

Patient Safety & Pharmacovigilance

European Union Risk Management Plan (EU RMP)

PIQRAY™ (Alpelisib)
BYL719

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Rationale for submitting an updated RMP:

This EU RMP v10.1 update has been prepared to remove the targeted follow-up (TFU) checklist of the important identified risk “osteonecrosis of the jaw” (ONJ) for Piqray. The proposal to remove the ONJ TFU checklist was initially driven by a comment from the Pharmacovigilance Risk Assessment Committee (PRAC) issued via the Vioice (alpelisib) Committee for Medicinal Products for Human Use (CHMP) Day 180 List of Outstanding Issues (EMA/CHMP/49420/2026, dated 27-Feb-2026, related to the procedure EMEA/H/C/006539/0000). On 09-Apr-2026, the European Medicines Agency (EMA) subsequently confirmed that this change could be assessed for Piqray within the scope of the EMA/VR/0000317159 procedure.

Summary of significant changes in this RMP:

Key changes for this RMP v10.1 include removal of the existing TFU checklist for ONJ.

Part	Major changes compared to RMP v10.1
Part I	No changes
Part II	Module SVII: There are no changes to the safety concerns in this RMP update; however, it includes information on the deletion of the TFU checklist for ONJ, along with the rationale for this change.
Part III	Deleted the information on the TFU checklist for ONJ.
Part IV	No changes
Part V	Deleted the information on the TFU checklist for ONJ.
Part VI	No changes
Part VII	Annex 4: Removal of the TFU checklist for ONJ.

Other RMP versions under evaluation:

No RMPs are currently under evaluation.

Details of the currently approved RMP:

Version number	9.0
Approved with procedure	EMA/VR/0000275207
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QPPV name: Dr Justin Daniels, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder’s QPPV. The electronic signature is available on file.

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List of abbreviations

aBC	advanced Breast Cancer
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Aromatase Inhibitor
ATC	Anatomical Therapeutic Chemical classification
BC	Breast Cancer
BP	Blood Pressure
CDK	Cyclin-Dependent Kinase
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DNA	Deoxyribose Nucleic Acid
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EEA	European Economic Area
EM	Erythema Multiforme
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Estrogen Receptor
EU	European Union
FCT	Film-Coated Tablet
FDA	Food and Drug Administration
FEC	Fluorouracil, epirubicin, cyclophosphamide
FPG	Fasting Plasma Glucose
GI	Gastrointestinal
HbA1c	Glycated Haemoglobin
HCP	Healthcare Professional
HER2	Human Epidermal Growth Factor Receptor 2
HHNKS	Hyperglycaemic Hyperosmolar Nonketotic Syndrome
HR	Hormone Receptor / Hazard Ratio
IBD	International Birth Date
INN	International Nonproprietary Name
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	mammalian Target Of Rapamycin
N	Number
NA	Not Applicable
NCCN	National Comprehensive Cancer Network
P	Probability
PAES	Post-authorization efficacy study
PFS	Progression Free Survival

PI3K	Phosphatidylinositol-3-Kinase
PIK3CA	Phosphatidylinositol-3-Kinase catalytic subunit alpha
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTY	Patient-Treatment-Year
qd	quaque die (once a day)
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety
SEER	Surveillance, Epidemiology, and End Results
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
TEN	Toxic Epidermal Necrolysis
ULN	Upper Limit of Normal
USA	United States of America
vs	versus

1 Part I: Product Overview

Table 1-1 Part I.1 - Product Overview

Active substance(s) (INN or common name)	Alpelisib
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, Protein kinase inhibitors, Phosphatidylinositol-3-kinase (PI3K) inhibitors (L01EM03)
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	PIQRAY™
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Alpelisib (BYL719) is an oral α-specific class I phosphatidylinositol-3-kinase (PI3K) inhibitor. Summary of mode of action: Alpelisib is α specific class I phosphatidylinositol3kinase (PI3Kα) inhibitor. Class I PI3K lipid kinases are key components of the PI3K/AKT/mTOR signalling pathway. Gain-of-function mutations in the gene encoding the catalytic α-subunit of PI3K (PIK3CA) lead to activation of PI3Kα manifested by increased lipid kinase activity, growth-factor independent activation of Akt-signalling, cellular transformation and the generation of tumors in a diverse array of preclinical models. In vitro, alpelisib treatment potently inhibited the phosphorylation of PI3K downstream targets Akt as well as its various downstream effectors in breast cancer cells and showed selectivity towards cell lines harboring a PIK3CA mutation. In vivo, alpelisib showed good tolerability as well as dose-and time-dependent inhibition of the PI3K/Akt pathway and dose-dependent tumor growth inhibition in relevant tumor xenograft models, including models of breast cancer. PI3K inhibition by alpelisib treatment has been shown to induce an increase in estrogen receptor (ER) transcription in breast cancer cells, therefore, sensitizing these cells to ER inhibition by fulvestrant treatment. Combination of alpelisib and fulvestrant demonstrated increased anti-tumour activity than either treatment alone in xenograft models derived from ER+, PIK3CA mutated breast cancer cell lines (MCF-7 and KPL1). Important information about its composition: Active drug substance: alpelisib List of excipients: Tablet core: Cellulose microcrystalline, Mannitol, Sodium starch glycolate, Hypromellose, and Magnesium stearate.

	Film coating: Hypromellose, Iron oxide (E172), Titanium dioxide (E171), Macrogol, Talc.
Hyperlink to the Product Information	[Proposed SmPC]
Indication(s) in the EEA	Current: Alpelisib is indicated in combination with fulvestrant for treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine-therapy as monotherapy. Proposed: Alpelisib is indicated in combination with fulvestrant for treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following an endocrine-based regimen.
Dosage in the EEA	Current: The recommended dose is 300 mg (2×150 mg film-coated tablets) taken once daily on a continuous basis. Alpelisib should be taken immediately after food, at approximately same time each day. The maximum recommended daily dose of alpelisib is 300 mg. Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Film-coated tablets 50 mg Film-coated tablets 150 mg Film-coated tablets 200 mg Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II: Safety specification

2.1 Part II: Module SI: Epidemiology of the indication(s) and target population

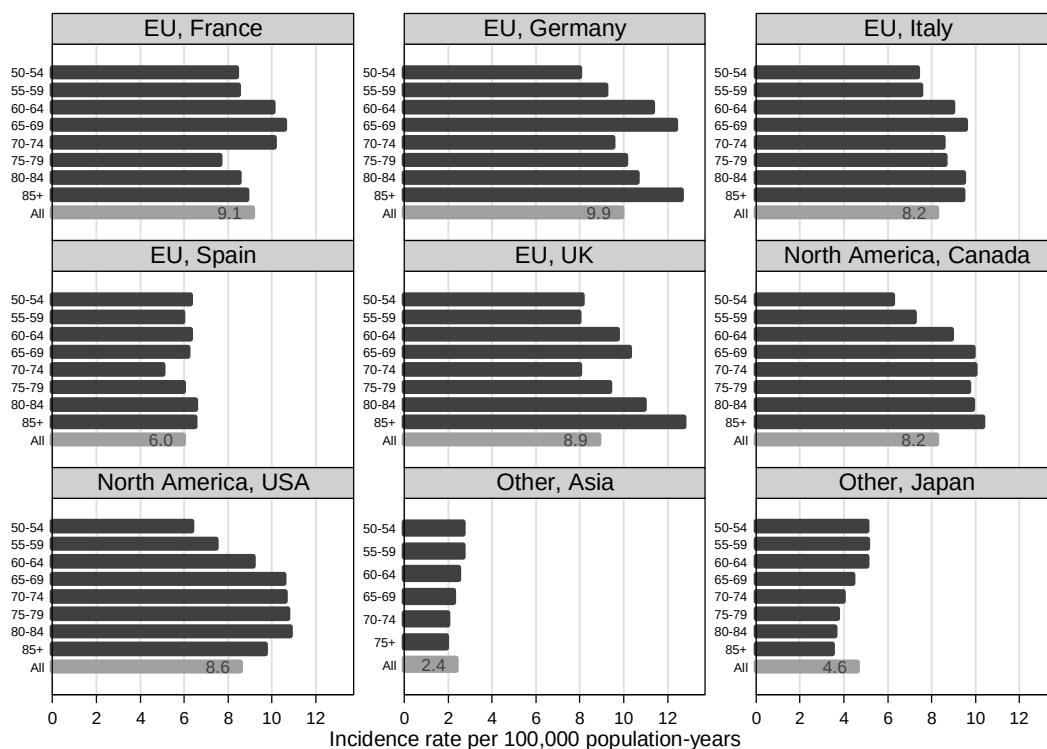
2.1.1 Indication

Alpelisib is indicated for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, advanced breast cancer with PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine-based regimen.

Incidence and prevalence

In the EU (European Union) in 2008-2012 the incidence rate per 100,000 population-years among women of HR-positive, HER2-negative advanced breast cancer (aBC) with PIK3CA mutation was 7.9. The incidence was similar between European countries and North America and was lower in Asia (Figure 2-1). Across numerous studies using varying assays/methods and gene locations, PIK3CA mutation was detected in the range of 4-80% of all breast cancers, however, the proportion is also dependent on the subtype of breast cancer. It has been estimated that the PIK3CA mutation is observed in approximately 40% of ER-positive breast cancers (Dirican et al 2016).

Figure 2-1 Estimated incidence* of HR-positive HER2-negative aBC in postmenopausal women with PIK3CA mutation



Incidence rates are standardized to the world population

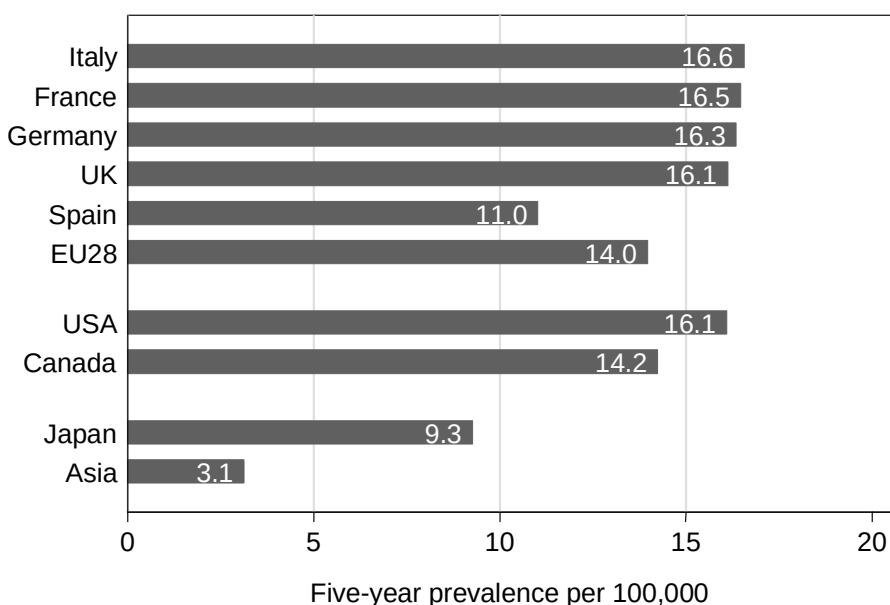
*Incidence rate of aBC with PIK3CA mutation was based on the following information (50 years old or older was used as proxy of postmenopausal):

- 1) Cancer Incidence in Five Continents Volume XI ([Bray et al 2017](#)) in women aged 50+ by 5-year age groups
 - 2) SEER data (USA cancer registry), proportion of HR-positive HER2-negative aBC in women aged 50+ represents among all BC by 5-year age-groups; ranging between 7.9-9.2% (SEER Stat Output 1)
 - 3) Proportion of PIK3CA mutation: [Abramson et al \(2014\)](#) (33.1% in HR+HER2-)
- Calculation: (1) x (2) x (3)

Among males the incidence rate per 10,000,000 population-years of HR-positive, HER2-negative aBC with PIK3CA mutation was 4.3 in Italy, Germany and France, and 3.2 in UK and Spain. In the USA this value was 4.8, 3.2 in Canada and 1.6 in Japan (for calculation method see footnote in [Figure 2-1](#), proportion of HR-positive HER2-negative aBC among males was obtained from SEER Stat Output 2). No information on the incidence for the whole EU in males was available.

Prevalence of HR-positive, HER2-negative aBC with PIK3CA mutation among postmenopausal women ranged between 3.1 and 16.6 per 100,000 ([Figure 2-2](#)). For men, in the USA the four-year prevalence in January 2014 was 2.0 per million (SEER Stat Output 4; assuming 33.1% have the PIK3CA mutation ([Abramson et al 2014](#))). No information on the prevalence in men was available for Europe or other countries.

Figure 2-2 **Estimated five-year prevalence* in 2012 of HR-positive, HER2-negative aBC with PIK3CA mutation among postmenopausal women**



*Five-year prevalence of aBC with PIK3CA mutation among postmenopausal women was based on the following information (50 years old or older was used as proxy of postmenopausal):

- 1) Globocan ([Bray et al 2013](#)), 5-year prevalence of all BC in 2012
 - 2) SEER data (US cancer registry), proportion HR-positive HER2-negative aBC in women aged 50+ represent among all BC (SEER Stat Output 3)
 - 3) Frequency of PIK3CA mutation: [Abramson et al \(2014\)](#) (33.1% in HR+HER2-)
- Calculation: (1) x (2) x (3)

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

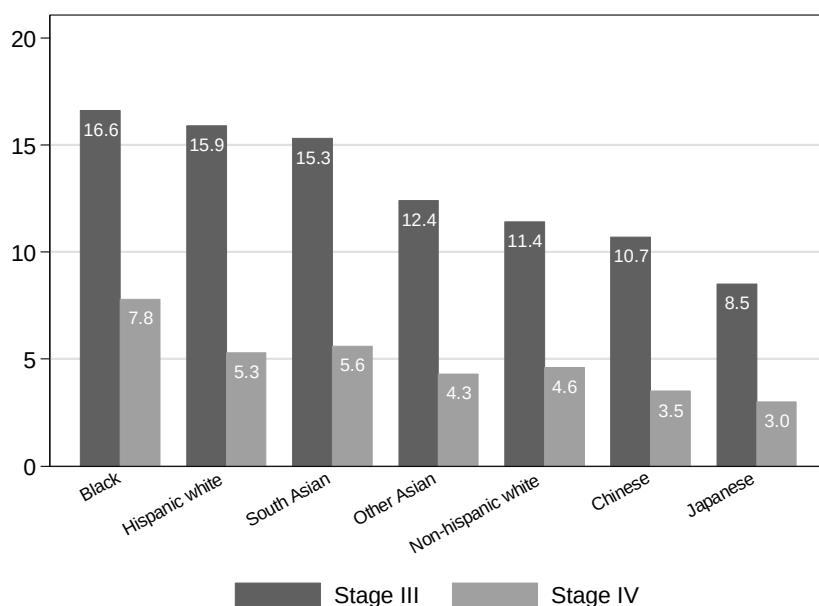
No clear trend across age groups is observed with respect to the incidence of HR-positive, HER2-negative aBC with PIK3CA mutation among women in European countries. In Canada and the USA, incidence increases with age while in Asia it appears that BC is more commonly diagnosed in younger age groups relative to older age groups ([Figure 2-1](#)).

Male breast cancer represents about 1% of all breast cancers diagnosed in the USA ([Siegel et al 2015](#)). Based on data from the International Agency for Research on Cancer, the highest female-to-male breast cancer incidence rate ratio is observed in Singapore (204.5) and the lowest in the Philippines (55) ([Ly et al 2013](#)).

Incidence rates of HR-positive breast cancer vary by race/ethnicity group and are generally higher in white women ([DeSantis et al 2014](#)). However, [Iqbal et al \(2015\)](#) observed, based on SEER data, that when stage of the disease at diagnosis by race/ethnicity is analyzed, black women have the highest percentage of Stage IV diagnoses (7.8%) and Japanese population the lowest (3.0%) ([Figure 2-3](#)). After multivariable analysis, including estrogen receptor status, black women still showed a lower probability of being diagnosed at early stages of the disease ([Iqbal et al 2015](#)).

The risk of disease recurrence or metastatic spread varies according to the characteristics of the tumor. Accordingly, there is a higher risk of metastatic spread with larger tumor size and nodal positivity, and a lower risk in HR-positive. Age at diagnosis is also an important factor as there is a lower risk of metastatic cancer at older ages ([Lord et al 2012](#), [Colzani et al 2014](#), [Kennecke et al 2010](#), [Purushotham et al 2014](#)).

Figure 2-3 Stage of breast cancer at diagnosis according to race/ethnicity



Source: [Iqbal et al \(2015\)](#)

The main existing treatment options:

Estrogen deprivation therapy is the core treatment modality in patients with HR-positive advanced breast cancer. Therefore, endocrine therapy is the standard treatment of choice for patients with HR-positive locally advanced or metastatic breast cancer, except for immediately life threatening/visceral crisis disease where chemotherapy is indicated (NCCN version 1.2018, [Cardoso et al 2014](#), [Partridge et al 2014](#)).

Endocrine therapy options for postmenopausal women with HR-positive advanced breast cancer include selective estrogen receptor modulators (SERM; tamoxifen), estrogen receptor antagonists (fulvestrant), aromatase inhibitors (AIs) which includes selective nonsteroidal aromatase inhibitors (NSAI; anastrozole and letrozole) and steroidal aromatase inhibitors (exemestane) ([Cardoso et al 2017](#)).

Upon treatment failure of endocrine therapy, continuation of a different type of endocrine therapy is a common option. However, despite the availability of hormone-directed therapies for the treatment of HR-positive advanced breast cancer, the development of endocrine resistance, and hence progression of disease, remains a significant challenge. Progressive disease ultimately develops in virtually all patients, either as early failure to respond to endocrine therapy (de novo resistance) or as relapse/progression after initial response (acquired resistance) ([Brufsky 2014](#), [Gonzalez-Angulo et al 2007](#), [Ring and Dowsett 2004](#), [Finn et al 2015](#)).

Several targeted agents have been developed to be combined with endocrine therapies to delay or reverse the endocrine resistance and to provide more options for treating HR-positive, HER2-negative advanced breast cancer. Two new classes of targeted compounds have demonstrated clinical efficacy in combination with endocrine therapy in advanced HR-positive breast cancer: the mammalian target of rapamycin (mTOR) inhibitor and the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor.

In Jul-2012, everolimus (mTOR inhibitor) was approved in combination with exemestane as a second line of treatment after progression on a non-steroidal AI on the basis of the randomized double-blind placebo-controlled BOLERO-2 study. At the interim analysis, median progression-free survival was 6.9 months with everolimus plus exemestane and 2.8 months with placebo plus exemestane, according to assessments by local investigators (hazard ratio for progression or death, 0.43; 95% confidence interval [CI], 0.35 to 0.54; $P < 0.001$). Median progression-free survival was 10.6 months and 4.1 months, respectively, according to central assessment (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; $P < 0.001$) ([Baselga et al 2012](#)). The final results with independent central radiology review after a median of 18 months follow-up show that median progression free survival (PFS) remained significantly longer with everolimus in combination with exemestane versus exemestane alone with a median PFS of 11 versus 4.1 months respectively with a hazard ratio (HR) of 0.38 (95% CI: 0.31-0.48; $P < 0.0001$) ([Yardley et al 2013](#)).

Co-targeting the estrogen receptor, together with various key intracellular proliferation and cell survival signalling pathways, such as CDK4/6 inhibitors that prevent cellular DNA synthesis and induce cell cycle arrest in tumor cells ([Johnston 2015](#)) has been confirmed to be a successful treatment option to overcome endocrine resistance. Recently, three CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) have been approved and considered a treatment option

for postmenopausal patients with HR-positive, HER2-negative metastatic breast cancer (NCCN guidelines version 1.2018).

In Feb-2015, in the US, palbociclib was granted accelerated approval (under subpart-H of the US Code of Federal Regulations) in combination with letrozole as an initial endocrine-based therapy for postmenopausal women with HR-positive, HER2-negative aBC based on an open-label, Phase II randomized study (1003; PALOMA-1) (Finn et al 2015). In March 2017, the FDA issued full approval of palbociclib based on the results from the confirmatory Phase III trial in combination with letrozole (1008; PALOMA-2) (Finn et al 2016). The palbociclib indication was subsequently expanded with another Phase III trial as a 2nd line therapy in combination with fulvestrant for metastatic breast cancer that has progressed on or after prior endocrine therapy in the adjuvant or metastatic setting (PALOMA-3). Palbociclib received approval in Europe for both 1st line (in combination with AIs) and 2nd line (in combination with fulvestrant).

In Mar-2017, ribociclib was approved in combination with AI as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced breast cancer (MONALEESA-2). In Jul-2018, ribociclib was approved in combination with AI as first line treatment for pre/peri/postmenopausal women with HR-positive, HER2-negative advanced breast cancer, and expanded the indication in combination with fulvestrant as both first- or second-line therapy in postmenopausal women (Slamon et al 2018, Tripathy 2018).

In September 2017, abemaciclib, was approved in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy based on a Phase III randomized MONARCH-2 study (Sledge et al 2017). Abemaciclib was also approved as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting based on a Phase II, single-arm, open-label MONARCH-1 study (Dickler et al 2017). On 26-Feb-2018, it was approved in combination with an AI as initial endocrine-based therapy for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer based on MONARCH-3 (Goetz et al 2017).

The approval of alpelisib represented a pivotal advancement as the first agent specifically targeting PIK3CA for the management of HR-positive, HER2-negative advanced or metastatic breast cancer. More recently, the emergence of an AKT inhibitor, and another PIK3CA inhibitor, Truqap[®] (capivasertib in combination with fulvestrant, approved in the EU on the 17-Jun-2024) and Itovebi[®] (inavolisib in combination with palbociclib and fulvestrant, approved in the EU on the 18-Jul-2025), respectively, have expanded the array of therapeutic options available to patients harboring PIK3CA mutations, but an unmet need still exists for these patients (Turner et al 2023, Turner et al 2024).

Natural history of the indicated condition in the population, including mortality and morbidity:

Advanced breast cancer is generally incurable. Consequently, the goals of treatment are generally no longer curative, but rather to prolong life and to palliate or prevent symptoms (Cardoso et al 2014).

Women with aBC have a significantly lower survival rate compared with all patients with breast cancer for whom five-year relative survival estimates ranges from 85% or higher in the developed countries to 60% or lower in many less developed countries ([Youlden et al 2012](#)) ([Table 2-1](#)).

Breast cancer in males occurs later and shows higher stage, lower grade, and more HR-positive tumors than in females. The biology of male breast cancer resembles that of postmenopausal female breast cancer, with low-grade and HR-positive tumors ([Anderson et al 2004](#), [Anderson et al 2006](#)).

Several factors contribute to the prognosis of aBC in women such as hormone receptor status (the lowest breast cancer-specific mortality being in women with both estrogen- and progesterone-receptor positive) ([Dunnwald et al 2007](#)), site of metastases (the lowest median survival rate being seen in breast cancer with liver, multiple sites and brain involvement) or patient's age (with a poor prognosis in ≥ 50 years) ([Largillier et al 2008](#)).

Changes in PI3K activity are associated with resistance to endocrine, chemo-, radio-, and anti-HER2 therapies ([Keegan et al 2018](#)). Targeted therapy with a PIK3CA inhibitor could therefore be considered a potentially valuable treatment option for subjects with HR-positive disease whose tumors with PI3K mutation (i.e., up to 40% of ER positive BC patients) have developed resistance to prior endocrine treatment. The expression profile of biological markers in breast cancer correlates with the prognosis and response to treatment. Results of a pooled analysis across 1929 subjects confirmed that the presence of a PIK3CA mutation represents an independent negative prognostic factor ([Sobhani et al 2018](#)).

Table 2-1 Relative survival of women and men (only USA) with aBC

Reference	Country	Relative survival according to stage	
Allemani et al (2013)¹	10-year survival (all BC subtypes)	Regional	Metastatic
	The Netherlands	63%	5%
	Finland	63%	14%
	Norway	65%	9%
	Poland	53%	5%
	Slovenia	55%	5%
	Switzerland	75%	19%
Walters et al (2013)²	3-year survival (all BC subtypes)	Stage III	Stage IV
	Canada	83.1%	39.9%
	Denmark	82.7%	35.6%
	Norway	79.2%	31.6%
	Sweden	76.2%	41.8%
	UK	70.2%	27.4%
Foukakis et al (2011)⁴	3-, 5-year survival (all BC subtypes)		Metastatic
	Sweden		26.0%/15.2%
USA (SEER registries)	USA	Stage III	Stage IV

Reference	Country	Relative survival according to stage	
SEER Stat Output 5 ⁵	3-, 5-, 10-year survival (all BC subtypes)	79.7% / 69.1% / 52.6%	37.1% / 22.8% / 10.0%
SEER Stat Output 6 ⁶	3-, 4-year survival (Aged 50+ and HR-positive HER2-negative)	87.5% / 82.0%	44.7% / 33.5%
SEER Stat Output 7 ⁶	3-, 4-year survival (Men, HR-positive HER2-negative)	89.3% / 80.8%	57.5% / -

Relative survival is defined as the ratio of the proportion of survivors observed among the cancer patients to the proportion of survivors that would be expected if they had experienced the same death rate as the general population from which they derive. It is a measure usually used in population-based cancer survival studies.

1: Survival was estimated for women who were alive at some point during 2000-2002. For The Netherlands, Poland and Switzerland information refers only to Amsterdam, Warsaw and Geneva, respectively. Age-standardized with the International Cancer Survival Standard 1 population

2: Period 2000-2007. Canada and Sweden covered only specific regions in the country.

Age-standardized to stage-specific weights derived from the age distribution of patients in all jurisdictions combined, in the age categories 15–44, 45–54, 55–64, 65–74, 75–84 and 85–99 years

3: Observed survival. Period 2006-2010

4: Period 2000-2004

5: Period 2000-2014. Age-standardized to the International Cancer Survival Standard 1 population

6: Period 2010-2014. Age-standardized to the International Cancer Survival Standard 1 population

Sources: [Allemanni et al \(2013\)](#), [Walters et al \(2013\)](#), [Foukakis et al \(2011\)](#), SEER Stat Output 5, SEER Stat Output 6, SEER Stat Output 7

Adverse events anticipated in the target population

In the aBC setting, fatigue, depression, insomnia, and pain are the most common symptoms in addition to those that occur based on the site of metastasis ([Irvin et al 2011](#)). Fatigue is the most commonly reported symptom in cancer patients, with an estimated prevalence of 25%-99% during treatment and 20%-35% off treatment, and insomnia between 20%-70% ([Bower 2008](#)). The prevalence of chronic pain in patients with advanced cancer is estimated at 70%–90% ([Irvin et al 2011](#)). In Denmark, among 61709 women with a breast cancer diagnosis, the 100 patient-years incidence rate of affective disorder was 0.13 (95% CI: 0.11, 0.14) and of anxiety disorder 0.05 (95% CI: 0.04, 0.05) ([Hjerl et al 2002](#)).

Patients in the target population may have received multiple cancer medications (tamoxifen and AIs, CDK4/6 inhibitors and chemotherapy) and also radiotherapy before starting treatment with alpelisib, which are associated with adverse events.

Endocrine therapy is associated with hot flushes and mood disturbances. Patients who were exposed to CDK4/6 inhibitors may have experienced neutropenia, leukopenia and anaemia ([Deng et al 2018](#)). In patients who were exposed to chemotherapy or radiotherapy drug induced interstitial lung disease can be observed and anthracycline-based therapies are associated with cardiotoxicity (clinical decompensation, structural change, biomarker rise or arrhythmia) ([Camus et al 2004](#), [Schwaiblmair et al 2012](#), [McGowan et al 2017](#)).

In patients exposed to fulvestrant in clinical trials the most frequent adverse events are gastrointestinal disturbances (20-49%), hot flashes (6-22%), injection site reactions (13-14%), ischemic cardiovascular disorders (1-2%), joint disorders (8-19%), thromboembolic events (1-

5%), urinary tract infection (1-9%), vaginitis (0.3-3%) and weight gain (0.3-2%) ([Ciruelos et al 2014](#), [Fulvestrant \(Faslodex®\) prescribing information](#)).

After diagnosis, the incidence of potential adverse events in patients with stages III or IV breast cancer based on the Surveillance, Epidemiology, and End Results-Medicare database was analyzed by [Danese et al \(2012\)](#) ([Table 2-2](#)). However, similar information is not yet available for CDK4/6 inhibitors, so it is not presented here.

Table 2-2 Three-month after diagnosis incidence rate of potential adverse events (per 1000 patient-years)

Potential adverse event	Stage III (95% CI) (N=2558)	Stage IV (95% CI) (N=2191)
Anaemia	303.79 (250.02-357.57)	761.84 (596.41-927.26)
Diarrhea	30.76 (16.97-44.55)	39.94 (22.87-57)
Electrolyte disorder	263.31 (212.71-313.91)	940.18 (842.83-1037.54)
Infectious disease	367.16 (309.08-425.23)	1010.18 (901.24-1119.11)
Infusion reaction	10.02 (2.96-17.08)	13.17 (2.88-23.45)
Neutropenia	70.61 (42.04-99.18)	129.38 (95.4-163.36)
Oral mucositis	9.71 (2.48-16.95)	18.24 (5.3-31.19)
Skin rash (from meds)	0.62 (0-1.83)	14.62 (4.03-25.2)
Skin rash (other)	76.94 (52.63-101.26)	124.38 (91.03-157.72)
Thrombocytopenia	28.05 (13.19-42.91)	65.22 (41.89-88.56)

Source: [Danese et al \(2012\)](#)

Important co-morbidities:

The prevalence and incidence of the main comorbidities in postmenopausal women is presented in [Table 2-3](#).

Table 2-3 Prevalence and incidence of comorbid conditions in women diagnosed of Stage III-IV breast cancer

Comorbidity	Prevalence (percent of included population) (N=2558)		Three-month after diagnosis incidence rate (per 1000 patient-years) (N=2191)	
	Stage III	Stage IV	Stage III	Stage IV
Cardiac/vascular				
Hypertension	51	42.46	611.48	642.25
Coronary artery disease (except myocardial infarction)	18.97	14.01	112.61	152.88
Congestive heart failure	10.16	7.08	122.48	292.86

	Prevalence (percent of included population) (N=2558)		Three-month after diagnosis incidence rate (per 1000 patient-years) (N=2191)	
Comorbidity	Stage III	Stage IV	Stage III	Stage IV
Cerebrovascular disease	12.53	11.31	94.29	109.35
Atrial fibrillation	8.07	7.9	130	172.74
Arrhythmia	6.76	5.14	114.22	89.43
Myocardial infarction	4.78	3.11	77.43	70.92
Peripheral vascular disease	3.26	2.48	32.99	45.68
Thromboembolism	2.27	2.45	42.52	208.33
Arterial thrombosis	0.29	0.35	4.72	13.3
Cardiac arrest	0.2	0.13	5.49	16.28
Gastrointestinal/hepatic				
Cholecystitis	1.16	1.49	15.2	39.99
Gastric ulcers	0.55	0.65	11.9	24.54
Liver disease	0.33	0.79	7.91	13.86
Metabolic				
Diabetes	16.89	15.39	74.94	132.74
Hyperglycaemia	0.05	0	0	3.64
Musculoskeletal/rheumatic				
Osteoarthritis	13.37	9.2	93.23	120.5
Rheumatologic disease	2.09	1.57	8.69	15.75
Neurological/psychiatric				
Alzheimer's disease and dementia	6.05	3.49	79.77	84.64
Depression	4.97	4.92	70.41	171.86
Hemiplegia	1.53	0.95	20.13	22.04
Pulmonary				
Chronic obstructive pulmonary disease	10.41	9.52	133.86	289.19
Renal				
Renal disease	1.52	1.35	19.57	40.32
Nephrotic syndrome	0.06	0.22	0	0

Source: [Danese et al \(2012\)](#)

Among postmenopausal women, the prevalence of prediabetes among Luminal A-like and Luminal B-like BC patients was 34.6% and 31.0%, respectively (Crispo et al 2017). The incidence of prediabetes among treated BC patients without previous history of diabetes was reported in two studies with incidence ranging from 15.4% among patients who had been treated with dexamethasone and either (i) 6 cycles of fluorouracil, epirubicin, cyclophosphamide (FEC) or (ii) 3 cycles of FEC and 3 cycles of docetaxel (Hickish et al 2009) and 46.9% among female BC patients after more than three months of systemic treatment (surgery and/or chemotherapy) (Lu et al 2014).

2.2 Part II: Module SII: Non-clinical part of the safety specification

Table 2-4 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Hematopoietic and lymphopoietic organs In both rats and dogs, effects in lymphatic and hematopoietic organs were among the most sensitive after treatment with alpelisib. In rats, decreases in reticulocytes, hemoglobin, hematocrit and other red blood cell parameters indicate an affected hematopoiesis, whereas white blood cell numbers showed an affected lymphopoiesis. In accordance with those blood parameters, histopathology investigations confirmed the effects in the associated solid organs, such as bone marrow hypocellularity with congestion/ hemorrhage, decreased hematopoiesis in the spleen, or lymphoid depletion in the thymus or lymph nodes. In dogs, lymphoid depletion in the thymus and gut-associated lymphoid tissue, mesenteric and/or retropharyngeal lymph nodes, together with a reduction in germinal centers of the latter, confirmed the effect particularly on lymphatic morphology. In both rats and dogs, reversibility of these hematopoietic system findings was seen after four weeks of a treatment-free recovery.	In the clinical development program, anaemia was very commonly reported in participants treated with alpelisib, while thrombocytopenia and lymphopenia were reported commonly.
Reproductive toxicity In both rats and dogs, reproductive organ morphology and function was affected in either gender, as evidenced in the repeated-dose toxicity studies, characterized as vaginal diffuse epithelial atrophy, atypical estrous cycle phases and uterine atrophy in rats. In dogs, dose-dependent decreases in prostate weight, correlating with glandular atrophy, were observed. In both rat and rabbit studies to investigate embryofoetal developmental effects, alpelisib induced clear effects to the developing embryo. In rats, when pregnant dams were treated daily on gestation days 6 to 17, at lower dose levels maternal toxicity was evident as body weight loss, concomitant with reduced food consumption, together with reduced mean fetal weights, and increased numbers of litters with fetal malformations and variations. At higher dose levels total fetal loss was found. In rabbits, upon	There are no clinical data available regarding effects of alpelisib on fertility or reproductive organs. Based on repeat dose toxicity studies on animals, alpelisib can cause foetal harm when administered to a pregnant woman and may impair fertility in males and females of reproductive potential. Alpelisib is indicated in men and postmenopausal women.

Key Safety findings (from non-clinical studies)	Relevance to human usage
treatment on gestation days 7 to 20, increased numbers of fetuses or litters with malformations were found. In the male rat fertility study, daily oral gavage administration of alpelisib, induced decrease in prostate and seminal vesicle weights. Male fertility and reproductive performance, including sperm count and motility parameters were unaffected. In the female rat fertility and early embryonal development study, daily oral gavage administration alpelisib, no effect was noted on estrous cycles and animals mated without effect on the numbers pregnant.	
Effects on pancreas including metabolic homeostasis In all species investigated, i.e., mouse, rat and dog, alpelisib interfered with glucose/ insulin homeostasis. In a mouse glucose and insulin tolerance test, alpelisib treatment revealed a clear induction of insulin insensitivity, together with minimal pancreatic cytoplasmic changes of the Langerhans islet cells. In rats, in repeated-dose toxicity study, insulin and glucose fluctuations were seen, associated with fructosamine elevations. In general, those fluctuations were mild up to intolerable dose levels and reversible after treatment cessation. In line with those clinical chemistry findings, in the endocrine pancreas islet cell hyperplasia/hypertrophy or vacuolation indicated increased pancreatic activity. In dogs, insulin and glucose effects were present as well but less prominent, with evidence that impaired glucose uptake was adequately compensated by secondary insulin release to control increased blood glucose concentrations.	Hyperglycaemia is an on-target effect of alpelisib in both non-clinical and clinical studies. Hyperglycaemia events including grade 3/4 events were very commonly reported in clinical studies with alpelisib. Severe complications of hyperglycaemia such as ketoacidosis and hyperglycemic hyperosmolar non-ketotic syndrome were uncommonly reported. In the clinical studies, hyperglycaemia often required dosing modifications and management with antidiabetic drugs. Analysis of data on participants who were permanently discontinued from alpelisib showed reversibility of hyperglycaemia. Hyperglycaemia is an important identified risk.
Gastrointestinal toxicity Particularly in dogs, alpelisib treatment was associated with mostly degenerative or atrophic changes in mucosal tissues, predominantly in the gastrointestinal tract. Microscopically those findings were characterized as degenerative or inflammatory, partially associated with erosions or ulcerations, consistent with inflammation markers observed in clinical pathology. In rats, the effect was less pronounced but also visible.	GI toxicity occurred very commonly in participants treated with alpelisib. Diarrhea, nausea and vomiting are the most common GI adverse reactions; the majority of cases were mild to moderate and were manageable with concomitant medication per local standards of care and dosing modification if indicated. While the majority of cases did not result in clinical consequences, dehydration and acute kidney injury, have been reported during treatment with alpelisib and resolved with appropriate intervention.
Skin and adnexal tissues In Han Wistar rats, in the 4-week repeated-dose study minimal to slight diffuse epidermal atrophy with hair follicle atrophy was noted at ■ mg/kg/day in females and in most	No effect on epidermis (atrophy) in humans has been observed.

Key Safety findings (from non-clinical studies)	Relevance to human usage
prematurely sacrificed animals of both sexes at ■ mg/kg/day. In the 13-week study, in the skin of females at ■ and ■ mg/kg/day, minor adnexal atrophy occurred in several animals, characterised by a reduction in number and activity of hair follicles, which was considered to exceed sectional and cyclic variation. In dogs, in the 4-week study, similarly diffuse epithelial atrophy in the epidermis and/or hair follicles. Additionally, studies were completed in Brown Norway rats to investigate the time course of skin toxicity of alpelisib and to identify biomarkers of the reactions. In these studies, clinically apparent skin lesions were observed in all treated rats. Broadly, the findings were indicative of a T-cell dependent hypersensitivity reaction. Two subsequent studies used the same Brown Norway rat strain to investigate the time course of the observed skin toxicity. Sequential immune activation steps in the periphery and skin preceded clinically apparent skin changes, and CD8⁺ CD163⁺, NK, and CD8⁺ T cells appeared to be key immune cells driving the skin changes indicating the mechanism was a T-cell dependent hypersensitivity reaction.	In clinical trials with alpelisib, rash, mainly in the form of maculopapular rash or generalized rash (unrelated to epidermal atrophy) was very commonly reported. Severe cutaneous reactions such as Stevens-Johnson Syndrome (SJS) and Erythema multiforme (EM), were reported during the development program of alpelisib. All participants recovered upon permanent discontinuation of alpelisib and medical treatment. Severe cutaneous reactions are an important identified risk.
Genotoxicity	
No evidence of genotoxicity in vitro or in vivo.	Based on the current available data, there is no concern relevant to human usage.
Carcinogenicity	
Alpelisib was not carcinogenic in a 2-year carcinogenicity study conducted in rats when administered by daily oral gavage at doses up to 4 mg/kg (approximately 0.2 times the clinical exposure in participants at the highest recommended dose of 300 mg/day based on area under the curve).	Based on the current available data, there is no concern relevant to human usage.
Phototoxicity	
The in vitro 3T3 Neutral Red Uptake phototoxicity profiling assay demonstrated no phototoxic potential for alpelisib	There are no clinical data available regarding phototoxicity effects of alpelisib. Based on the current available data, there is no concern relevant to human usage.
Cardiovascular function	
In patch clamp experiments using HEK cells that heterologously express hERG channels, an IC ₅₀ of ■ μM was determined in a GLP-compliant test. In telemetered dogs, in a GLP-compliant study, no relevant electrophysiological effect was seen up to a single dose of 180 mg/kg alpelisib. Similarly, in electrocardiographic readouts obtained in the 2-week, 4-week and 13-week repeated-dose toxicity studies in dogs, no electrophysiological effect was seen up to dose levels of ■ mg/kg/day. However, in a single dose invasive telemetry study in dogs, at doses of ■ or ■ mg/kg, an increase in	Hypertension was commonly reported as an adverse event in clinical studies with alpelisib. The negligible risk of electrophysiological effect of alpelisib observed in preclinical studies is not expected to have a clinical impact since there were no overt treatment-related effects on electrocardiogram morphology, rhythm or P, PQ, QRS, QT and QTc duration. In the

Key Safety findings (from non-clinical studies)	Relevance to human usage
systolic and diastolic blood pressure was seen, in the absence of any electrophysiological abnormality. As a consequence, a decrease in heart rate was observed, which was considered to be equivocal at the low and mid dose but significant at the high dose. Overall, based on the hERG inhibition seen in vitro but the absence of any in vivo signal, the results of the cardiovascular safety pharmacology studies, indicate a negligible risk of an electrophysiological effect of alpelisib, with evidence of blood pressure effects. Ophthalmologic events Preclinical data showed increased corneal mitosis or reduced epithelial layers in dogs with no ophthalmological findings.	CBYL719C2301 study, hypertension events were generally mild to moderate in intensity and easily manageable with antihypertensive therapy.
Other toxicity-related information or data	No corneal events were reported in participants taking alpelisib. Systematic slit lamp examination at inclusion and after end of treatment were performed in study CBYL719X2101 and did not reveal any clinically significant ophthalmologic anomaly assessed as related to alpelisib. In the CBYL719C2301 study, vision blurred, dry eye, eye pain, lacrimation increased occurred more in the alpelisib arm as compared to the placebo arm, but none of these AEs were grade 3/4 or SAEs. The vast majority of events recovered without any treatment.
In rats, degenerative effects were seen in the incisors and some growth plates of bones, characterized e.g., in the 4-week repeated-dose toxicity study as discolored incisors, thinned dentin/predentin layer, irregular dentin structure due to odontoblast degeneration, necrosis of the pulpa and reduction of the pulpa blood vessel density. In dogs, similar effects were not observed, at comparable or even higher exposure levels. Therefore, these findings were ascribed to a growth-inhibiting activity of alpelisib in the permanently growing teeth of rats, with limited relevance for adult humans.	This growth-inhibiting activity of alpelisib on permanently growing teeth of rats is not expected to have any clinical relevance in adult humans.

2.3 Part II: Module SIII Clinical trial exposure

Alpelisib received the European Commission approval on 27-Jul-2020 for use in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, locally advanced, or metastatic breast cancer with a PIK3CA-mutation after disease progression following endocrine therapy as monotherapy. The approval which restricted the use of Piqray to following monotherapy was due to the small number of participants with prior CDK4/6 inhibitor use enrolled in Phase III Study CBYL719C2301 (SOLAR-1; hereafter referred to as Study C2301), as CDK4/6 inhibitors were not widely available when the study was enrolling. Hence, the number of participants randomized in Study C2301 harboring the PIK3CA-mutation and who had prior treatment with CDK4/6 inhibitors was limited (n=20).

The pivotal Study CBYL719C2303 (Study C2303) was designed to complement the original registration Study C2301 and enrolled only participants with PIK3CA mutation and with prior CDK4/6 inhibitor treatment, thus providing additional efficacy and safety data to better characterize the benefit-risk of alpelisib in this patient population.

The Piqray indication is proposed to be extended for the use of alpelisib in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following an endocrine-based regimen.

Pooled data from Study C2303 primary analysis (DCO 15-Oct-2024) and Study C2301 final analysis (DCO 09-Jun-2023) are included in the RMP analyses to support the characterization and evaluation of the alpelisib safety profile.

Study C2303: This is a Phase III, randomized, double-blind, placebo-controlled study of alpelisib (BYL719) in combination with fulvestrant for men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after AI and a CDK4/6 inhibitor.

Study C2301: This was an international, multicenter, randomized, double-blind, placebo-controlled Phase III trial designed to evaluate the efficacy and safety of alpelisib in combination with fulvestrant vs. fulvestrant alone for the treatment of postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer after disease progression following endocrine based therapy.

[Table 2-5](#) provides an overview of these Phase III clinical studies. Details regarding overall duration of exposure from studies C2303, C2301 and pooled data ([Table 2-6](#)), exposure by age group (pooled safety set, [Table 2-7](#)), exposure by race (pooled safety set, [Table 2-8](#)), exposure by region (pooled safety set, [Table 2-9](#)), and exposure by PIK3CA mutation status in tissue (pooled safety set, [Table 2-10](#)), is provided below.

Table 2-5 Overview of the Phase III clinical studies

Key features	Study C2303	Study C2301
Controlled study	Yes	Yes
Phase	III	III
Study design	Double-blind, randomized, placebo controlled	Double-blind, randomized, placebo controlled
Population	Postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer with a PIK3CA mutation, who progressed on or after aromatase inhibitor and a CDK4/6 inhibitor	Postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer whose disease progressed on or after aromatase inhibitor-based treatment
Dose	300 mg alpelisib q.d. administered orally, together with fulvestrant 500 mg intramuscularly (i.m.) on Days 1 and 15 of Cycle (month) 1, thereafter on Day 1 of every cycle (month)	300 mg alpelisib q.d. administered orally together with fulvestrant 500 mg intramuscularly (i.m.) on Days 1 and 15 of Cycle (month) 1, thereafter on Day 1 of every cycle (month)
Treatment duration	Until disease progression per RECIST v1.1 as per BIRC assessment, unacceptable toxicity that precludes further treatment, or until discontinuation of study treatment due to any other reason	Until disease progression (radiologically documented according to RECIST 1.1) or until discontinuation of study treatment due to any other reason
No. participants (total) No. randomized/treated	188 (188 with PIK3CA mutation)* Alpelisib + Fulvestrant: 94/92 Placebo + Fulvestrant: 94/94	571 (340 with PIK3CA mutation)** Alpelisib + Fulvestrant: 284/284 Placebo + Fulvestrant: 288/287
Completed/Ongoing	Ongoing DCO: 15-Oct-2024	Completed LPLV: 09-Jun-2023

*188 participants were randomized at the time of the data cut-off (15-Oct-2024), but 2 participants never received any study treatment, resulting in 186 participants for the Safety Set.

**572 participants were randomized at the time of the data cut off (09-Jun-2023), but 1 participant never received any study treatment, resulting in 571 participants for the Safety Set, including 340 participants in the PIK3CA mutant cohort.

Only data related to the double-blind period was pooled.

Source: [CBYL719C2303](#), [CBYL719C2301](#), [BYL719C SCS 2025](#)

Table 2-6 SIII.1: Duration of exposure (Safety set)

	C2303		C2301		Pool	
	Alpelisib + Fulv N = 92 n (%)	Placebo + Fulv N = 94 n (%)	Alpelisib + Fulv N = 284 n (%)	Placebo + Fulv N = 287 n (%)	Alpelisib + Fulv N = 376 n (%)	Placebo + Fulv N = 381 n (%)
Duration						
Less than 1 month	4 (4.3)	7 (7.4)	15 (5.3)	9 (3.1)	19 (5.1)	16 (4.2)
at least 1 month	88 (95.7)	87 (92.6)	269 (94.7)	278 (96.9)	357 (94.9)	365 (95.8)
at least 2 months	73 (79.3)	65 (69.1)	246 (86.6)	223 (77.7)	319 (84.8)	288 (75.6)
at least 3 months	67 (72.8)	46 (48.9)	231 (81.3)	192 (66.9)	298 (79.3)	238 (62.5)
at least 4 months	60 (65.2)	39 (41.5)	205 (72.2)	161 (56.1)	265 (70.5)	200 (52.5)
at least 6 months	44 (47.8)	25 (26.6)	168 (59.2)	141 (49.1)	212 (56.4)	166 (43.6)
at least 12 months	18 (19.6)	7 (7.4)	102 (35.9)	85 (29.6)	120 (31.9)	92 (24.1)
at least 18 months	5 (5.4)	2 (2.1)	70 (24.6)	62 (21.6)	75 (19.9)	64 (16.8)
Subject-time (months)					4577.6	3607.2

	C2303		C2301		Pool	
	Alpelisib + Fulv N = 92 n (%)	Placebo + Fulv N = 94 n (%)	Alpelisib + Fulv N = 284 n (%)	Placebo + Fulv N = 287 n (%)	Alpelisib + Fulv N = 376 n (%)	Placebo+ Fulv N = 381 n (%)
Duration						

Pooled participants refer to participants in Study C2303 (excluding data during the crossover period from participants who switched from placebo + fulvestrant to open-label alpelisib + fulvestrant) and in Study C2301 (regardless of mutation status).
Participant-time is the sum of each participant's treatment exposure in months.
Source: RMP version 10.0 Attachment to [Annex 7](#) Table 4-1.1, Table 4-1.7

Table 2-7 SIII.2: Exposure by age group (Pooled Safety set)

Age	Pool			
	Alpelisib + Fulvestrant N=376		Placebo + Fulvestrant N=381	
	Subjects n(%)	Subject- time (months)	Subject n(%)	Subject- time (months)
Total	376 (100)	4577.6	381 (100)	3607.2
< 65 Years	219 (58.2)	2784.4	211 (55.4)	1826.8
>= 65 Years	157 (41.8)	1793.2	170 (44.6)	1780.4
< 75 Years	330 (87.8)	4213.5	332 (87.1)	3019.2
>= 75 Years	46 (12.2)	364.1	49 (12.9)	588.0

Subject-time is the sum of each subject's treatment exposure in months. Subject-time is based on the number of subjects in each category.
Source: RMP version 10.0 Attachment to [Annex 7](#) Table 4-1.2, Table 4-1.3

Table 2-8 SIII.3: Exposure by race (Pooled Safety set)

Race	Pool			
	Alpelisib + Fulvestrant N=376		Placebo + Fulvestrant N=381	
	Subjects n(%)	Subject- time (months)	Subject n(%)	Subject- time (months)
Total	376 (100)	4577.6	381 (100)	3607.2
White	283 (75.3)	3420.7	260 (68.2)	2287.3
Asian	60 (16.0)	808.0	66 (17.3)	800.1
Black or African	2 (0.5)	21.0	6 (1.6)	65.6
American Indian or Alaska Native	1 (0.3)	6.4	4 (1.0)	62.0
Unknown	21 (5.6)	206.2	28 (7.3)	212.7
Other	9 (2.4)	115.2	17 (4.5)	179.6

Subject-time is the sum of each subject's treatment exposure in months. Subject-time is based on the number of subjects in each category.
Source: RMP version 10.0 Attachment to [Annex 7](#) Table 4-1.4

Table 2-9 SIII.4: Exposure by region (Pooled Safety set)

Region	Pool			
	Alpelisib + Fulvestrant N=376		Placebo + Fulvestrant N=381	
	Subjects n(%)	Subject- time (months)	Subject n(%)	Subject- time (months)
Total	376 (100)	4577.6	381 (100)	3607.2
Europe	242 (64.4)	2709.1	238 (62.5)	2022.8
North America	32 (8.5)	393.6	37 (9.7)	261.6
Asia	56 (14.9)	780.6	64 (16.8)	780.8
Latin America	17 (4.5)	232.4	26 (6.8)	403.9
Other	29 (7.7)	462.0	16 (4.2)	138.1

Subject-time is the sum of each subject's treatment exposure in months. Subject-time is based on the number of subjects in each category.

Source: RMP version 10.0 Attachment to [Annex 7](#) Table 4-1.5

Table 2-10 SIII.5: Exposure by PIK3CA mutation status in tissue (Pooled Safety set)

PIK3CA mutation status	Pool			
	Alpelisib + Fulvestrant N=376		Placebo + Fulvestrant N=381	
	Subjects n(%)	Subject- time (months)	Subject n(%)	Subject- time (months)
Total	376 (100)	4577.6	381 (100)	3607.2
Mutant	261 (69.4)	3281.8	265 (69.6)	2315.9
Non-Mutant	115 (30.6)	1295.8	116 (30.4)	1291.3

Subject-time is the sum of each subject's treatment exposure in months. Subject-time is based on the number of subjects in each category.

Source: RMP version 10.0 Attachment to [Annex 7](#) Table 4-1.6

2.4 Part II: Module SIV: Populations not studied in clinical trials

2.4.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 2-11 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for non-inclusion as missing information
Patients with Child Pugh score B or C of	As a standard precaution, participants with chronic liver disease Child Pugh score B or C, active chronic disease,	No	A dedicated study on hepatic impairment (CBYL719A2105) was conducted, and results showed no impact of moderate

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for non-inclusion as missing information
chronic liver disease	severe hepatic impairment were excluded from BYL719C2301 study. Also, fulvestrant is contraindicated in severe hepatic impairment participants and dose adjustment is required in moderate hepatic impairment.		or severe hepatic impairment on the clearance, elimination, or distribution of alpelisib, supporting that no dose adjustment of alpelisib is required in participants with mild, moderate, or severe hepatic impairment.
Patients with severe renal impairment	These participants were excluded from the clinical development program as a standard precaution. In addition, fulvestrant is contraindicated in severe renal impairment participants.	No	Alpelisib was only excreted to a minor extent (~2%) in urine, showing that renal excretion of alpelisib in human is negligible. Based on the current model on the disposition of alpelisib, i.e., negligible renal clearance and metabolism (hydrolysis) by multiple, largely non-hepatic pathways, the likelihood of an impact of any degree of renal impairment on the pharmacokinetics of alpelisib can be considered low. In participants with mild or moderate renal impairment, based on population PK analysis, no dose adjustment was necessary.
Patients with an established diagnosis of diabetes mellitus type I or uncontrolled type II diabetes mellitus	Hyperglycaemia is an on-target effect of alpelisib which was observed during clinical development, leading to exclusion of the population with diabetes mellitus type I or uncontrolled type II diabetes mellitus.	No	Hyperglycaemia is an on-target effect of alpelisib. Therefore, adequate control of pre-existing diabetes mellitus/hyperglycaemia must be obtained before initiation of alpelisib treatment. Hyperglycaemia is an important identified risk of alpelisib.
Patients with currently documented pneumonitis	Non-infectious pneumonitis is a known effect of PI3K/mTOR pathway inhibitors.	No	Non-infectious pneumonitis is a known effect of PI3K/mTOR pathway inhibitors and is a known adverse reaction to alpelisib. Pneumonitis is an important identified risk of alpelisib.
Patients with clinically significant, uncontrolled	Preclinical Cardiac safety studies, in vitro and in vivo, indicated a negligible risk of an electrophysiological	No	Preclinical cardiac safety studies, in vitro and in vivo, indicated a minimal risk of an electrophysiological effect. In the

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for non-inclusion as missing information
heart disease or a recent history of cardiac events	effect. This population was excluded as a precaution.		clinical development program (alpelisib as single agent and in combination with fulvestrant), no cardiac ischemia reactions, no clinically evident arrhythmias attributed to alpelisib and no significant shifts in the cardiac enzyme levels were observed.
Sexually active males with child conceiving potential who do not use effective contraceptive method	This patient population was excluded in anticipation of a possible teratogenic effect of the drug since this is a class effect. More recently, in both rat and rabbit studies alpelisib demonstrated embryofetal developmental and teratogenic effects.	No	Reproductive toxicity is a known effect of alpelisib as identified in rat and rabbit studies. The possibility of alpelisib transmission to a pregnant female or to female partners of child-bearing potential through seminal fluid must be avoided.
Patients with a history of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis	Pancreatitis was identified as a risk based on the results of an overall assessment of the risk of acute pancreatitis, which was performed across the development program, after one case of acute pancreatitis was reported in study BYL719C2301. Patients with history of acute pancreatitis or chronic pancreatitis were excluded from studies, after the assessment.	No	Pancreatitis is a known adverse reaction to alpelisib. It was reported uncommonly in the clinical studies. Lipase increased was reported commonly.
Premenopausal women of child-bearing potential	In both rat and rabbit studies alpelisib demonstrated embryofetal developmental and teratogenic effects.	No	The targeted indication is for postmenopausal women.
Participant with unresolved osteonecrosis of the jaw	Osteonecrosis of the jaw was reported in clinical studies. All participants experiencing osteonecrosis of the jaw were also exposed to prior or concomitant bisphosphonates (e.g., zoledronic acid). Therefore, in participants receiving alpelisib and bisphosphonates, an increased risk of development of	No	Osteonecrosis of the jaw is an important identified risk. Osteonecrosis of the jaw is included as adverse drug reaction in alpelisib SmPC.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for non-inclusion as missing information
	osteonecrosis of the jaw cannot be excluded.		
Participant has a history of severe cutaneous reaction, such as Stevens-Johnson Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN), or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	Skin toxicity is a class-effect adverse event observed with PI3Ki agents. Although, less commonly reported, severe cutaneous reaction is clinically important adverse reaction of alpelisib. Hence, this patient population was excluded.	No	Severe cutaneous reaction is an important identified risk of alpelisib.

2.4.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 2-12 SIV.2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	Patients with mild and moderate hepatic impairment were included in the clinical development program (patients with chronic liver disease Child Pugh score B or C, active chronic disease, severe hepatic impairment were excluded).
Patients with hepatic impairment	
Patients with renal impairment	Patients with mild and moderate renal impairment were included in the clinical development program. Patients with severe renal impairment were not included in the clinical development program.
Patients with cardiovascular impairment	

Type of special population	Exposure
	Limited exposure in patients with cardiovascular impairment.
Immunocompromised patients	Not included in the clinical development program.
Population with relevant different ethnic origin	Population from different race and ethnic origins were included in the clinical development program (for race please refer Table 2-8).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Elderly patients (≥ 65 years)	Included in the clinical development program (Table 2-7).
Paediatric patients (<18 years of age)	Not included in the clinical development program.
Male patients	Included in the clinical development program.

2.5 Part II: Module SV: Post-authorization experience

2.5.1 Part II Module SV.1. Post-authorization exposure

2.5.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in number of tablets of active substance sold during the reporting interval.

To estimate exposure, the following assumptions are used:

- A patient always uses two tablets of 150 mg for a standard daily dose of 300 mg.
- Any sold tablet of 50 mg is used together with a 200 mg tablet for a daily dose of 250 mg.
- Any leftover tablet of 200 mg is used alone for a daily dose of 200 mg.

For any tablets not covered by the above assumptions, the defined daily dose of 300 mg is used.

The defined daily dose of 300 mg will be considered for calculation of patient-treatment-years (PTY).

2.5.1.2 Part II Module SV.1.2. Exposure

The estimated exposure is provided in the [Table 2-13](#) below.

Table 2-13 Cumulative exposure from marketing experience

	EEA (PTY)	USA and Canada (PTY)	ROW (PTY)	Total
Piqray FCT 150 mg	1600	4926	3454	9980
Piqray FCT 200 mg	260	840	283	1383
Piqray FCT 250 mg	609	1091	687	2387
Total	2469	6857	4424	13750

EEA: European Economic Area; FCT: Film-Coated Tablet; PTY: Patient-Treatment-Year; ROW: Rest of the World; USA: United States of America. This table includes cumulative data obtained from IBD (24-May-2019) to May-2025.

Source of data: [PSUR](#) (24-May-2024 to 23-May-2025)

2.6 Part II: Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes

A possible risk of misuse or dependence is not anticipated based on the mechanism of action and lack of psychopharmacologic effects of alpelisib. Based on non-clinical studies, it is clear that alpelisib and its metabolite BZG791 are unlikely to cross the blood-brain-barrier in human. While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged from clinical trials that would suggest a potential for abuse or dependence. Given the pattern of side effects and given the absence of effects that could lead to dependence, there is no known potential for abuse of alpelisib.

2.7 Part II: Module SVII: Identified and potential risks

2.7.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

2.7.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

The list of risks and adverse reactions that were not considered important for inclusion in the list of safety concerns in the RMP and the reasons for non-inclusion are provided below.

Table 2-14 Risks not considered important for inclusion in the list of safety concerns

Risk	Reason for not being an important risk
GI toxicity (Nausea, Diarrhea, Vomiting)	In preclinical toxicology studies, animals treated at the Maximal Tolerated Dose (MTD) of alpelisib experienced GI toxicity, mainly consisting of vomiting and diarrhea. Clinical experience shows that nausea, vomiting and diarrhea are very common AEs when alpelisib is administered either as a single agent or in combination. The vast majority of cases in the clinical program, including study CBYL719C2301, were mild to moderate and were effectively managed with dose adjustments and standard of care; Grade 3 events occurred in 8.8% vs 1.0% of subjects treated with alpelisib + fulvestrant vs placebo + fulvestrant (by PT: diarrhea 6.7% vs 0.3%; nausea 2.5% vs 0.3%; vomiting 0.7% vs 0.3%). No grade 4 diarrhea, nausea, or vomiting occurred in either treatment group. In 2 instances, SAE acute kidney injury (pre-renal failure linked to dehydration due to diarrhea) occurred, and all events recovered completely following alpelisib interruption or reduction and treatment when indicated. In addition, GI toxicity is a well-known risk associated with oncologic medications, and its management is part of common medical practice.

Risk	Reason for not being an important risk
Hypertension	Therefore, this risk is considered to have low impact on individual patients and to be manageable. Preclinical data showed an increase in systolic blood pressure and diastolic blood pressure, observed in a dog telemetry study. Cases of hypertension reported in clinical trials with alpelisib were generally moderate in intensity, without complications and recovered with adequate antihypertensive treatment. In study CBYL719C2301, blood pressure values collected through the study were not supportive of relevant blood pressure alterations. A systolic BP ≥ 180 mmHg with ≥ 20 mmHg increase from baseline was observed in 1.4% vs 1.8% (alpelisib vs placebo), and diastolic BP ≥ 105 mmHg with ≥ 15 mmHg increase from baseline was observed in 1.4% vs 2.5%. In this study, hypertension was reported as an AE in 8.1% vs 4.9% of subjects in alpelisib + fulvestrant vs. placebo + fulvestrant. Events were mild to moderate in intensity and manageable with antihypertensive therapy. One Grade 4 case of worsening of pre-existing Grade 2 hypertension was reported, which recovered completely upon drug interruption and medical treatment [BYL719 SCS]. This risk is considered to have low impact on individual patients and to be manageable.
Ophthalmologic events	Preclinical data showed increased corneal mitosis or reduced epithelial layers in dogs with no ophthalmological findings. Systematic slit lamp examination performed in study CBYL719X2101 did not reveal any clinically significant ophthalmologic anomaly. Cases of ophthalmologic related events reported during clinical trials with alpelisib were generally mild in intensity and did not result in disability or incapacity or the need of dose reduction and interruption. There were no noteworthy serious adverse events. In the CBYL719C2301 study, reported adverse reactions were mainly blurred vision and dry eye. No grade 4 events or SAEs were reported. One Grade 3 event was reported (blurred vision which recovered completely after drug discontinuation). This risk is considered to have a low impact on individual patients.
Haematological toxicity	Preclinical data showed affected hematopoiesis and lymphopoiesis in both rats and dogs. In the CBYL719C2301 study, hematology abnormalities that were more frequent in the alpelisib plus fulvestrant vs the placebo plus fulvestrant group were ($\geq 10\%$ difference, all grades) decreased hemoglobin (41.5% vs 28.9%) and decreased lymphocytes (51.8% vs 40.4%). Decreased neutrophil counts were comparable between alpelisib and placebo groups. Most of these abnormalities were grade 1 or grade 2 [BYL719 SCS]. In total, 6 SAEs were reported (5 anaemia and 1 febrile neutropenia). Five of these events recovered completely. One event of anaemia was an accidental finding in a subject who experienced hip fracture and died due to cardiac arrest on the same day. Overall, hematology-related events were manageable and resolved with adequate therapy. The risk is considered to have a low impact on individual subjects.
Rash	Rash was very commonly reported as rash, maculo-papular rash or generalized rash. Rash was accompanied by pruritus and dry skin, in some subjects treated with alpelisib. In study CBYL719C2301, the rash AEs were mild to moderate in intensity with no life-threatening or grade 4 events reported. The majority of events recovered with dose adjustments and/or rash medication. Permanent discontinuation due to rash was infrequent (12 subjects). Ten subjects had SAEs of rash all of which recovered completely [BYL719 SCS].

Risk	Reason for not being an important risk
	In the subgroup of subjects who received prophylactic anti-rash medications, rash AEs were less frequent than in the overall population, and the events were less severe. The risk is considered to have a low impact on individual subjects.
Pancreatitis	In non-clinical studies with alpelisib, endocrine pancreas was identified as a secondary target organ due to changes in peripheral glucose uptake. However, there is no evidence that the exocrine pancreas is a primary toxicity target organ of alpelisib. Elevations of pancreatic enzymes were frequently observed in the clinical studies but were of limited clinical consequence. In study CBYL719C2301, elevated lipase values (laboratory data) were more frequent in the alpelisib plus fulvestrant group (41.9%) vs the placebo plus fulvestrant group (25.4%), primary due to grade 1 and grade 2 elevations occurring on alpelisib. No difference between the treatment groups was observed for grade 3 or 4 lipase elevations based on laboratory data. One case of acute pancreatitis was reported, and the subject fully recovered with standard of care. Alpelisib treatment was discontinued [BYL719 SCS].
Hypersensitivity	Evidence for an involvement of the PI3K signalling pathway in immunological functions has been reported (Browne 2009 , Lopez-Fauqued 2010). Various members of the PI3K family are activated in the immune system according to cell and/or receptor type. Cases of hypersensitivity reactions suspected to be related to alpelisib by the Investigators were reported across the alpelisib clinical trial program, including life-threatening events of anaphylactic reactions. In all these cases, alpelisib was permanently discontinued and the subjects recovered. The risk was well characterized in alpelisib clinical trials; hence, no further characterization is planned, and the risk will be followed up via routine pharmacovigilance. No additional risk minimisation measures are planned. Clinicians are well aware of this medical risk and its management as part of standard clinical practice. Therefore, hypersensitivity is not considered an important risk.

2.7.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 2-15 Important identified risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Hyperglycaemia	Hyperglycaemia is a reversible, on-target effect of PI3K inhibition, which has been observed both in preclinical and clinical studies with alpelisib. Life-threatening consequences of hyperglycaemia, such as diabetic ketoacidosis have been reported. Hyperglycaemia affects a large proportion of subjects and can result in severe outcomes if not managed adequately; hence, it is considered an important identified risk.
Pneumonitis	Pneumonitis is a known class effect of PI3K/mTOR pathway inhibitors and of PI3K inhibitors. Lung toxicity was not observed in the pre-clinical studies of alpelisib. In the clinical development program, cases of pneumonitis, acute interstitial pneumonitis, and interstitial lung disease were reported with alpelisib. Four cases had a fatal outcome, and in all 4 cases, alpelisib was administered as combination therapy with other drugs such as cetuximab, MEK162 (binimetinib), LJM716, and everolimus. Of these 4 fatal cases, one case each was reported in a subject with breast cancer, squamous cell carcinoma of head and neck, metastatic pancreatic neuroendocrine tumor and

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	squamous cell carcinoma of esophagus. In the fatal case in breast cancer, event causality was confounded by concomitant administration of MEK162 (binimetinib). No fatal cases were reported in study CBYL719C2301. Pneumonitis is considered as a risk associated with the use of alpelisib, which may result in severe outcomes with a significant impact on individual subjects, and alpelisib should be permanently discontinued in all patients with confirmed pneumonitis; hence, it is considered an important identified risk.
Severe cutaneous reactions	Severe cutaneous reactions such as SJS, EM, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in subjects treated with alpelisib. Severe cutaneous reactions can be life-threatening. It is critical to inform physicians and raise awareness of signs and symptoms so discontinuation of alpelisib and early medical treatment is initiated; hence are considered an important identified risk.
Osteonecrosis of the jaw	In study CBYL719C2301, osteonecrosis of the jaw was reported in 4.6% of subjects (13/284) in the alpelisib plus fulvestrant group compared to 1.4% of subjects (4/287) in the placebo plus fulvestrant arm. Majority of the events in alpelisib arm were Grade 1-2 (6/10). No grade 4 events were reported [BYL719 SCS]. Osteonecrosis of the jaw was reported as an SAE in five subjects (1.8%) in the alpelisib plus fulvestrant group (including four subjects (1.4%) with a grade 3 event), and one subject (0.3%) in the placebo plus fulvestrant group. In 4/5 subjects, alpelisib dose was not changed. All the SAEs were resolved/resolving, at the time of data cut-off [BYL719 SCS]. All subjects experiencing osteonecrosis of the jaw were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid) and there was no imbalance in the administration of bisphosphonates between the groups. Thus, in subjects receiving alpelisib and bisphosphonates, an increased risk of development of osteonecrosis of the jaw cannot be excluded [BYL719 SCS].

Table 2-16 Important potential risks

There are no important potential risks for alpelisib.

Table 2-17 Missing information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Safety with long-term use	The number of subjects in alpelisib clinical studies who received the medicine for ≥ 12 months is limited and the safety of alpelisib beyond this duration is not known.

2.7.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There are no changes to the safety concerns in this RMP update; however, the TFU checklist (a routine PV activity beyond ADR reporting and signal detection) for ONJ was deleted and the rationale is provided below.

The TFU checklist for ONJ was initially implemented to support further characterization of this important identified risk for Piqrax (alpelisib) and is removed in this RMP update subsequent to the comment from the PRAC captured in the Vioice (alpelisib) CHMP Day 180 List of

Outstanding Issues (EMA/CHMP/49420/2026, dated 27-Feb-2026, related to the procedure EMEA/H/C/006539/0000) to assess the possibility to discontinue the checklist for Piqray after 6 years in use in the EU. After several years of post-marketing experience and cumulative periodic safety reporting, MAH is of the opinion that the continued use of the TFU checklist is no longer warranted. Since the first Piqray PSUR (22-Jan-2021; reporting period 24-May-2019 to 23-Nov-2020), no new safety signals, clinically relevant trends, nor changes in the severity, frequency, nor clinical presentation of ONJ have emerged. No life-threatening or fatal events have been reported and out of the cases where outcome was reported, outcome was described as recovered/recovering. Subsequent PSURs continued to confirm that the risk is well-characterized. ONJ will remain classified as an important identified risk in the Piqray RMP, ensuring continued systematic monitoring through routine pharmacovigilance, including case follow-up as per standard procedures and ongoing assessment in future PSURs.

2.7.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

2.7.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

2.7.3.1.1 Important Identified Risk: Hyperglycaemia

Table 2-18 Clinical trial data of hyperglycaemia (Safety set)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	67 (72.8) [62.6-81.6]	16 (17.0) [10.1-26.2]	191 (67.3) [61.5-72.7]	29 (10.1) [6.9- 14.2]	258 (68.6) [63.7-73.3]	45 (11.8) [8.7-15.5]
Maximum grade						
Grade 2 AEs	20 (21.7)	1 (1.1)	45 (15.8)	6 (2.1)	65 (17.3)	7 (1.8)
Grade 3 AEs	28 (30.4)	0	98 (34.5)	2 (0.7)	126 (33.5)	2 (0.5)
Grade 4 AEs	2 (2.2)	0	13 (4.6)	1 (0.3)	15 (4.0)	1 (0.3)
Treatment-related AEs	67 (72.8)	16 (17.0)	179 (63.0)	17 (5.9)	246 (65.4)	33 (8.7)
SAEs	4 (4.3)	0	31 (10.9)	0	35 (9.3)	0
Action taken						
Permanently discontinued	3 (3.3)	0	20 (7.0)	0	23 (6.1)	0
Dose adjusted	19 (20.7)	0	83 (29.2)	2 (0.7)	102 (27.1)	2 (0.5)
Temporarily interrupted	29 (31.5)	0	76 (26.8)	1 (0.3)	105 (27.9)	1 (0.3)
None/NA/Unknown	66 (71.7)	16 (17.0)	170 (59.9)	28 (9.8)	236 (62.8)	44 (11.5)
Medication or therapy taken	57 (62.0)	7 (7.4)	165 (58.1)	13 (4.5)	222 (59.0)	20 (5.2)
AE outcome						
Recovered/resolved	53 (57.6)	10 (10.6)	174 (61.3)	23 (8.0)	227 (60.4)	33 (8.7)
Recovering/resolving	6 (6.5)	2 (2.1)	9 (3.2)	1 (0.3)	15 (4.0)	3 (0.8)
Not recovered/not resolved	16 (17.4)	4 (4.3)	39 (13.7)	6 (2.1)	55 (14.6)	10 (2.6)
Recovered/resolved with sequelae	1 (1.1)	0	6 (2.1)	1 (0.3)	7 (1.9)	1 (0.3)
Unknown	0	0	3 (1.1)	1 (0.3)	3 (0.8)	1 (0.3)

Numbers (n) represent counts of participants.

MedDRA version 27.1, CTCAE version 4.03

Source: [BYL719C SCS 2025](#)-Section 1.1.3.2, RMP version 10.0 Attachment to [Annex 7](#) Table 5-1

Table 2-19 Characterization of hyperglycaemia

Hyperglycaemia	Details
Potential mechanisms	Hyperglycaemia is a reversible, on-target effect of PI3K inhibition. Preclinical study data indicate that alpelisib has the potential to interfere with the glucose and insulin homeostasis. The mechanism of hyperglycaemia is suggested to be the result of insulin resistance.

Hyperglycaemia	Details
Evidence source(s) and strength of evidence	Hyperglycaemia has been observed both in preclinical and clinical studies with alpelisib. Cases of severe hyperglycaemia, in some cases associated with Hyperglycaemic Hyperosmolar Non-Ketotic Syndrome (HHNKS) or ketoacidosis have been reported in post-marketing setting.
Characterization of the risk	In the pooled safety set, - Hyperglycaemia was frequently observed with alpelisib plus fulvestrant treatment. In the alpelisib + fulvestrant group, hyperglycaemia related events were reported in 68.6% of participants, the maximum severity was grade 3 in 33.5% and grade 4 in 4.0%. Severe complications of hyperglycaemia, such as ketoacidosis, were reported rarely (3 cases, all resolved) (Table 2-18), (RMP version 10.0 Attachment to Annex 7 Table 8-1.1). - Hyperglycaemia developed typically early (median time to first occurrence of grade ≥ 2 hyperglycaemia was 14.5 days (range: 2 days to 1012 days) during the treatment and was generally manageable with oral anti-diabetic agents (primarily metformin) and alpelisib dosing modification as needed; and 6.1% participants discontinued alpelisib due to hyperglycaemia (Table 2-18), (RMP version 10.0 Attachment to Annex 7 Table 8-3.1). - The median duration of a grade ≥ 2 and grade ≥ 3 hyperglycaemia was 15.0 days, indicating that with appropriate intervention, hyperglycaemia is manageable. Hyperglycaemia is manageable with oral antidiabetic medication (primarily metformin). Most participants in the alpelisib + fulvestrant group had recovered (60.4%). There were no fatal cases (Table 2-18), (RMP version 10.0 Attachment to Annex 7 Table 10-6.2, Table 10-6.3). - In the alpelisib + fulvestrant group, of the 258 participants for whom a hyperglycaemia AEs were reported, anti-diabetic medication was given to 204 participants. Among these 192 participants, the most frequent medication used was metformin (117 participants, 31.1%). Other, medications included metformin hydrochloride (22.6%), metformin hydrochloride with sitagliptin (0.5%), dapagliflozin propanediol monohydrate (0.3%) and others (Table 2-18), (RMP version 10.0 Attachment to Annex 7 Table 5-1.2, Table 5-1.3). - Participants with glucose metabolism abnormalities at baseline were more prone to develop hyperglycaemia with alpelisib treatment. Increases in FPG and Glycated Haemoglobin (HbA1c) were more pronounced in participants who were diabetic or pre-diabetic at baseline, compared to participants with normal glucose tolerance at baseline. In pre-diabetic and diabetic participants, mean FPG levels peaked within the first 2 weeks of treatment, and subsided thereafter towards baseline levels (RMP version 10.0 Attachment to Annex 7 Figure 1-2.3). - Hyperglycaemia was generally reversible upon discontinuation of alpelisib treatment. - No on-treatment deaths due to hyperglycaemia related AEs were reported in both the treatment groups. - The results were generally similar in the cohort with PIK3CA mutation participants.

Hyperglycaemia	Details
	Severe hyperglycaemia, in some cases associated with HHNKS or ketoacidosis, has been observed in participants treated with alpelisib. Some cases of ketoacidosis with fatal outcome have been reported in the post-marketing setting. HHNKS has been added as a post-marketing ADR.
Risk factors and risk groups	Patients with diabetes mellitus or pre-diabetic conditions such as impaired fasting glucose and other risk factors such as BMI ≥ 30 and age ≥ 75 . Patients with diabetes mellitus type I were not included in the clinical program.
Preventability	Warnings and precautions in the SmPC include appropriate language to inform patients of early signs and symptoms of hyperglycaemia and the need for close monitoring of glucose levels/Fasting glucose (FG) and/or HbA1c, especially in patients carrying risk factors, who are more prone to develop severe reactions. Awareness of serious complications (e.g., ketoacidosis) and how to manage them is also mentioned. Dosing modifications or discontinuation and consultation with diabetologist are aiming to prevent severe outcomes.
Impact on the benefit-risk balance of the product	The benefit-risk balance of alpelisib with respect to hyperglycaemia remains positive in the target population of advanced metastatic breast cancer. Life-threatening consequences of hyperglycaemia, such as diabetic ketoacidosis have been reported infrequently. The impact on individual patients can be high mainly due to potentially life-threatening complications of hyperglycaemia, such as ketoacidosis and hyperglycemic hyperosmolar non-ketotic syndrome. Adequate monitoring, medical management of hyperglycaemia, alpelisib dosing modifications, and dietary recommendations are usually sufficient to prevent acute complication of hyperglycaemia during treatment with alpelisib.
Public health impact	The impact on public health is expected to be low. Hyperglycaemia can be managed with regular monitoring, dose adjustments and treatment where indicated.

2.7.3.1.2 Important Identified Risk: Pneumonitis

Table 2-20 Clinical trial data of pneumonitis (Safety set)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	1 (1.1) [0.0- 5.9]	3 (3.2) [0.7- 9.0]	5 (1.8) [0.6- 4.1]	1 (0.3) [0.0- 1.9]	6 (1.6) [0.6- 3.4]	4 (1.0) [0.3- 2.7]
Maximum grade						
Grade 2 AEs	0	0	3 (1.1)	0	3 (0.8)	0
Grade 3 AEs	1 (1.1)	3 (3.2)	1 (0.4)	1 (0.3)	2 (0.5)	4 (1.0)
Treatment-related AEs	1 (1.1)	0	4 (1.4)	1 (0.3)	5 (1.3)	1 (0.3)
SAEs	1 (1.1)	2 (2.1)	3 (1.1)	1 (0.3)	4 (1.1)	3 (0.8)
Action taken						
Permanently discontinued	1 (1.1)	0	4 (1.4)	1 (0.3)	5 (1.3)	1 (0.3)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Temporarily interrupted	1 (1.1)	1 (1.1)	0	0	1 (0.3)	1 (0.3)
None/NA/Unknown	1 (1.1)	2 (2.1)	1 (0.4)	0	2 (0.5)	2 (0.5)
Medication or therapy taken	1 (1.1)	1 (1.1)	4 (1.4)	1 (0.3)	5 (1.3)	2 (0.5)
AE outcome						
Recovered/resolved	1 (1.1)	1 (1.1)	5 (1.8)	0	6 (1.6)	1 (0.3)
Not recovered/not resolved	0	2 (2.1)	0	1 (0.3)	0	3 (0.8)

Numbers (n) represent counts of participants.

MedDRA version 27.1, CTCAE version 4.03

Source: [BYL719C SCS 2025](#)-Section 1.1.3.2, RMP version 10.0 Attachment to [Annex 7](#) Table 5-3

Table 2-21 Characterization of pneumonitis

Pneumonitis	Details
Potential mechanisms	Pneumonitis is a known toxicity of PI3K/mTOR pathway inhibitors.
Evidence source(s) and strength of evidence	Serious cases of pneumonitis/acute interstitial pneumonitis/ interstitial lung disease have been reported with alpelisib across all studies.
Characterization of the risk	In pooled safety set, pneumonitis AEs occurred in 6 (1.6%) of participants in the alpelisib + fulvestrant group (the PTs were pneumonitis in 5 participants, interstitial lung disease in 1 participant). None of these events had a fatal outcome. Of the 6 cases, 5 cases (4 pneumonitis, 1 interstitial lung disease) were suspected to be related to study treatment and all 6 participants recovered (Table 2-20), (RMP version 10.0 Attachment to Annex 7 Table 8-1.3).
Risk factors and risk groups	There are no identified risk factors for the occurrence of pneumonitis in alpelisib-treated patients.
Preventability	Observation of newly occurring or worsening of respiratory signs and symptoms could signal the occurrence of pneumonitis. Alpelisib should be interrupted if patients have new or worsening respiratory symptoms or are suspected to have developed pneumonitis. If drug related pneumonitis is confirmed, alpelisib should be permanently discontinued. Warnings and precautions section of SmPC contains comprehensive language to minimize the risk of severe outcomes related to pneumonitis.
Impact on the benefit-risk balance of the product	The benefit-risk balance with respect to pneumonitis remains positive in the target population of advanced metastatic breast cancer. Pneumonitis is considered as a risk associated with the use of alpelisib, which may result in severe outcomes with a significant impact on individual patients.
Public health impact	The impact on public health is expected to be low. Events are generally manageable with treatment interruption and/or discontinuation and medical management.

2.7.3.1.3 Important Identified Risk: Severe cutaneous reactions

Table 2-22 Clinical trial data of severe cutaneous reactions (Safety set)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	1 (1.1) [0.0- 5.9]	0 [0.0- 3.8]	4 (1.4) [0.4- 3.6]	0 [0.0- 1.3]	5 (1.3) [0.4- 3.1]	0 [0.0- 1.0]
Maximum grade						
Grade 2 AEs	0	0	1 (0.4)	0	1 (0.3)	0
Grade 3 AEs	0	0	3 (1.1)	0	3 (0.8)	0
Grade 4 AEs	1 (1.1)	0	0	0	1 (0.3)	0
Treatment-related AEs	1 (1.1)	0	4 (1.4)	0	5 (1.3)	0
SAEs	1 (1.1)	0	4 (1.4)	0	5 (1.3)	0
Action taken						
Permanently discontinued	1 (1.1)	0	3 (1.1)	0	3 (0.8)	0
Dose adjusted	0	0	2 (0.7)	0	2 (0.5)	0
Temporarily interrupted	1 (1.1)	0	2 (0.7)	0	3 (0.8)	0
None/NA/Unknown	0	0	2 (0.7)	0	2 (0.5)	0
Medication or therapy taken	1 (1.1)	0	4 (1.4)	0	5 (1.3)	0
AE outcome						
Recovered/resolved	1 (1.1)	0	4 (1.4)	0	5 (1.3)	0

Numbers (n) represent counts of participants.

MedDRA version 27.1, CTCAE version 4.03

Source: [BYL719C SCS 2025](#)-Section 1.1.3.2, RMP version 10.0 Attachment to [Annex 7](#) Table 5-7

Table 2-23 Characterization of severe cutaneous reactions

Severe cutaneous reactions	Details
Potential mechanisms	Skin and subcutaneous tissue disorders are a known effect of PI3K/mTOR pathway inhibitors, including severe cutaneous reactions such as SJS, EM, Toxic Epidermal Necrolysis (TEN) and DRESS.
Evidence source(s) and strength of evidence	Severe cutaneous adverse reactions such as SJS, EM, and DRESS have been reported in clinical studies and in post-marketing setting.
Characterization of the risk	In the pooled safety set, severe cutaneous reaction was reported for 5 (1.3%) participants in the alpelisib + fulvestrant group. The events reported were erythema multiforme (n=3) and Stevens-Johnson syndrome (n=2). All cases were considered related to study treatment, and all resolved without sequelae (Table 2-22), (RMP version 10.0 Attachment to Annex 7 Table 8-1.7).
Risk factors and risk groups	There are no identified risk factors for the occurrence of severe cutaneous reactions in alpelisib treated patients.
Preventability	Alpelisib treatment should not be initiated in patients with history of SJS, EM, TEN or DRESS.

Severe cutaneous reactions	Details
	Adherence to the recommendations provided in the warnings and precautions section of SmPC should ensure the early detection and appropriate management of clinically relevant severe cutaneous reaction. Awareness of risk and its signs and symptoms, discontinuation of treatment in case of suspected severe cutaneous reaction, appropriate treatment and no rechallenge are the main measures to prevent this risk. Dermatologist consultation is recommended.
Impact on the benefit-risk balance of the product	The benefit-risk balance with respect to severe cutaneous reaction remains positive. Severe cutaneous reactions can be life-threatening and with significant impact on individual patients.
Public health impact	The impact on public health is expected to be low. Events are generally manageable with treatment interruption and/or discontinuation and medical management.

2.7.3.1.4 Important Identified Risk: Osteonecrosis of the jaw

Table 2-24 Clinical trial data of osteonecrosis of the jaw (Safety set)

	C2303		C2301		Pool	
	Alpelisib + Fulv N=92 n (%) 95% CI	Placebo + Fulv N=94 n (%) 95% CI	Alpelisib + Fulv N=284 n (%) 95% CI	Placebo + Fulv N=287 n (%) 95% CI	Alpelisib + Fulv N=376 n (%) 95% CI	Placebo + Fulv N=381 n (%) 95% CI
Number of participants with at least one event	2 (2.2) [0.3- 7.6]	0 [0.0- 3.8]	17 (6.0) [3.5- 9.4]	5 (1.7) [0.6- 4.0]	19 (5.1) [3.1- 7.8]	5 (1.3) [0.4- 3.0]
Maximum grade						
Grade 2 AEs	1 (1.1)	0	9 (3.2)	2 (0.7)	10 (2.7)	2 (0.5)
Grade 3 AEs	1 (1.1)	0	8 (2.8)	3 (1.0)	9 (2.4)	3 (0.8)
Treatment-related AEs	0	0	2 (0.7)	0	2 (0.5)	0
SAEs	1 (1.1)	0	9 (3.2)	2 (0.7)	10 (2.7)	2 (0.5)
Action taken						
Permanently discontinued	0	0	1 (0.4)	0	1 (0.3)	0
Dose adjusted	0	0	0	1 (0.3)	0	1 (0.3)
Temporarily interrupted	0	0	5 (1.8)	0	5 (1.3)	0
None/NA/Unknown	2 (2.2)	0	16 (5.6)	4 (1.4)	18 (4.8)	4 (1.0)
Medication or therapy taken	1 (1.1)	0	15 (5.3)	5 (1.7)	16 (4.3)	5 (1.3)
AE outcome						
Recovered/resolved	1 (1.1)	0	10 (3.5)	3 (1.0)	11 (2.9)	3 (0.8)
Recovering/resolving	0	0	1 (0.4)	0	1 (0.3)	0
Not recovered/not resolved	1 (1.1)	0	9 (3.2)	2 (0.7)	10 (2.7)	2 (0.5)

Numbers (n) represent counts of participants.

MedDRA version 27.1, CTCAE version 4.03

Source: [BYL719C SCS 2025](#)-Section 1.1.3.2, RMP version 10.0 Attachment to [Annex 7](#) Table 5-8

Table 2-25 Characterization of osteonecrosis of the jaw

Osteonecrosis of the jaw	Details
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	Osteonecrosis of the jaw was reported in clinical studies, in different populations and combination treatment.
Characterization of the risk:	In the pooled safety set, 5.1% of participants had osteonecrosis of the jaw in the alpelisib + fulvestrant group versus 1.3% in the placebo + fulvestrant group. All participants with osteonecrosis of the jaw took bisphosphonates and/or denosumab before or concurrently during study treatment. Most of the events were grade 2 or grade 3 with no grade 4 events. The event was resolved for approximately half of participants (2.9% participants in the alpelisib + fulvestrant group and 0.8% in the placebo + fulvestrant group). The outcome was not recovered or not resolved in 2.7% of participants. There were no fatal or life-threatening events (Table 2-24).
Risk factors and risk groups	Patients receiving bisphosphonates and/or denosumab before or during treatment with alpelisib are at a higher risk of developing osteonecrosis of the jaw.
Preventability	- Caution should be exercised when alpelisib and bisphosphonates or RANK-ligand inhibitors (e.g., denosumab) are used either simultaneously or sequentially. - Alpelisib treatment should not be initiated in patients with active osteonecrosis of the jaw from previous or concurrent treatment with bisphosphonates/ denosumab.
Impact on the benefit-risk balance of the product	The benefit-risk balance with respect to osteonecrosis of the jaw remains positive in the target population of advanced metastatic breast cancer. The impact on individual patients might be high; however, taking into account the life-threatening nature of the indication, the impact of osteonecrosis of the jaw is acceptable in the patient population being treated with alpelisib. In addition, osteonecrosis of the jaw is a well-known pathological condition in oncology, derived from the use of medication for bone metastases (bisphosphonates (BPs) and denosumab). Appropriate management according to established medical guidelines for osteonecrosis of the jaw (e.g. prevention, prompt treatment) are expected to minimize the impact on individual patients.
Public health impact	The impact on public health is expected to be low.

2.7.3.2 Part II Module SVII.3.2. Presentation of the missing information

Table 2-26 Characterization of safety with long-term use

Safety with long-term use	Details
Evidence source	The number of patients in alpelisib clinical studies who received the medicine for ≥ 12 months is limited. As of 23-May-2025, the PSUR DLP included 219 cases reported from patients receiving treatment for a time duration of one year or longer. The events from these cases were compared with events reported in cases

Safety with long-term use	Details
	where the patient received the drug for a duration of less than one year (<365 days). No trend/pattern of AEs was reported upon review of the events reported in long-term cases (PSUR DLP 23-May-2025).
Anticipated risk/consequence of the missing information	Alpelisib's long-term safety is limited due to the participants' poor prognosis and relatively short survival (Largillier et al 2008). The number of participants in alpelisib clinical studies who received the medicine for ≥ 12 months is limited. The review of safety profile of alpelisib in cases with treatment exceeding ≥ 12 months did not uncover any unexpected differences with compared to events reported in cases with treatment exposure < 12 months. The evaluation of the information received cumulatively for long-term use of alpelisib did not suggest any change of the characterization of the missing information "Safety with long-term use" (PSUR DLP 23-May-2025)

2.8 Part II: Module SVIII: Summary of the safety concerns

Table 2-27 Part II SVIII.1: Summary of safety concerns

Important identified risks	Hyperglycaemia Pneumonitis Severe cutaneous reactions Osteonecrosis of the jaw
Important potential risks	None
Missing information	Safety with long-term use

3 Part III: Pharmacovigilance plan (including post-authorization safety studies)

3.1 Part III.1. Routine pharmacovigilance activities

3.1.1 Routine pharmacovigilance activities beyond ADR reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

- Hyperglycaemia

This checklist is provided in [Annex 4](#) of the RMP.

Other forms of routine pharmacovigilance activities

There are no other forms of routine pharmacovigilance activities.

3.2 Part III.2. Additional pharmacovigilance activities

There are no additional pharmacovigilance activities ongoing.

3.3 Part III.3 Summary Table of additional pharmacovigilance activities

There are no additional pharmacovigilance activities that are planned or ongoing.

4 Part IV: Plans for post-authorization efficacy studies

There are no planned or ongoing post-authorization efficacy studies.

5 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

5.1 Part V.1. Routine risk minimization measures

Table 5-1 Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Hyperglycaemia	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 4.9 Overdose

Safety concern	Routine risk minimization activities
	PL Section 2 What you need to know before you take Piqray - Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.2 provides guidance on management of hyperglycaemia through alpelisib dose-modification and additional treatment SmPC Section 4.4 provides guidance on precautionary measures, monitoring and handling of hyperglycaemia including the following: • The need to optimize blood glucose before initiating treatment with alpelisib. • The need for regular, closer monitoring/ self-monitoring of fasting glucose levels frequently after initiation of alpelisib treatment, more frequently in the first 4 weeks and especially within the first 2 weeks, according to the instructions of a healthcare professional; and monitoring HbA1c after 4 weeks of treatment and every 3 months. • The recommendation for diabetic or pre-diabetic patients, with a BMI ≥ 30 or age ≥ 75 years (who may be more likely to develop severe reactions) to monitor /self-monitor fasting glucose daily for the first 2 weeks of treatment. Then continue to monitor fasting glucose as frequently as needed according to instructions by a healthcare professional with expertise on the monitoring and management of hyperglycaemia. • The recommendation to consult a healthcare professional experienced in treatment of hyperglycaemia for pre-diabetic patients or patients with FPG >250 mg/dl or 13.9 mmol/l, a BMI ≥ 30 or age ≥ 75 years. • The recommendation to always consult a diabetologist or a healthcare professional experienced in treatment of hyperglycaemia for patients with diabetes. • The awareness of possible severe hyperglycaemia events, including hyperglycaemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis and information that some cases of ketoacidosis with fatal outcome have been reported in post-marketing setting. • Recommendation to patients on lifestyle changes that may reduce hyperglycaemia (e.g., dietary restrictions and physical activity). • Guidance on how to detect early signs and symptoms of hyperglycaemia and on fasting blood glucose monitoring is provided in PL section 2. Other routine risk minimization measures beyond the Product Information None
Pneumonitis	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Piqray - Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimization activities
	Patients should be advised to promptly report any new or worsening respiratory symptoms. In SmPC Section 4.4 the recommendation is given to interrupt alpelisib treatment in those patients with new or worsening respiratory symptoms or who are suspected to have developed pneumonitis, and to consider the diagnosis of non-infectious pneumonitis in those patients presenting with non-specific respiratory signs and symptoms by means of appropriate investigations. Alpelisib should be permanently discontinued in all patients with a confirmed diagnosis of pneumonitis. Other routine risk minimization measures beyond the Product Information None
Severe cutaneous reactions	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Piqray - Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: Guidance for the clinical management of severe cutaneous reactions is provided in the SmPC Section 4.4. including the following: - Alpelisib treatment should not be initiated and should not be reintroduced in those patients with a history of severe cutaneous reactions. - The recommendation to advise patients of signs and symptoms of severe cutaneous reactions: if those are present, alpelisib is to be interrupted and a consultation with a dermatologist is recommended. - If a diagnosis of severe cutaneous reaction is confirmed, then alpelisib should be permanently discontinued. - If severe cutaneous reaction is not confirmed, then alpelisib dose interruption, reduction, or discontinuation may be required. Other routine risk minimization measures beyond the Product Information None
Osteonecrosis of the jaw	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Piqray - Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: In the section 4.4 of the SmPC recommendation is given not to start alpelisib treatment when patients have an active osteonecrosis of the jaw developed due to a previous treatment or other reasons.

Safety concern	Routine risk minimization activities
	- Caution is to be exercised when patients are already on treatment with bisphosphonates/ RANK-ligand inhibitors (e.g., denosumab) and had this treatment before alpelisib. - Important information is to be provided to patients in signs or symptoms of this disease, so prompt reporting is required, and medical management is initiated.
	Other routine risk minimization measures beyond the Product Information
	None
Important potential risks	
	None
Missing information	
Safety with long-term use	Routine risk communication None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information None

5.2 Part V.2. Additional Risk minimization measures

There are no additional risk minimization measures ongoing. Routine risk minimization activities as described in Part V.1 are considered sufficient to manage the safety concerns of the medicinal product.

5.3 Part V.3. Summary of risk minimization measures

Table 5-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Hyperglycaemia	Routine risk minimization measures: SmPC Sections 4.2, 4.4, 4.8, and 4.9 PL Sections 2, 3, 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up checklist Additional pharmacovigilance activities: None
Pneumonitis	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 PL Sections 2, 3, 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
Severe cutaneous reactions	Routine risk minimization measures: SmPC Sections 4.2, 4.4, and 4.8 PL Sections 2, 3, 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Osteonecrosis of the jaw	Routine risk minimization measures: SmPC Sections 4.4, 4.8 PL Sections 2, 3, 4 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety with long-term use	Routine risk minimization measures: Currently available data are limited and do not support the need for risk minimization. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

6 Part VI: Summary of the risk management plan for PIQRAY™ (alpelisib)

This is a summary of the risk management plan (RMP) for Piqray. The RMP details important risks of Piqray, how these risks can be minimized, and how more information will be obtained about Piqray's risks and uncertainties (missing information).

Piqray's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Piqray should be used.

This summary of the RMP for Piqray should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Piqray's RMP.

6.1 Part VI: I. The medicine and what it is used for

Piqray is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation after disease progression following an endocrine-based regimen. It contains alpelisib as the active substance and it is given by oral route.

Further information about the evaluation of the benefits of Piqray can be found in the EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: <https://www.ema.europa.eu/en/medicines/human/EPAR/piqray>.

6.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Piqray, together with measures to minimize such risks and the proposed studies for learning more about the risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Piqray is not yet available, it is listed under ‘missing information’ below.

6.2.1 Part VI: II.A: List of important risks and missing information

Important risks of Piqray are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Piqray. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Hyperglycaemia Pneumonitis Severe cutaneous reactions Osteonecrosis of the jaw
Important potential risks	None
Missing information	Safety with long-term use

6.2.2 Part VI: II.B: Summary of important risks

Table 6-2 Important identified risk: Hyperglycaemia

Evidence for linking the risk to the medicine	Hyperglycaemia is a reversible, on-target effect of PI3K inhibition. Preclinical study data indicate that alpelisib has the potential to interfere with the glucose and insulin homeostasis. Hyperglycaemia has been observed both in preclinical and clinical studies with alpelisib. Cases of severe hyperglycaemia, in some cases associated with Hyperglycaemic Hyperosmolar Non-Ketotic Syndrome (HHNKS) or ketoacidosis have been reported in post-marketing setting.
Risk factors and risk groups	Patients with diabetes mellitus or pre-diabetic conditions such as impaired fasting glucose and other conditions such as BMI ≥30 and age ≥75.
Risk minimization measures	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 4.9 Overdose PL Section 2 What you need to know before you take Piqray -Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects Additional risk minimization measures None

Table 6-3 Important identified risk: Pneumonitis

Evidence for linking the risk to the medicine	Pneumonitis is a known toxicity of PI3K/mTOR pathway inhibitors. Serious cases of pneumonitis/acute interstitial pneumonitis/ interstitial lung disease have been reported with alpelisib across all studies.
Risk factors and risk groups	There are no identified risk factors for the occurrence of pneumonitis in alpelisib-treated patients.
Risk minimization measures	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Piqray -Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects Additional risk minimization measures None

Table 6-4 Important identified risk: Severe cutaneous reactions

Evidence for linking the risk to the medicine	Skin and subcutaneous tissue disorders including severe cutaneous reactions are a known effect of PI3K/mTOR pathway inhibitors. Cases of severe cutaneous reactions have been reported in clinical studies.
Risk factors and risk groups	There are no identified risk factors for the occurrence of severe cutaneous reactions in alpelisib treated patients.
Risk minimization measures	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Piqray -Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects Additional risk minimization measures None

Table 6-5 Important identified risk: Osteonecrosis of the jaw

Evidence for linking the risk to the medicine	Osteonecrosis of the jaw was reported in clinical studies, in different populations and combination treatment.
Risk factors and risk groups	Patients receiving bisphosphonates and/or denosumab before or during treatment with alpelisib are at a higher risk of developing osteonecrosis of the jaw.
Risk minimization measures	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you take Piqray -Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects

Additional risk minimization measures
None

Table 6-6 **Missing information: Safety with long-term use**

Risk minimization measures	Routine risk minimization measures
	None
	Additional risk minimization measures
	None

6.2.3 Part VI: II.C: Post-authorization development plan

6.2.3.1 II.C.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Piqray.

6.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies in the post-authorization development plan.

7 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Hyperglycaemia – Piqray_Hyperglycaemia (Version 1.0, Oct-2024)

In addition to collecting routine information for these adverse events, please ensure the following additional information is provided and/or confirmed.

Event Description:

Did the patient present with any of the following signs or symptoms or experienced them in last few weeks?

Check all that apply:

- | | | |
|---|---|---|
| ☐ Blurred vision | ☐ Fever | ☐ Polyphagia |
| ☐ Cardiac arrhythmia | ☐ Hallucinations | ☐ Polyurea |
| ☐ Coma | ☐ Impotence (male) | ☐ Poor wound healing |
| ☐ Confusion | ☐ Kussmaul hyperventilation | ☐ Recurrent infections |
| ☐ Dry mouth | ☐ Nausea | ☐ Thick, dark patches around the neck, armpits, elbow pits and groin |
| ☐ Dry or itchy skin | ☐ Numbness in fingers and toes | |
| ☐ Fatigue | ☐ Polydipsia | |
| ☐ Weight loss | ☐ Weakness | |
| ☐ None of the above | | |
| ☐ Other relevant symptoms (please specify) | | |

Additional information (if any): _____

Were any of the following diagnostic tests performed at the time of event? **Check all that apply** and please specify test(s), dates and results in additional information below:

- | | | |
|--|--|---|
| ☐ Blood glucose - Fasting | ☐ Hemoglobin A1c (HbA1c) | ☐ Urine or blood ketones |
| ☐ Blood glucose - Random | ☐ Oral glucose tolerance test | ☐ Urine albumin |
| ☐ Blood glucose - Post-prandial | | ☐ Urine glucose |
| ☐ Blood glucose - Unknown | | |
| ☐ None of the above | | |

Additional information (if any): _____

Does the patient have any of the following risk factors for hyperglycaemia prior to starting alpelisib? **Check all that apply** and please specify test(s), dates and results in additional information below:

- | | | |
|---|--|--|
| ☐ Age $\geq$ 75 years | ☐ BMI $\geq$ 30 | ☐ Elevated Hemoglobin A1c (HbA1c) |
| ☐ Elevated Fasting Blood Glucose | ☐ History of Type II Diabetes Mellitus (T2DM) | |
| ☐ None of the above | | |

Additional information (if any): _____

Patient History:

Did the patient have a history of any of the following prior to the onset of hyperglycaemia? **Check all that apply** and please specify onset dates and the current status in additional information section below:

☐ Recent acute illness	Medical History:
☐ Recent Infectious disease including sepsis and osteomyelitis	☐ History of bariatric surgery
☐ Diabetes mellitus (DM) (Type I or II, or secondary DM)	☐ History of high blood pressure
☐ Excessive Intake of alcohol	☐ History of smoking
☐ Recent weight gain/obesity	☐ History of overweight/obesity
☐ Recent weight loss/malnutrition	☐ History of abnormal HbA1c
☐ Renal failure	☐ History of diabetic eye complications (retinopathy)
☐ Unusual physical activity/exercise just before the event	☐ History of diabetic foot ulcer
☐ Previous episodes of hyperglycaemia/ ketotic coma	☐ History of positive urine albumin test (albuminuria, nephropathy)
☐ Gestational diabetes	☐ History of peripheral neuropathy
Medications:	☐ History of cardiovascular disease
☐ Concomitant use of anti-hyperglycemic agents	☐ History of autonomic neuropathy
☐ Recent change in insulin therapy or Anti-hyperglycaemia medication	☐ History of dyslipidemia (high triglycerides and/or low HDL cholesterol)
	☐ Family history of Diabetes mellitus
☐ None of the above	

Additional information (if any): -----

Was the patient taking any of the following drugs at the time of the event of hyperglycaemia? **Check all that apply** and please specify dosage, treatment start and end dates in additional information below:

- | | |
|--|--------------------------------------|
| ☐ Beta blockers | ☐ Pentamidine |
| ☐ Cimetidine | ☐ Quinine |
| ☐ Herbals | ☐ Salicylates |
| ☐ Insulin | ☐ Steroids |

- | | |
|--|--|
| ☐ Lithium | ☐ Sulfa drugs |
| ☐ Oral hypoglycaemics | ☐ Other drugs known to cause hyperglycaemia |
| ☐ OTCs | |
|
 | |
| ☐ None of the above | |
| ☐ Other relevant co-medication (please specify) | |

Additional information (if any): -----

Treatment:

What was the treatment given for hyperglycaemia? **Check all that apply** and please specify dosage (including any dose titration), treatment start and end dates in additional information below:

- ☐ Metformin (please specify: Extended release / Immediate release)
- ☐ SGLT2 inhibitor (please specify)
- ☐ Insulin (please specify)
- ☐ Any other treatment (please specify)

Additional information (if any): -----

Other relevant information (if any): -----

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable.