risk factors for ONJ; To describe other AESIs, including GI toxicity (nausea, vomiting, diarrhea), rash, hypersensitivity (e.g. anaphylactic reaction), pancreatitis, pneumonitis and severe cutaneous adverse reactions (SCARs); To describe other safety and tolerability events of alpelisib in combination with fulvestrant in a non-interventional setting.
Country (-ies) of study	Region Europe
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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
BSA	Body Surface Area
CDKi	Cyclin-Dependent Kinases 4 and 6 inhibitors
CI	Confidence Interval
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethic Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER	Estrogen Receptor
EU	European Union
FG	Fasting Glucose
FPFV	First Patient First Visit
FPG	Fasting Plasma Glucose
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practices
HbA1c	Hemoglobin A1c
HCP	Health Care Provider
HER2	Human Epidermal Growth Factor Receptor 2
HER2-	Human Epidermal Growth Factor Receptor 2 Negative
HHNKS	Hyperglycemic Hyperosmolar Non-Ketotic Syndrome
HR	Hormone Receptor
HR+	Hormone Receptor Positive
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
ISPE	International Society for Pharmacoepidemiology
LPLV	Last Patient Last Visit
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg/dl	Milligrams per deciliter
mmol/l	Millimoles per liter
NIS	Non-Interventional Study
ONJ	Osteonecrosis of the Jaw
PAS	Post-Authorization Study

PASS	Post-Authorization Safety Study
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	PI3K Catalytic Subunit Alpha
PRAC	Pharmacovigillance Risk Assessment Committee
PR	Progesterone Receptor
PT	Preferred Term
RANK	Receptor Activator of Nuclear factor Kappa-B
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCAR	Severe Cutaneous Adverse Reactions
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SOC	System Organ Class
ULN	Upper Limit of Normal
US	United States
v	Version
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1 Responsible parties

The Marketing Authorization Holder (MAH) has contracted [redacted] (third party) to manage this study.

Contact details for key parties are listed in Table 1-1.

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	[redacted] [redacted] Novartis Email: [redacted] [redacted] Novartis Email: [redacted] [redacted] Novartis Email: [redacted] [redacted] Novartis Email: [redacted]
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MAH	Novartis Europharm Limited
MAH primary contact(s)	[redacted] [redacted] Novartis Email: [redacted]
CRO	[redacted]
CRO scientific oversight	[redacted] MD PhD

Role	Person
CRO lead epidemiologists(s)	[redacted] PhD [redacted] PhD

CRO = Contract Research Organization; MAH = Marketing Authorization Holder; PI = Principal investigator; Sr = Senior.

2 Abstract

Title

Alpelisib (Piqray®) Post-Authorization Safety Study (PASS): a non-interventional study of alpelisib in combination with fulvestrant in postmenopausal women, and men, with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), locally advanced or metastatic breast cancer with a phosphatidylinositol-3-kinase catalytic subunit alpha (PIK3CA) mutation, in the real-world setting.

Version and date

Version (v) 00, 16 Mar 2021

Name and affiliation of main author

[redacted], Novartis.

Email: [redacted]

Background

Biomarkers such as hormone receptors (HR, including estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor-2 (HER2) are commonly evaluated to determine the optimal approach to manage breast cancer. The phosphatidylinositol-3-kinase (PI3K) pathway is commonly activated in HR+ breast cancer and has been implicated in endocrine therapy resistance.

Alpelisib is an oral, alpha-specific class IA PI3K inhibitor belonging to the 2-aminothiazole class of compounds. The European Union (EU) Marketing Authorization for alpelisib was granted by the European Commission on 27 July 2020 and is supported by data from a large global pivotal phase III randomized, double-blind, placebo-controlled trial (SOLAR-1) where patients were randomized 1:1 to receive either alpelisib in combination with fulvestrant or placebo in combination with fulvestrant. The study demonstrated a statistically and clinically significant improvement for patients whose tumors harbored a PIK3CA mutation in progression-free survival (PFS) in the alpelisib in combination with fulvestrant arm (median PFS of 11.0 months vs 5.7 months; Hazard Ratio=0.65, 95% confidence interval [CI]: 0.50-0.85; one-sided p<0.001).

The adverse events of special interest (AESI) described in the Summary of Product characteristics (SmPC) for alpelisib in combination with fulvestrant are: gastrointestinal (GI) toxicity (nausea, vomiting, diarrhea), hyperglycemia, rash, hypersensitivity (e.g. anaphylactic reaction), pancreatitis, osteonecrosis of the jaw (ONJ), pneumonitis and severe cutaneous reactions (SCARs). The most common adverse events (AEs) of grade 3 or 4, that occurred in at least 5% of patients in the alpelisib in combination with fulvestrant arm versus the placebo in combination with fulvestrant arm of the SOLAR-1 trial, were hyperglycemia (36.6% vs. 0.7%), rash (9.9% vs 0.3%), maculopapular rash (8.8% vs 0.3%) and diarrhea (6.7% vs 0.3%).

The most frequent AEs leading to discontinuation of alpelisib in combination with fulvestrant were hyperglycemia (6.3%) and rash (3.2%). ONJ (all-grade) was reported in more patients in the alpelisib in combination with fulvestrant arm compared to patients in the placebo in combination with fulvestrant arm (4.2% vs 1.4%). Although no patients discontinued treatment due to ONJ, the majority of patients who had ONJ were also exposed to prior or concomitant bisphosphonates (n=15/16), and so in patients receiving alpelisib and bisphosphonates, an increased risk of developing ONJ cannot be excluded.

Rationale

The purpose of this study is to further evaluate the safety of alpelisib in combination with fulvestrant in the described population in the real-world setting. As per the risk management plan (RMP) approved by the European Medicines Agency (EMA), this study will primarily focus on the risk of hyperglycemia (primary outcome) and the risk factors for hyperglycemia (secondary outcome). Other secondary outcomes include ONJ and the risk factors for ONJ, non-compensated hyperglycemic state (ketoacidosis, hyperglycemic hyperosmolar non-ketotic syndrome [HHNKS]), other AESIs (GI toxicity [nausea, vomiting, diarrhea], rash, hypersensitivity [e.g. anaphylactic reaction], pancreatitis, pneumonitis,

and SCARs), and safety and tolerability of alpelisib in combination with fulvestrant. The collection and analysis of these data will allow for better characterization of the risk of AEs for alpelisib in combination with fulvestrant in this patient population in a real-world setting. Importantly, the examination of risk factors for hyperglycemia and ONJ will help understand at-risk populations.

Research question and objectives

The *primary objective* is to assess the incidence of the AESI of hyperglycemia observed during follow-up of patients treated with alpelisib in combination with fulvestrant.

The *secondary objectives* are:

- To assess risk factors for hyperglycemia observed during follow-up of patients treated with alpelisib in combination with fulvestrant;
- To estimate the incidence of complications of a non-compensated hyperglycemic state, such as ketoacidosis and HHNKS, observed during follow-up of patients treated with alpelisib in combination with fulvestrant;
- To assess the incidence of AESI of ONJ and the risk factors for ONJ observed during follow-up of patients treated with alpelisib in combination with fulvestrant;
- To describe other AESIs, including GI toxicity [nausea, vomiting, diarrhea], rash, hypersensitivity [e.g. anaphylactic reaction], pancreatitis, pneumonitis and SCARs, observed during follow-up of patients treated with alpelisib in combination with fulvestrant;
- To describe other safety and tolerability events observed during follow-up of patients treated with alpelisib in combination with fulvestrant.

Study design and eligibility

This is a prospective, multi-national, non-interventional study (NIS) collecting data from postmenopausal women, and adult men, with HR+, HER2- locally advanced or metastatic breast cancer whose tumor harbors a PIK3CA mutation, and who are treated with alpelisib in combination with fulvestrant in the real-world setting.

Inclusion criteria:

- Signed informed consent from the patient or a legally acceptable representative, obtained before any study-related activities are undertaken
- Diagnosis of HR+, HER2- locally advanced or metastatic breast cancer with a PIK3CA mutation
- Patients must be postmenopausal women, or men, ≥18 years of age
- Patients recruited on or before their first prescribed dose of alpelisib in combination with fulvestrant

Exclusion criteria:

- Use of alpelisib prior to signing the informed consent form for this study
- Participation in an interventional study within 30 days prior to the initiation of alpelisib

Setting and study population

Patients will be treated according to local clinical practice in the real-world setting; there will be no examinations or laboratory testing performed specifically for this study. Patients will be enrolled from several countries in the Region Europe. Since the commercial availability of alpelisib will be staggered, patients will be recruited from the time of alpelisib availability in their individual country. Patients can have received fulvestrant without alpelisib prior to recruitment. Patients will be allowed to participate in the study if they fulfill the eligibility criteria. Once the patient provides informed consent, he or she is enrolled in the study. Patients will be followed from enrollment until 1) 30 days after alpelisib treatment discontinuation, or 2) death, or 3) loss to follow-up, or 4) withdrawal of consent, or 5) physician decision to end treatment/study, or 6) end of the study, whichever occurs first. The end of the study is defined as

a maximum of 12 months after the date the last patient was enrolled (LPFV); if the last patient is still on treatment on that date, they will not be followed up any further.

Data collection

The following risk factors for AESIs (which include those identified / postulated from the SOLAR-1 trial) will be assessed at baseline: patient characteristics (age, sex, Body Mass Index [BMI]), medical history of diabetes (including gestational diabetes), PIK3CA mutation status, Eastern Cooperative Oncology Group (ECOG) status, physical examination results and vital signs, family history of diabetes, and patient's medical history of diabetes, tobacco use, relevant laboratory results including blood glucose levels, diabetic status as per laboratory values for hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG), clinically relevant self-monitoring test results (e.g. fasting glucose [FG]), prior and concomitant medications of interest, i.e. systemic corticosteroids, statins, quinolones, thiazides and thiazide-like diuretics, beta blockers, atypical antipsychotics, protease inhibitors and calcineurin inhibitors, prior use of bisphosphonate medications or receptor activator of nuclear factor kappa-b (RANK) ligand inhibitors medical history of breast cancer, SCARs or other skin disorder, and any prior antineoplastic therapy provided as a treatment for cancer.

The following data will be collected during the follow-up period: physical examination results and vital signs, ongoing diabetes, ongoing tobacco use, concomitant medications, relevant laboratory results forglucose levels, HbA1c and FPG, white blood cell count and platelets, clinically relevant self-monitoring test results (e.g. FG), concomitant medications for rash, concomitant use of bisophosphonate medications, concomitant use of RANK-ligand inhibitors, AEs or serious adverse events (SAEs) or AESIs (graded using CTCAE v4.03), study treatment dose interruptions or reductions or permanent discontinuation, AEs or SAEs or AESIs leading to dose interruptions or reductions or permanent discontinuation of alpelisib in combination with fulvestrant.

Data sources

Only data available from routine clinical practice will be collected. Patient visits should follow routine clinical practice. Data will be retrieved from the treating physicians' charts and data will be recorded in electronic case report forms (eCRFs). [redacted] will build the database.

Study size

Approximately 208 patients will be enrolled in this study. No formal hypothesis testing will be conducted. Different scenarios were created for the incidence proportions (between 5% and 75%), at 4 different margins of error (5%, 7%, 7.5% and 10%). Based on the calculations using the Exact Clopper-Pearson method, two-sided 95% CIs, a sample size of 208 patients corresponds to a 2-sided 95% CI with a width equal to 0.14 (i.e., margin of error is equal to 7%) for an assumed incidence proportion of 50% (i.e. the point with the highest variability). The margin of error is smaller for all other assumed proportions.

Data analysis

Summary statistics for continuous variables will include n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum values, missing values, and interquartile range. Categorical data will be summarized as frequencies and proportions. No hypothesis testing and, therefore, no inferential statistical analysis is planned for this study. All analyses will be used for descriptive purposes only. The primary endpoint (i.e. incidence of hyperglycemia, indicated by CTCAE v4.03 grading) will be summarized descriptively using the number and proportion of patients along with exact binomial 95% CI, as applicable. Using data collected during patient visits as per real-world practice, the cumulative incidence proportions of hyperglycemia will be estimated at specific time points after the first dose of alpelisib in combination with fulvestrant is administered (e.g. 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks, 6 months, and 1 year) to facilitate assessment of any temporal relationship, using cumulative incidence function and taking competing risks into consideration. Further details will be provided in the Statistical Analysis Plan (SAP).

Milestones

Planned start of data collection (First Patient First Visit, FPFV): Sep-2021
Planned end of data collection (Last Patient Last Visit, LPLV): Feb-2025

Planned submission of interim clinical study report (CSR): Dec-2024
Planned submission of final CSR: Feb-2026

3 Amendments and updates

None.

4 Milestones

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Full Summary Protocol submitted to PRAC	Mar-2021
PRAC approval	Jun-2021
Registration in the EU PAS register	May-2021
FPFV	Sep-2021
Submission of Interim CSR [1]	Dec-2024
LPLV	Feb-2025
Submission of Final CSR[2]	Feb-2026

CSR = Clinical Study Report; EU PAS = European Union Post-Authorization Study; FPFV = First Patient First Visit; LPLV = Last Patient Last Visit; PRAC = Pharmacovigilance Risk Assessment Committee.

[1] Interim CSR will be based on data from the first 100 patients enrolled.

[2] Final study report will be provided within 1 year after LPLV.

5 Rationale and background

5.1 Breast cancer

Globally, nearly 2 million new cases of breast cancer and over 600,000 breast cancer deaths were recorded in 2018 (Bray et al 2018, Breast Cancer Research Foundation 2018). Biomarkers such as hormone receptors (HR, including estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor-2 (HER2) are commonly evaluated to determine the optimal approach to manage breast cancer. According to United States (US) Surveillance, Epidemiology, and End Results (SEER) program data, HR-positive (HR+), HER2-negative (HER2-) breast cancer cases accounts for approximately 73% of all breast cancer cases (Howlader et al 2014). Further analysis of SEER program data found that HR+, HER2-, locally advanced or metastatic breast cancer accounts for 8-9% of all female breast cancers in women aged ≥ 50 years.

Male breast cancer is a rare disease, which has different clinicopathological and immunohistochemical features to female breast cancer, accounting for about 0.98% and 1.18% of breast cancer morbidity and mortality, respectively (Xie et al 2019). The incidence of male breast cancer has increased in the past few decades by 20–25% and continues to rise. The prognosis is worse than that of female patients due to older age and advanced stage at diagnosis. Metastatic breast cancer accounts for 7 to 9% of all breast cancers in male patients (Harlan et al 2010, Hong et al 2016), with HR+ and HER2- breast cancer accounting for 52% of male breast cancer (Harlan et al 2010).

The phosphatidylinositol-3-kinase (PI3K) pathway is commonly activated in HR+ breast cancer and has been implicated in endocrine therapy resistance (Miller et al 2011). Approximately 40% of HR+, HER2- breast cancers harbor gain-of-function mutations in the PIK3CA gene, which encodes the α-isoform of the catalytic subunit (p110α) of PI3K, leading to hyperactivation of the PI3K pathway (Cancer Genome Atlas Network 2012). These pathways influence cellular functions such as growth, death, and proliferation (Fruman et al 2017).

5.2 Alpelisib (Piqray®) and the SOLAR-1 trial

Alpelisib (brand name Piqray®) is an orally administered PI3K inhibitor that selectively inhibits the α-isoform of PIK3, p110α (Fritsch et al 2014). Alpelisib potently inhibits p110α, in its wild-type form and when constitutively activated by somatic mutations, and less strongly inhibits the β, δ, and γ isoforms of PI3K. The European Union (EU) Marketing Authorization for alpelisib was granted by the European Commission on 27 July 2020 and is supported by data from a large global pivotal phase III randomized, double-blind, placebo-controlled trial (SOLAR-1).

SOLAR-1 was a randomized, double-blind, placebo-controlled Phase III trial of male and female patients with HR+, HER2- advanced breast cancer (Study Code: CBYL719C2301, EudraCT: 2015-000340-42) (Andre et al 2019). Patients were assigned to cohorts based on their tumor-tissue PIK3CA mutation status and randomized 1:1 to receive either treatment with alpelisib and fulvestrant (n = 169 with PIK3CA mutations and n = 115 without PIK3CA mutations) or placebo and fulvestrant (n = 172 with PIK3CA mutations and n = 116 without PIK3CA mutations). In patients with PIK3CA-mutated cancer, progression-free survival (PFS) at a median follow-up of 20 months was 11.0 months (95% confidence interval [CI], 7.5 to 14.5) in the alpelisib in combination with fulvestrant group and 5.7 months (95% CI, 3.7 to 7.4) in the placebo in combination with fulvestrant group (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; one-sided $p<0.001$). For the cohort without PIK3CA-mutated cancer, the proof of concept criteria was not met (PFS hazard ratio 0.85 (95% CI, 0.58 to 1.25)) (Andre et al 2019).

The safety profile of alpelisib in combination with fulvestrant is based on the combined PIK3CA mutant and non-mutant data from 284 patients in the alpelisib in combination with fulvestrant arm and 287 patients in the placebo in combination with fulvestrant arm of the SOLAR-1 trial. Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) of any grade reported in at least 35% of the patients in either arm were hyperglycemia (in 63.7% of the patients who received alpelisib in combination with fulvestrant and 9.8% of those who received placebo in combination with fulvestrant), diarrhea (in 57.7% and 15.7%, respectively), nausea (44.7% vs 22.3%), decreased appetite (35.6% vs 10.5%), and rash (35.6% vs 5.9%) or maculopapular rash (14.1% vs 1.7%). The most common adverse events (AEs) of grade 3 or 4, that occurred in at least 5% of patients in either arm, were hyperglycemia (in 36.6% of the patients who received alpelisib in combination with fulvestrant and 0.7% of those who received placebo in combination with fulvestrant), rash (9.9% vs 0.3%), maculopapular rash (8.8% vs 0.3%), and diarrhea (6.7% vs 0.3%).

5.2.1 Adverse Events

Permanent discontinuation of alpelisib or placebo due to AEs occurred in 71 patients (25.0%) receiving alpelisib in combination with fulvestrant and in 12 patients (4.2%) receiving placebo

in combination with fulvestrant. The most frequent AEs leading to the discontinuation of alpelisib in combination with fulvestrant were hyperglycemia (in 18 patients [6.3%]) and rash (in 9 [3.2%]); no patients discontinued the placebo in combination with fulvestrant due to hyperglycemia or rash (Andre et al 2019).

Hyperglycemia is an expected, on-target effect of alpelisib since p110α facilitates the ability to lower serum glucose levels (Goncalves et al 2018). In the SOLAR-1 trial, hyperglycemia was identified as an Adverse Event of Special Interest (AESI) based on standardized MedDRA query (SMQ) terms; this AESI was reported in 187 patients (65.8%) who received alpelisib in combination with fulvestrant and 30 patients (10.5%) who received placebo in combination with fulvestrant (EMA 2021a). In the SOLAR-1 trial, hyperglycemia was among the most frequent AEs reported by MedDRA PT in the alpelisib in combination with fulvestrant group, as described above (EMA 2021a).

Based on the data from SOLAR-1, baseline diabetic and prediabetic status (hemoglobin A1c [HbA1c] and fasting plasma glucose [FPG] values), baseline body mass index (BMI) (i.e. BMI $\geq$ 30 kg/m^2), and baseline age (i.e. age $\geq$ 75 years), were risk factors for hyperglycemia in patients treated with alpelisib. These risk factors occurred in 74.7% of patients with any grade of hyperglycemia and in 86.2% of patients with grade 3 or 4 hyperglycemia (EMA 2021a). Furthermore, osteonecrosis of the jaw (ONJ) occurred more frequently in the alpelisib in combination with fulvestrant arm than the placebo in combination with fulvestrant arm. Among patients who received alpelisib in combination with fulvestrant, ONJ (all-grade) was reported in 4.2% of patients (n/N=12/284) compared to 1.4% patients (n/N=4/287) in the placebo in combination with fulvestrant arm (EMA 2021a). No patient discontinued the trial treatment due to ONJ (EMA 2021a). The majority of patients who had ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid) (n/N=15/16) (EMA 2021a). Therefore, in patients receiving alpelisib and bisphosphonates, an increased risk of developing ONJ cannot be excluded.

5.3 Alpelisib and the BYLieve trial

The BYLieve trial is a Phase II, multicenter, open-label, 3-cohort, non-comparative study of alpelisib plus endocrine therapy (fulvestrant or letrozole) in men and women with HR+, HER2-, PIK3CA-mutated advanced breast cancer whose disease has progressed on or after prior therapy, including cyclin-dependent kinases 4 and 6 inhibitors (CDKi) (NCT03056755; Study Code CBYL719X2402) (Rugo et al 2018). Results from the cohort of patients (cohort A) with CDKi in combination with aromatase inhibitor as an immediate prior treatment and centrally confirmed PIK3CA mutation (n = 121) have been published (Rugo et al 2020). The primary endpoint was the proportion of patients who were alive without disease progression at 6 months (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1; local assessment). Based on a median follow-up of 11.7 months, 50.4% of patients (95% CI: 41.2 to 59.6) met the primary endpoint, and median PFS was 7.3 months (95% CI: 5.6, 8.3).

5.3.1 Adverse events

The AE analysis was based on PT. The most frequent all-grade AEs and grade $\geq$ 3 AEs in this BYLieve cohort were similar to those reported in the SOLAR-1 trial. The most frequent all-grade AEs included diarrhea (60%), hyperglycemia (58%), nausea (46%), fatigue (29%),

decreased appetite (28%), and rash (28%). The most frequent AEs at grade ≥3 were hyperglycemia (28%), rash (9%), and rash maculopapular (9%). The most frequent AEs leading to treatment discontinuation were rash (in 5 patients [3.9%]), colitis, hyperglycemia, urticaria, and vomiting (in 2 patients each [1.6%]) (Rugo et al 2020). The full publication on results of the BYLieve trial is in progress.

5.4 Study Rationale

The purpose of the current study is to further evaluate the safety of alpelisib in combination with fulvestrant for the treatment of postmenopausal women and men with HR+, HER2-, locally advanced or metastatic breast cancer harboring PIK3CA mutation(s) in the tumor in the real-world setting. The study will focus on the important identified risk of hyperglycemia, as per the Risk Management Plan (RMP) approved by the European Medicines Agency (EMA) (EMA 2021b). The collection and analysis of these data will allow for a better characterization of the risk of hyperglycemia in the real-world setting. The collection of risk factors will facilitate the identification of at-risk populations.

6 Research question and objectives

Table 6-1 provides a list of the primary and secondary objectives and their corresponding endpoints.

Table 6-1 Study objectives and endpoints

Primary objective	**Primary endpoint**
To assess the incidence of hyperglycemia (AESI) observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The incidence proportion of hyperglycemia (based on AE data)
Secondary objectives	**Secondary endpoints**
To assess risk factors for hyperglycemia observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The risk factors of interest for hyperglycemia include: • Patient characteristics: age, BMI, sex • Medical history: diabetes mellitus (including gestational diabetes), tobacco use, baseline diabetic status per laboratory values for HbA1c and FPG, clinically relevant self-monitoring test results (e.g. FG) • Family history of diabetes mellitus • Concomitant medications known to affect blood glucose levels: systemic corticosteroids, statins, quinolones, thiazides and thiazide-like diuretics, beta blockers, atypical antipsychotics, protease inhibitors and calcineurin inhibitors
To estimate the incidence of complications of a non-compensated hyperglycemic state, such as ketoacidosis and HHNKS, observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The incidence proportion of ketoacidosis and HHNKS (based on AE data)
To assess the incidence of the AESI of ONJ, and the risk factors for ONJ observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The incidence proportion of ONJ (based on AE data). Risk factors for ONJ include: • Patient characteristics: age, BMI, sex • Prior and/or concomitant use of bisphosphonates (e.g. zoledronic acid). • Prior and/or concomitant use of RANK-ligand inhibitors (e.g. denosumab).
To describe other AESIs of alpelisib in combination with fulvestrant observed during follow-up of treated patients.	The incidence proportion of AESIs: • GI toxicity (nausea, vomiting and diarrhea) • Rash • Hypersensitivity (e.g. anaphylactic reaction) • Pancreatitis • Pneumonitis • SCARs
To describe other safety and tolerability events observed during follow-up of patients treated with alpelisib in combination with fulvestrant.	The incidence proportion and severity of: • AEs • AEs leading to dose interruptions

	• AEs leading to dose reductions • AEs leading to permanent discontinuation of alpelisib in combination with fulvestrant • SAEs • Hematological and biochemical laboratory abnormalities To describe the duration of exposure to alpelisib in combination with fulvestrant

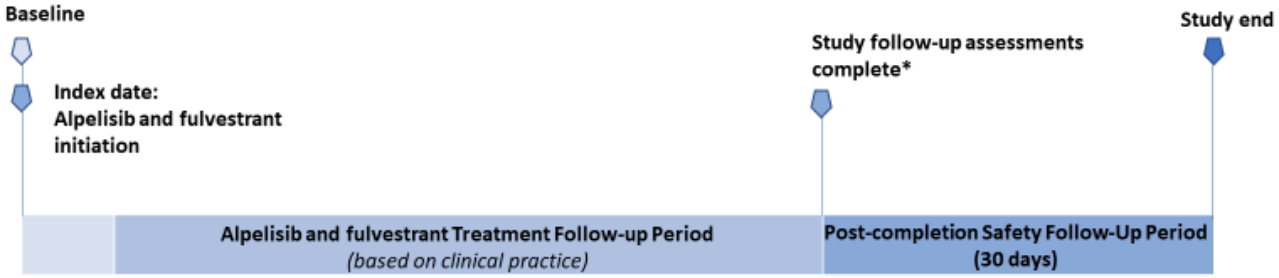
AEs = Adverse Events; AESIs = Adverse Events of Special Interest; BMI = Body Mass Index; FG = Fasting Glucose; FPG = Fasting Plasma Glucose; GI = Gastrointestinal; HbA1c = Hemoglobin A1c; HHNKS = Hyperglycemic Hyperosmolar Non-Ketotic Syndrome; RANK = Receptor Activator of Nuclear factor Kappa-B; ONJ = Osteonecrosis of jaw; SAEs = Serious Adverse Events; SCARs = Severe Cutaneous Adverse Reactions

7 Research Methods

7.1 Study Design

This is a prospective, multi-national, non-interventional study (NIS) collecting data from postmenopausal women and adult men with HR+, HER2- locally advanced or metastatic breast cancer whose tumor harbors a PIK3CA mutation, who are treated with alpelisib in combination with fulvestrant in the real-world setting. The decision to treat with alpelisib in combination with fulvestrant must be made by the treating oncologist prior to and independently of the decision to enroll the patient into the study. Figure 7-1 provides a visual description of the study design. The schedule of assessments and the study variables of interest are described in Section 7.5.

Figure 7-1 Alepelisib and fulvestrant Post-Authorization Safety Study (PASS) Design



* Patients will be followed from enrollment until 1) 30 days after alpelisib treatment discontinuation, or 2) death, or 3) loss to follow-up, or 4) withdrawal of consent, or 5) physician decision to end treatment/study, or 6) end of the study, whichever occurs first.

7.2 Setting

7.2.1 Study population

The study population includes postmenopausal women or men aged 18 years or older, with HR+, HER2- locally advanced or metastatic breast cancer with a PIK3CA mutation, who will

be treated with alpelisib in combination with fulvestrant. Patients can have received fulvestrant without alpelisib prior to recruitment. The study will be conducted in Region Europe.

7.2.2 Recruitment of patients

It is expected that the study will recruit 6-8 patients per month over 26 to 35 months across Europe. Approximately 208 patients are expected to be enrolled during the enrollment period. Physicians who use alpelisib in combination with fulvestrant in their routine clinical practice, and are interested in participating in this study as investigators, will be approached to participate. Since the commercial availability of alpelisib will be staggered, patients will be recruited in this study from the time of alpelisib availability in their individual country. Patients will be allowed to participate in the study if they fulfill the eligibility criteria outlined below. Once the patient provides informed consent, he or she will be enrolled in the study.

7.2.3 Inclusion criteria

The inclusion criteria are:

- Signed informed consent from the patient or a legally acceptable representative, obtained before any study-related activities are undertaken
- Diagnosis of HR+, HER2- locally advanced or metastatic breast cancer with a PIK3CA mutation
- Patients must be postmenopausal women, or men, ≥18 years of age
- Patients recruited on or before their first prescribed dose of alpelisib in combination with fulvestrant

7.2.4 Exclusion criteria

The exclusion criteria are:

- Use of alpelisib prior to signing the informed consent form for this study
- Participation in an interventional study within 30 days prior to the initiation of alpelisib

7.2.5 Patient follow-up

Patients will be treated according to local clinical practice in the real-world setting; there will be no examinations or laboratory tests performed specifically for this study. There will be no mandated study visits. Data from all visits and communications (including telephone) with the treating oncologist from baseline through the end of study will be collected.

Patients will be followed from enrollment until 1) 30 days after alpelisib treatment discontinuation, or 2) death, or 3) loss to follow-up, or 4) withdrawal of consent, or 5) physician decision to end treatment/study, or 6) end of the study, whichever occurs first. The end of the study is defined as a maximum of 12 months after the date the last patient was enrolled (LPFV); if the last patient is still on treatment on that date, they will not be followed up any further.

7.2.6 Patient withdrawal

Patients may discontinue participation in the study at any time. Withdrawal will not affect their medical care or access to treatment. Patients who have an ongoing AE at the point of withdrawal will be followed-up for 30 days from the point of their last dose of alpelisib in combination with

fulvestrant. Other than safety follow-up related to AEs, no efforts will be made to obtain additional information regarding the patient and their outcomes if a patient withdraws from the study. All information collected as part of the study up until the point of withdrawal will be retained for analyses, unless the patient has ongoing AEs at the point of withdrawal, in which case their 30 day follow-up data will be collected and retained. The primary reason for any study withdrawal should be recorded in the electronic Case Report Form (eCRF).

7.3 Variables

7.3.1 Exposure Definition and Measures

The main exposure of interest is alpelisib in combination with fulvestrant. There will be no restrictions on concomitant treatments given to study patients as part of their routine clinical care.

The approximate date and time that (alpelisib, in combination with fulvestrant) was started and discontinued will be extracted from patient records. The difference between these two date and time points will allow for the duration of exposure to alpelisib in combination with fulvestrant to be estimated.

7.3.2 Safety Outcome Definitions and Measures

Safety will be monitored by assessing physical examination results, vital signs, performance status evaluations, laboratory evaluations for hematology and biochemistry (including glucose monitoring), and any AE reports from each visit. Data on all AEs reported in the study will be collected (further details of the AESIs are provided in Section 7.4.1). The standard definitions and reporting periods for AEs, AESIs and SAEs are presented in Section 9.

7.3.3 Adverse Events of Special Interest

All AESIs will be collected and graded using the Common Terminology Criteria for AEs (CTCAE) v4.03, which includes grading definitions for the below AESIs. Gradings range from 1 to 4, with higher gradings indicating more severe outcomes. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form. AESIs [hyperglycemia, ONJ, pneumonitis, SCARs, rash, hypersensitivity (e.g. anaphylactic reaction), pancreatitis, gastrointestinal (GI) toxicity (nausea, vomiting and diarrhea)]will be analyzed.

7.3.4 Safety and tolerability

Study investigators are responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance. Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs, as appropriate. Local laboratory data (especially toxicities) will be summarized using the CTCAE v4.03, as per routine clinical practice, particularly for hyperglycemia.

7.3.5 Other covariates/variables

Patient characteristics and clinical covariates include demographics (i.e. age, BMI, sex), ongoing medical conditions and diseases as recorded in medical records, past medical history related to breast cancer, diabetes, SCARs and other skin disorders, and tobacco use. Treatment characteristics include prior and concomitant use of medications of interest (i.e. systemic corticosteroids, statins, quinolones, thiazides and thiazide-like diuretics, beta blockers, atypical antipsychotics, protease inhibitors and calcineurin inhibitors).

In this study, *prior use* is defined as all medications and non-drug therapies taken up to 30 days before the first dose of alpelisib is administered in combination with fulvestrant (i.e. for hyperglycemia), unless prior use of specific medications/therapies taken at any point before the start of the study are of interest (i.e. for ONJ/pneumonitis). Drug names (brand/generic), their prescribed dosage (amount and frequency), and prescription start and end dates, will be recorded. In the context of hyperglycemia, *prior use* is limited to previous medicines/therapies taken up to 30 days before the first dose of alpelisib is administered in combination with fulvestrant in this study. In the context of ONJ and pneumonitis, *prior use* refers to any previous antineoplastic therapies (including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies) provided as treatment(s) for cancer, and any prior use of bisphosphonates (e.g. zoledronic acid) or RANK-ligand inhibitors (e.g. denosumab) taken at any point before the first dose of alpelisib is administered with fulvestrant in this study. If start and end dates of such prior medication use/therapy are available in patient medical records, these will be extracted. If dates are not available, they will be considered missing.

In this study, *concomitant medication use* is defined as all medications and non-drug therapies taken during the course of the study, including prescription medications, over-the-counter drugs or dietary supplements that a patient is taking in addition to alpelisib in combination with fulvestrant. Drug names (brand/generic), their prescribed dosage (amount and frequency), and prescription start and end dates, will be recorded.

Clinical characteristics include PIK3CA mutation status (including information on the type of mutation, if available), Eastern Cooperative Oncology Group (ECOG) status, vital signs and relevant laboratory test results over time (i.e., full blood chemistry profile, complete blood count, FPG, and glycosylated HbA1c.

7.4 Data sources

Data collection will begin after written informed consent is obtained from the patient. Only available data from routine clinical practice will be collected.

This is a NIS and does not impose a therapy protocol, diagnostic or therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. The treating physician is asked to complete – if possible – the appropriate case report form (CRF) at every patient visit.

The recommended data collection schedule is summarized in Table 7-1. Data will be retrieved from the treating physicians' charts and data will be recorded in eCRFs.

Table 7-1 describes the data that is recommended for capture during this study, and the study time points that this data will be captured and recorded.

Table 7-1 Schedule of assessments

Recommended Data Collection	Baseline/ Enrollment	Study Follow-up Period	Post-completion Safety Follow-up Period
Informed consent	X		
Demographic data	X		
PIK3CA mutation status	X		
ECOG status	X		
Medical history related to breast cancer	X		
Prior history of SCAR / other skin disorder	X		
Family history of diabetes	X		
Medical history / concurrent diabetes	X	X	X
History of and current tobacco use	X	X	X
Prior and concomitant medications	X	X	X
Prior systemic antineoplastic treatment	X		
Prior and/or concomitant use of bisphosphonates (e.g. zoledronic acid)	X	X	X
Prior and/or concomitant use of RANK-ligand inhibitors (e.g. denosumab)	X	X	X
Physical examination	X	X	X
Vital signs	X		X
Safety outcomes			
Safety events		X	X
Dose adjustments		X	X
Patient disposition	X	X	X
Laboratory tests			
Full blood chemistry profile	X	as clinically indicated	X
Complete blood count	X	X	X
FPG	X	X	X
HbA1c	X	X	X

ECOG = Eastern Cooperative Oncology Group; FPG = Fasting Plasma Glucose; HbA1c = Hemoglobin A1c; RANK = Receptor Activator of Nuclear Factor Kappa-B; PIK3CA = Phosphatidylinositol-3-Kinase Catalytic Subunit Alpha; SCAR = Severe Cutaneous Adverse Reactions

7.4.1 Baseline data collection

Baseline data are defined as data collected at enrollment. The following data on demographic, clinical and treatment characteristics in patients treated with alpelisib in combination with fulvestrant will be collected at baseline, where available.

- Demographic characteristics including age, BMI, and sex
- PIK3CA mutation status, including any information on the type of mutation
- ECOG status (score ranges from 0 to 5, with higher scores indicating greater disability)
- Physical examination results and vital signs
- Medical history of breast cancer, SCARs or other skin disorders
- Family history of diabetes, and patient's medical history of diabetes (including gestational diabetes)
- Any other currently ongoing diseases or conditions
- Past and current tobacco use
- Relevant laboratory test results, including test results relating to baseline diabetic status (i.e., full blood chemistry profile, complete blood count, FPG and HbA1c); clinically relevant self-monitoring test results (e.g. FG); and laboratory test result ranges will be captured, where available
- Prior medication use (i.e. systemic corticosteroids, statins, quinolones, thiazides and thiazide-like diuretics, beta blockers, atypical antipsychotics, protease inhibitors and calcineurin inhibitors). Prior use of bisphosphonates and RANK-ligand inhibitors are of particular interest. Available data on prior medications will be extracted from medical records, including dose, frequency, length of therapy, first treatment date, and last treatment date.
- Prior antineoplastic therapies (including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies) provided as treatment(s) for cancer.

7.4.2 Treatment follow-up and post-completion safety follow-up data collection

The study follow-up and post-completion safety follow-up data will be collected after the baseline visit. The following data on clinical and treatment characteristics will be collected during these follow-up periods:

- Physical examination results and vital signs
- Ongoing diabetes
- Ongoing tobacco use
- Relevant laboratory test results (i.e., full blood chemistry profile, complete blood count, FPG and HbA1c) and/or clinically relevant self-monitoring test results (e.g. FG); and laboratory test result ranges will be captured, where available
- Concomitant medication use (i.e. systemic corticosteroids, statins, quinolones, thiazides and thiazide-like diuretics, beta blockers, atypical antipsychotics, protease inhibitors and calcineurin inhibitors). Concomitant use of bisphosphonates and RANK-ligand inhibitors are of particular interest. Available data on concomitant medication will be

extracted from medical records, including dose, frequency, length of therapy, first treatment date, and last treatment date.

- Safety events, including AESIs (as described in Section 7.3.3) and dose adjustments (i.e. interruption, reduction, permanent discontinuation)
- Treatment exposure to alpelisib in combination with fulvestrant (dose, frequency, length of therapy, first treatment date, last treatment date)
- Patient disposition.

7.5 Study size

Approximately 208 patients will be enrolled in this study. No formal hypothesis testing will be conducted. Table 7-2 below shows different scenarios for the incidence proportions (between 5% and 75%), at 4 different margins of error (5%, 7%, 7.5% and 10%). Based on the calculations using the Exact Clopper-Pearson method, two-sided 95% CIs, a sample size of 208 patients corresponds to a 2-sided 95% CI with a width equal to 0.14 (i.e., margin of error is equal to 7%) for an assumed incidence proportion of 50% (i.e. the point with the highest variability). The margin of error is smaller for all other assumed proportions.

Table 7-2 Sample size estimates

Confidence level=95%, 2-sided interval, Exact (Clopper-Pearson) method				
Margin Of Error (%)	**Assumed Incidence Proportion (%)**	**Sample Size (Patients)**	**Lower Limit (%)**	**Upper Limit (%)**
5%	5%	94	1.6	11.6
	50%	402	45.0	55.0
	60%	387	54.9	64.9
	70%	341	64.8	74.8
	75%	306	69.8	79.8
7%	5%	52	0.9	14.9
	50%	**208**	**43.0**	**57.0**
	60%	200	52.9	66.8
	70%	177	62.7	76.6
	75%	159	67.5	81.5
7.5%	5%	47	0.8	15.6
	50%	182	42.5	57.5
	60%	175	52.3	67.3
	70%	155	62.1	77.1
	75%	139	67.0	82.0
10%	5%	29	0.3	20.1
	50%	104	40.0	60.0
	60%	100	49.7	69.7
	70%	89	59.4	79.3

Confidence level=95%, 2-sided interval, Exact (Clopper-Pearson) method				
Margin Of Error (%)	**Assumed Incidence Proportion (%)**	**Sample Size (Patients)**	**Lower Limit (%)**	**Upper Limit (%)**
	75%	80	64.1	84.0

7.6 Data management

All data collected in this study will be stored in accordance with local laws and regulatory requirements.

[redacted] will be involved in building the database. Electronic data collection will be performed using eCRFs. Sites will enter data into the electronic data capture (EDC) system. The system used for capturing patients' data complies with industry standards and regulatory expectations for software developers and service providers within the global regulatory environment (US 21 CFR Part 11, EU Commission Directive 2005/28/EC). The platform is a secure, easy to use and reliable web-based EDC platform for the collection and reporting of clinical data. Patients will be identified using a study identification number assigned to them when they enroll in the study.

The Investigator and site staff will receive training on recording the data on the eCRFs using the EDC system. Only authorized personnel will have access to the EDC system. Data will be entered into eCRFs in accordance with the study's data entry guidelines. The Investigator is responsible for ensuring that accurate data are entered into the eCRFs in a timely manner. Online logic checks will be built into the system, so that missing or illogical data are not submitted. If inconsistent data persist, queries may be issued electronically to the study site and answered electronically by site staff. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable), as well as the Investigator's approval of any data changes in the eCRF will be recorded.

The Investigator will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor and/or designee via the system, providing missing or corrected data, approving all changes performed on patient data, and a password that together will represent a traditional handwritten signature.

All submitted eCRFs will be checked for missing information and queries will be generated to prevent the occurrence of missing data.

Concomitant or prior medications entered into the database will be coded using the World Health Organisation (WHO) Drug Reference List. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

Safety data will be transferred to Novartis at a frequency as defined in Section 9 of this protocol and/or CRO contract. All study data will be transferred to Novartis after closure of the study.

7.7 Data analysis

All analyses will be performed by [redacted] All analyses will be used for descriptive purposes only. In addition to the statistical methods outlined below, further details will be described in the Statistical Analysis Plan (SAP).

7.7.1 General considerations

The analyses of the data collected within this study will be exploratory in nature and no formal hypothesis will be tested. All the analyses will be descriptive and will be presented as per the primary and secondary objectives. Two-sided 95% CIs will be presented if required. No hypothesis testing and, therefore, no inferential statistical analysis is planned for this study. Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be described with measures of central tendency and dispersion: the number of patients, missing observations, mean, standard deviation, minimum, median, 25th and 75th percentiles , interquartile range, and maximum. Frequency, percentage, and number of missing observations will be provided for categorical variables. In general, descriptive statistics of quantitative parameters (results and change from baseline) will be provided for observed cases (i.e., patients having non-missing assessments at a specific timepoint). Missing data count will also be presented. Individual patient data will be presented in listings considering all patients provide signed informed consent.

All AE verbatim terms and medical history terms will be recorded and coded using the MedDRA. All previous and concomitant medication being recorded will be coded using the World Health Organization Drug Dictionary (WHO-DD), to the hierarchy level described in patient records. The total number of patients included in each analysis set along with the number of patients for each of the following categories will be provided as disposition analyses:

- Patients consented (patients providing signed informed consent)
- Patients eligible (consented and defined eligible as per inclusion and exclusion selection criteria)
- Patients included in the primary analysis set (eligible patients assuming at least one dose of alpelisib in combination with fulvestrant and having at least one post baseline evaluation)
- Patients who completed the study
- Time to discontinuation and reasons for discontinuation of the study

For all categories, the percentages will be calculated using the number of consented patients as the denominator for each treatment cohort.

7.7.2 Analysis of the primary endpoint

The incidence of hyperglycemia (i.e. the primary endpoint) will be assessed using CTCAE grading (v4.03), which grades hyperglycemia using laboratory values of glucose. FPG values will be used for the primary endpoint analysis. FG values collected through self-monitoring will be presented as descriptive statistics. The number and proportion of patients with hyperglycemia (along with exact binomial 95% CIs, as applicable) will be summarized descriptively.

For patients who have recurrent hyperglycemia during the study period, data on each episode will be collected and the most severe will be used for analyses.

The cumulative incidence proportions of hyperglycemia will be estimated at specific time points after the first dose of alpelisib in combination with fulvestrant is administered (e.g. 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks, 6 months, and 1 year), irrespective of

alpelisib dose interruptions, reductions or discontinuations. Data collected during patient visits (on the date-time of alpelisib in combination with fulvestrant administration) as per real-world practice will facilitate assessment of any temporal relationship, using cumulative incidence function and taking competing risks into consideration (i.e. events that lead to alpelisib in combination with fulvestrant discontinuation, e.g. death).

The time from alpelisib in combination with fulvestrant administration to hyperglycemia onset will be estimated using date-time data reported in the eCRF, and categorized by AE grade. The mean and standard deviation (or median and interquartile range) of time to hyperglycemia onset will be presented.

7.7.3 Analysis of the secondary endpoints

Risk factors for hyperglycemia

Descriptive statistics will be presented for the risk factors for hyperglycemia, including:

- Patient characteristics: age, BMI, sex.
- Medical history of diabetes mellitus (None, Pre-diabetes, and Diabetes), including gestational diabetes (Yes/No).
- Family history of diabetes mellitus (Yes/No).
- Tobacco use (Never, Prior, Current).
- Concomitant medications known to affect blood glucose levels (Yes/No): systemic corticosteroids (Yes/No), statins (Yes/No), quinolones (Yes/No), thiazides and thiazide-like diuretics (Yes/No), beta blockers (Yes/No), atypical antipsychotics (Yes/No), protease inhibitors (Yes/No) and calcineurin inhibitors (Yes/No).
- Laboratory values for HbA1c and FG (mean and standard deviation, median and interquartile range)
- Other variables of interest

Logistic regression may be fitted for the above risk factors, as applicable.

A summary of these baseline risk factors will be presented overall, and separately for patients with and without hyperglycemia.

In addition, these risk factors for hyperglycemia will be assessed taking time into consideration

Ketoacidosis and HHNKS

The incidence of ketoacidosis and HHNKS:

- Number and incidence proportion of patients with ketoacidosis and HHNKS will be summarized along with exact binomial 95% CI as applicable.

ONJ

The incidence of ONJ and its risk factors will include the following summaries:

- Number and incidence proportion of patients with ONJ will be summarized descriptively along with exact binomial 95% CI as applicable.
- Cumulative incidence proportion of ONJ will be estimated at specified time points (i.e. 1 month, 3 months, 6 months, and 1 year) utilizing the cumulative incidence function taking competing risks into consideration (e.g. death).
- The following risk factors will be assessed taking time into consideration:

- Concomitant use of bisphosphonates (e.g. zoledronic acid) (Yes/No).
- Concomitant use of RANK-ligand inhibitors (e.g. denosumab) (Yes/No).
- Prior use of bisphosphonates (e.g. zoledronic acid) (Yes/No).
- Prior use of RANK-ligand inhibitors (e.g. denosumab) (Yes/No).

In addition, logistic regression may be fitted for the above risk factors, as applicable.

AEs and AESIs

The baseline demographic and clinical characteristics of patients who develop the below AESIs will be described.

The incidence of other AESIs, including, pneumonitis and SCARs, GI toxicity, hypersensitivity (e.g. anaphylactic reaction), pancreatitis, and rash:

- Number and incidence proportion of patients with pneumonitis and SCARs, GI toxicity, hypersensitivity (e.g. anaphylactic reaction), pancreatitis, and rash, will be summarized along with exact binomial 95% CI as applicable.

Incidence of AEs and AESI will include the following summaries:

- Number and incidence proportion of patients with AEs and severity of AEs, grade 3 and 4 AEs, and SAEs will be summarized by system organ class (SOC) and PT.
- Number and incidence proportion of patients with AESI will be summarized by PT.
- Laboratory toxicities per CTCAE v4.03 will be summarized descriptively.
- Number and incidence proportion of patients with AEs leading to dose interruptions.
- Number and incidence proportion of patients with AEs leading to dose reductions.
- Number and incidence proportion of patients with AEs leading to permanent alpelisib plus fulvestrant discontinuation.

Details will be described in the SAP.

7.7.4 Data reporting

Data will be reported in an interim clinical study report (CSR) and a final CSR.

7.8 Quality Control

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative sites and ensure the collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, eCRF pages, and on the use of the EDC system. Retraining will be conducted as needed. Investigators will be reminded of the processes and importance of reporting adverse reactions, SAEs, and other information.

Monitoring will be performed to ensure that Informed Consent Forms (ICFs) have been completed for all enrolled patients. Subsequently, escalated monitoring may be performed at selected sites as needed, according to the study Monitoring Plan. At monitoring visits, the progress of the study and any procedural or data issues will be discussed with the Investigator and/or site staff. The Investigator will make patient source documents available for review and will permit the Sponsor, representatives of the Sponsor, Independent Ethics Committee (IEC), or regulatory authorities to inspect the facilities and original records relevant to this study. The

Investigator will allocate adequate time to discuss findings and relevant issues and, after the visit, to complete appropriate corrective actions as necessary.

7.8.1 Data quality management

[redacted] will assure database quality processes are followed including review of the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

A standardized training of all individuals performing data abstraction from medical records to minimize possible discrepancies between interpretation of the information recorded by the prescriber in the medical records and the individual performing the review and abstraction of the data.

7.8.2 Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the CRF must be traceable to these source documents in the patient's file.

The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the CRF entries. No information in source documents about the identity of the patients will be disclosed.

7.8.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study. [redacted] will assure compliance monitoring.

7.9 Limitations of the research methods

Some potential limitations of the study must be noted. As a NIS, any evidence for a relationship between alpelisib and the outcomes of interest indicate association rather than causation. Furthermore, patient loss to follow-up is more likely than in a clinical trial in which the treatment is provided to the patients and follow-up is mandated in the protocol. The data collected in a NIS is also likely to be less comprehensive compared to a clinical trial, since the planned NIS will not interfere with local clinical practice (i.e. this study will not mandate study visits or collect data in addition to that available in routine clinical practice). To address and explore the impact of this potential limitation, for the primary endpoint of hyperglycemia, all sources of evidence of hyperglycemia (e.g. diagnosed events, laboratory values, etc.) will be collected and evaluated. Every effort will be made to ensure an objective and complete assessment of the outcomes of interest.

Differences in recommended schedules of FG and HbA1c level monitoring between patients who belong to a hyperglycemia risk group and those who do not, might have an impact on the estimation of number and incidence proportion of patients with hyperglycemia, thereby potentially introducing bias for comparisons between risk group patients and those who do not belong to a risk group. However, no hypothesis testing and therefore no inferential statistical analysis is planned for this study. All analyses will be used for descriptive purposes only.

The representativeness of findings will be limited by the countries and the types of treatment centers (e.g. academic vs. community) included in the study. Novartis will work with the local network and the CRO to ensure the most representative data are collected. Importantly however, the results can still be generalizable even if they are not representative (Rothman et al 2013).

Despite limitations, the study will provide important safety data on hyperglycemia and other AESIs in the non-interventional setting in European countries.

No risk associated with the study execution is expected.

7.10 Other Aspects

N/A at this stage.

8 Protection of human subjects

8.1 Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in NIS are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (EMA 2010).

8.2 Informed consent procedures

Before any protocol-specified assessments are carried out, the Investigator or designee will explain details of the protocol and study procedures to patients and/or their legally acceptable representative. Patients will be informed that they are free to withdraw from the study at any time.

Each patient, or legally acceptable representative, must sign an informed consent form (ICF) specific to this study, approved by the IEC, indicating their consent to participate. ICFs and assent forms will conform to the requirements of International Council for Harmonisation E6 4.8, Principles of Good Clinical Practices. The original signed ICFs must remain in the patient's file in the clinic. Each patient will receive a copy of the signed ICF.

In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before any data are

collected. The process of obtaining informed consent should be documented in the patient source documents.

Each patient enrolled in the study, or a legally acceptable representative, must also sign a medical records release form permitting abstraction of medical data for entry in the study EDC system. Individual patient data included in the study database will be treated in compliance with all applicable laws and regulations regarding privacy protection.

8.3 Independent ethics committee approval

Investigators will be required to obtain approval from the appropriate IEC, and will be responsible for maintaining all related documents, before enrollment of any patient into the study. The Investigator is responsible for informing the IEC of the completion of the study and should provide any required study status and/or safety report(s).

8.4 Adherence to the protocol

The study must be conducted as described in the approved protocol. Any significant deviation from the protocol must be reported immediately to the Sponsor and the IEC.

8.5 Protocol amendment

Any amendment to the protocol will be created by the Sponsor, and subsequently submitted by the site to the IEC and appropriate regulatory authority for approval. If the protocol amendment substantially alters the study design or increases the potential risk of discomfort to the patients, written consent for continued participation in the study must be obtained.

8.6 Retention of patient records

When the study is completed, the Investigator must retain the essential documents for as long as needed to comply with regulatory guidelines and Sponsor requirements. The Investigator will notify the Sponsor prior to moving or destroying any study documents.

8.7 Confidentiality

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted below, is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare.

Data generated as a result of this study are to be available for inspection on request of the Sponsor's representative, the IEC, or local regulatory agency.

9 Management and reporting of adverse events/adverse reactions

All AEs will be collected and recorded in the study database, irrespective of seriousness or causal association. All SAEs that occurred in patients exposed to the Novartis drug(s) of interest,

irrespective of causality, will be reported to Novartis Patient Safety within 24 hours of becoming aware of the event. All non-serious AEs will be reported to Novartis Patient Safety within at least one month of awareness of the non-serious AE.

Adverse Drug Reactions (ADRs) occurring in patients exposed to a Novartis drug other than the Novartis drug of interest, can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or to Novartis Patient Safety as a spontaneous report.

All ADRs identified for non-Novartis drugs should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the marketing authorization holder as these will not be recorded in the Novartis safety database.

9.1 Definitions

For NIS with primary data collection and a Novartis drug of interest, where there will be investigators involved/Health Care Provider (HCP) to perform seriousness and causality assessments on the safety information collected from the patients, the following definitions apply. The Novartis drug of interest evaluated in this study is alpelisib.

9.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

9.1.2 Serious Adverse Events

A SAE is defined as an AE which:

- Results in death or is life threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above, e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.

Note: Transmission of infectious disease via medication is considered to be a serious adverse reaction and should be reported and assessed as medically significant in the absence of other seriousness criteria.

9.1.3 Adverse Drug Reaction

An ADR is a response to a medicinal product which is noxious and unintended. An ADR implies at least a reasonable possibility of a causal relationship between a medicinal product and an AE.

9.1.4 Adverse Events of Special Interest

An AESI is an AE (serious or non-serious) that is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. AESIs will be identified by investigator, sponsor or programming based on standardized MedDRA query or based on the list of AESIs below:

- GI toxicity (nausea, vomiting, diarrhea)
- Hyperglycemia
- Rash
- Hypersensitivity (e.g. anaphylactic reaction)
- Pancreatitis
- ONJ
- Pneumonitis
- SCARs

9.2 Adverse Event data collection

All AEs from all patients enrolled in the study must be collected and recorded in the study database, irrespective of seriousness or causal association.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Medical conditions / diseases ongoing before starting treatment with a study drug are only considered AEs if they worsen after starting the study drug.

All AEs must be recorded on the AE CRF with the following information:

- The severity grade (mild, moderate, severe) or grade per CTCAE v4.03 (1-4).
    - If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used.
    - CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.
- Its relationship to the drug(s) of interest (suspected/not suspected)
- Its duration (start and end dates or if continuing at final exam)
- Whether it constitutes a SAE

In addition, all reports of the following special scenarios, whether or not associated with AEs, are also collected and reported in the same manner as AEs:

- Drug-drug or drug-food interaction
- Drug use during lactation
- Lack of efficacy
- Overdose
- Intentional drug abuse and misuse
- Medication errors including drug maladministration
- Dispensing or prescribing errors
- Unexpected beneficial effect
- Treatment non-compliance (with clinical symptoms)

Occupational or accidental exposure, for example of study personnel or family members of the patient should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or to Novartis Patient Safety as a spontaneous report.

9.2.1 Adverse Event reporting

Any action taken with study drug or addition of treatment medication as a result of an AE should be recorded on the AE CRF. Some examples to be recorded are: no action taken (i.e., further observation only); study drug dosage adjusted/ temporarily interrupted; study drug permanently discontinued due to this AE.

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

AE monitoring should be continued for at least 30 days following the last dose of study treatment. AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Information about common AEs already known about the study drug(s) can be found in the locally available labeling document for the approved indication under evaluation in this study.

9.2.2 Laboratory abnormalities

Laboratory abnormalities that constitute an AE in their own right (i.e., are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AE CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AE should be followed until they have returned to normal or an adequate explanation of the abnormality is found . When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the lab/test result as an additional event.

A grade 3 or 4 event (severe) as per CTCAE v4.03 does not automatically indicate an SAE unless it meets the definition of serious as defined below and/or as per investigator’s discretion.

A dose hold or medication for the laboratory abnormality may be required by the protocol, in which case the laboratory abnormality would still, by definition, be an AE and must be reported as such.

9.2.3 Serious Adverse Event reporting

Information about all SAEs that occurred in patients exposed to the Novartis drug(s) of interest, irrespective of causality, must also be recorded in the Novartis safety database. The treating physician or other involved HCP must assess the relationship to the Novartis drug, complete the AE Report Form and send the completed, signed form by fax/ email within 24 hoursto the local Novartis Patient Safety department.

The email address, telephone and telefax number of the contact persons in the local Patient Safety department, specific to the site, are listed in the treating physician/ HCP folder provided to each site. The original copy of the AE Report Form and the fax confirmation sheet or the email must be kept with the CRF documentation at the study site.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAE experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

9.3 Follow-up information

Recurrent episodes, complications, or progression of the initial event must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within the same timelines as defined for the initial information. Any event that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is sent to the same contact person to whom the initial information was sent, stating, where an AE report form is used, that this is a follow-up to the previously reported event and providing the date of the original report. If known, the information missing from the initial report should be completed. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

In case an SAE is not previously documented in the labeling document for the study, a Novartis Patient Safety associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

In case an AE is considered to be of particular interest, a Novartis Patient Safety associate may seek additional information concerning the event. Corresponding questionnaires will then be provided by Novartis Patient Safety to the treating physician or other involved health care professional on a case-by-case basis.

9.4 Safety reporting period

Every SAE, non-serious AE, and special scenario, regardless of causality assessment, that occurred in patients exposed to the Novartis drug(s) of interest must be reported to Novartis:

- After the patient has provided informed consent
- Until 30 calendar days after the patient discontinued the Novartis drug of interest during the study conduct.

Any SAEs experienced after the 30 days period should only be reported to Novartis if the Investigator suspects a causal relationship to the Novartis drug(s) of interest.

10 Plans of disseminating and communicating study results

The Sponsor and/or designee will prepare progress reports as required by the competent authority. In addition, these data may be summarized periodically for presentation at professional conferences and sessions, as appropriate.

Upon study completion and finalization of the study report, the results of this NIS may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

If applicable (in the EU or mandated by an EU Health Authority outside the EU), the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within 2 weeks after first acceptance for publication.

The study protocol and synopsis of findings will be entered on the ENCePP register of studies (EMA 2016), and the STROBE reporting guidelines will be followed (Vanderbroucke et al 2007).

None of the parties involved in the management/conduct/analysis of this study may publish any study-related data without the written permission of Novartis.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

None.

12.2 Annex 2 – Alpelisib (Piqray®) dose guidelines

The following tables detail the alpelisib dose reduction guidelines for ADRs (Table 12-1), dose modification and management guidelines for hyperglycemia (Table 12-2), rash (Table 12-3), diarrahea (Table 12-4), and other toxicities (Table 12-5); as detailed in the Summary of Product characteristics (SmPC) for alpelisib (EMA 2021a). Note that references to alpelisib in the below tables were originally "Piqray®" in the SmPC, and have been changed here to ensure consistency throughout this protocol.

Table 12-1 Recommended dose reduction guidelines for ADRs for alpelisib[1]

Alpelisib dose level	Dose and schedule	Number and strength of tablets
Starting dose	300 mg/day continuously	2x 150 mg tablets
First dose reduction	250 mg/day continuously	1x 200 mg tablet and 1x 50 mg tablet
Second dose reduction	200 mg/day continuously	1x 200 mg tablet

ADR = Adverse Drug Reaction; mg = milligram.

[1] Only one dose reduction is permitted for pancreatitis.

Table 12-2 Dose modification and management for hyperglycaemia[1]

Fasting glucose values[1]	Recommendation
Dose reductions should only be based on fasting glucose (plasma/blood) values.	
	Consultation with a health-care professional experienced in the treatment of hyperglycemia should always be considered and is recommended for patients who are pre-diabetic or those with FG >250 mg/dl or 13.9 mmol/l, BMI ≥30 or age ≥75 years. Consultation with a diabetologist or a healthcare professional experienced in the treatment of hyperglycemia should always take place for patients with diabetes. All patients should be instructed on lifestyle changes that may reduce hyperglycemia (e.g. dietary restrictions and physical activity).
>ULN-160 mg/dl or >ULN-8.9 mmol/l	No alpelisib dose adjustment required. Initiate or intensify oral antidiabetic treatment[2].
>160-250 mg/dl or >8.9-13.9 mmol/l	No alpelisib dose adjustment required. Initiate or further 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 alpelisib dose by 1 dose level and follow FG value specific recommendations.

Fasting glucose values[1]	Recommendation
>250-500 mg/dl or >13.9-27.8 mmol/l	Interrupt alpelisib. Initiate or intensify oral antidiabetic treatment[2] and consider additional antidiabetic medicinal products (such as insulin[3]) for 1-2 days until hyperglycemia resolves. 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 alpelisib 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 hyperglycemia 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 alpelisib treatment.
>500 mg/dl or ≥27.8 mmol/l	Interrupt alpelisib. 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 alpelisib treatment.

BMI = Body Mass Index; FG = Fasting Glucose; FPG; Fasting Plasma Glucose; mg/dl = milligrams per deciliter; mmol/l = millimoles per liter; ULN = Upper Limit of Normal.

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

[2] Applicable antidiabetic medicinal products 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.

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

Table 12-3 Dose modification and management for rash[1]

Grade	Recommendation
All grades	Consultation with a dermatologist should always be considered.
Grade 1 (<10% BSA with active skin toxicity)	No alpelisib dose adjustment required. Initiate topical corticosteroid treatment. Consider adding oral antihistamine treatment to manage symptoms.

Grade	Recommendation
Grade 2 (10-30% BSA with active skin toxicity)	No alpelisib dose adjustment required. Initiate or intensify topical corticosteroid and oral antihistamine treatment. Consider low-dose oral corticosteroid treatment.
Grade 3 (e.g. severe rash not responsive to medical management) (>30% BSA with active skin toxicity)	Interrupt alpelisib until rash is grade ≤1. Initiate or intensify topical/oral corticosteroid and antihistamine treatment. Once improved to grade ≤1, then resume alpelisib at the same dose level for first occurrence of rash and at next lower dose level, in case of second occurrence.
Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions) (any % BSA associated with extensive superinfection, with intravenous antibiotics indicated; life threatening consequences)	Permanently discontinue alpelisib.

BSA = Body Surface Area

[1] Grading according to CTCAE Version 5.0

Table 12-4 Dose modification and management for diarrhea[1]

Grade[1]	Recommendation
Grade 1	No alpelisib dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt alpelisib dose until recovery to grade ≤1, then resume alpelisib at same dose level.
Grade 3 or 4[2]	Initiate or intensify appropriate medical therapy and monitor as clinically indicated. Interrupt alpelisib dose until recovery to grade ≤1, then resume alpelisib at the next lower dose level.

[1] Grading according to CTCAE Version 5.0.

[2] Patients should additionally be managed according to local standard of care, including electrolyte monitoring, administration of antiemetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.

Table 12-5 Dose modification and management for other toxicities (excluding hyperglycemia, rash and diarrhea)[1]

Grade	Recommendation
Grade 1 or 2	No alpelisib dose adjustment required. Initiate appropriate medical therapy and monitor as clinically indicated[2,3].
Grade 3	Interrupt alpelisib dose until improvement to grade ≤1, then resume alpelisib at the next lower dose level[2].
Grade 4	Permanently discontinue alpelisib[3].

[1] Grading according to CTCAE Version 5.0

[2] For grade 2 and 3 pancreatitis, interrupt alpelisib dose until recovery to grade ≤1 and resume at next lower dose level. Only one dose reduction is permitted. If toxicity recurs, permanently discontinue alpelisib treatment.

Grade	Recommendation

[3] For grade 2 total bilirubin elevation, interrupt alpelisib 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.

12.3 Annex 3 – CTCAE v4.03 terms, gradings and AE term definitons

A non-exhaustive list of the CTCAE v4.03 terms, gradings, and AE term definitions, for primary and secondary outcomes of interest are listed in Table 12-6.

Table 12-6 CTCAE v4.03 terms, gradings and AE term definitions for primary and secondary outcomes (non-exhaustive)

CTCAE v4.03 Term	Grade1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a necrotic process occurring in the bone of the mandible.
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death	A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.

CTCAE v4.03 Term	Grade1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Pancreatitis	-	Enzyme elevation or radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the pancreas.
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.

CTCAE v4.03 Term	Grade1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death	A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-	A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous AE, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.

CTCAE v4.03 Term	Grade1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death	A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-	A disorder characterized by a circumscribed and elevated skin lesion filled with pus.

AE = Adverse Event; ADL = Activities of Daily Living; BSA = Body Surface Area; CTCAE = Common Terminology Criteria for Adverse Events ; IV = Intravenous; mg/dl = Milligram/Deciliter; mmol/L = Millimol/Liter ; ULN = Upper Limit of Normal