NOVARTIS

Patient Safety & Pharmacovigilance

Alpelisib

BYL719

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Alpelisib
Product(s) concerned (brand name(s)):	PIQRAY™
Document status:	Final
Version number:	8.1
Data lock point for this RMP	12-Jun-2018 (clinical trial data lock point, CBYL719C2301) 23-May-2023 (post-marketing data lock point, PSUR)
Date of final sign off	01-Jul-2024

Rationale for submitting an updated RMP: This EU RMP update is prepared to consolidate the RMP v7.2 with RMP v8.0 to reflect the removal of Study CBYL719C2404 (Category 3) from additional pharmacovigilance activities.

Summary of significant changes in this RMP:

Key changes for this RMP v8.1 update compared to RMP v 7.2 include:

- Removal of Study CBYL719C2404 (Category 3) from additional pharmacovigilance activities.
- Inclusion of alpelisib specific targeted follow-up checklist for hyperglycaemia.

Part	Major changes compared to RMP v 7.2
Part I	No changes
Part II	No changes
Part III	Study CBYL719C2404 details removed Alpelisib specific targeted follow-up checklist for hyperglycaemia is included
Part IV	No changes
Part V	Study CBYL719C2404 details removed Table 12.2 - Added alpelisib specific targeted follow-up checklist.
Part VI	Study CBYL719C2404 details removed
Part VII	Study CBYL719C2404 details removed from Annex 2 and Annex 3 Annex 4 - Alpelisib specific targeted follow-up checklist for hyperglycaemia is included

Other RMP versions under evaluation:

No RMPs are currently under evaluation.

Details of the currently approved RMP:

Version number: 7.2

Approved with procedure: EMEA/H/C/004804/II/0022/G

Date of approval (opinion date): 30-May-2024

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
AIs	Aromatase Inhibitors
ATC	Anatomical Therapeutic Chemical classification
BC	Breast Cancer
BP	Blood Pressure
CDK	Cyclin-Dependent Kinases
CI	Confidence Interval
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribose Nucleic Acid
ECG	Electrocardiogram
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
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)	L01EM03
Marketing Authorization Applicant	Novartis Europharm Limited
Medicinal products to which this RMP refers	PIQRAY™ 50 mg, 150 mg, 200 mg film-coated tablets
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	[Current approved SmPC] [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: Not applicable
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?	Yes

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

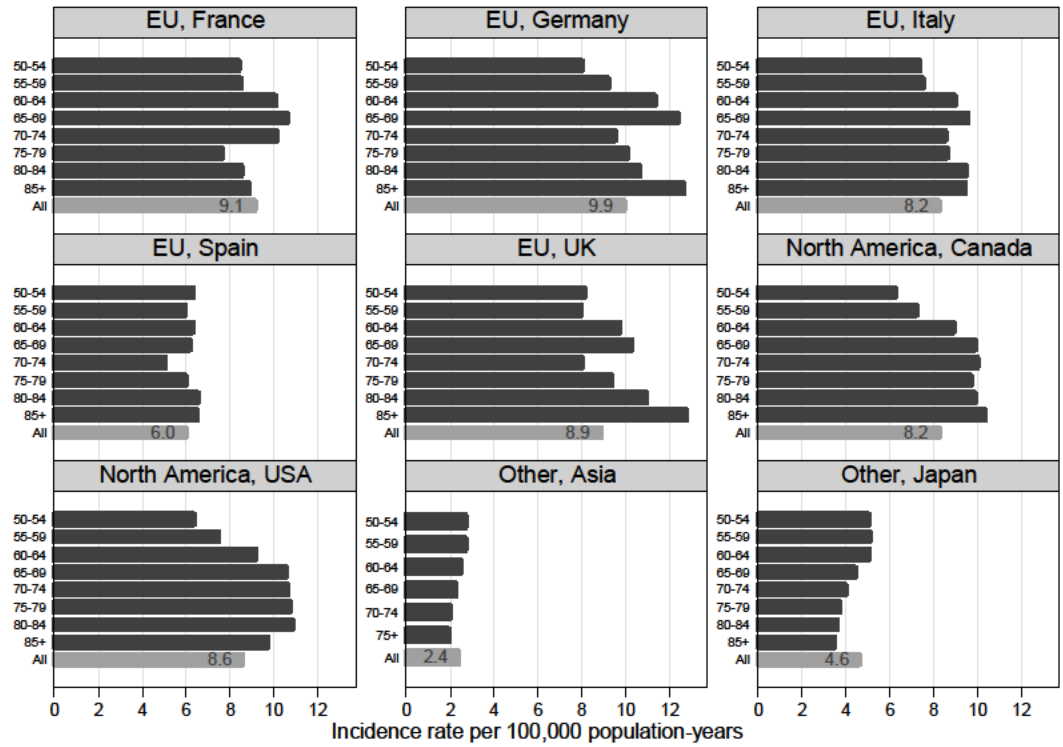
2.1 Indication

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)

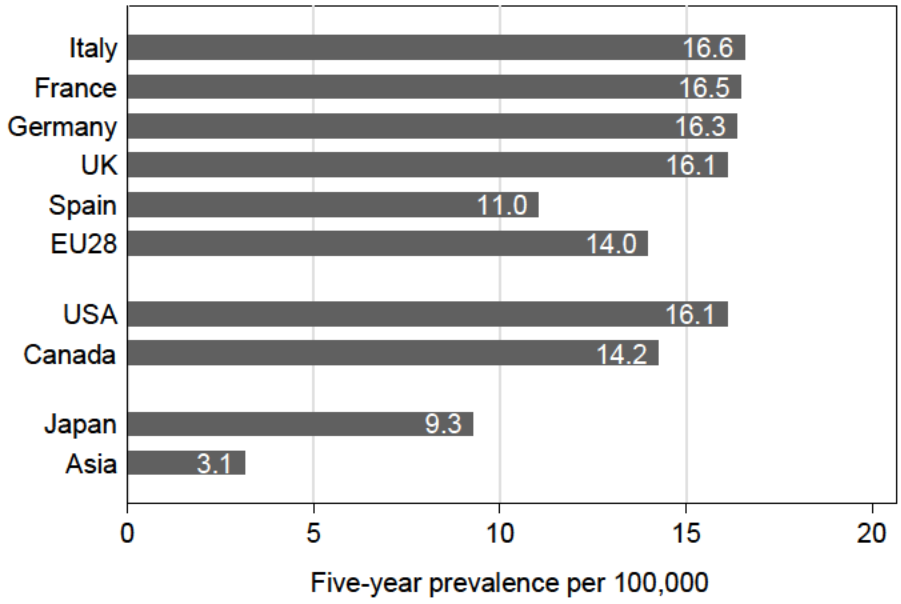
3) Proportion of PIK3CA mutation: Abramson et al (2014) (33.1% in HR+HER2-)

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:

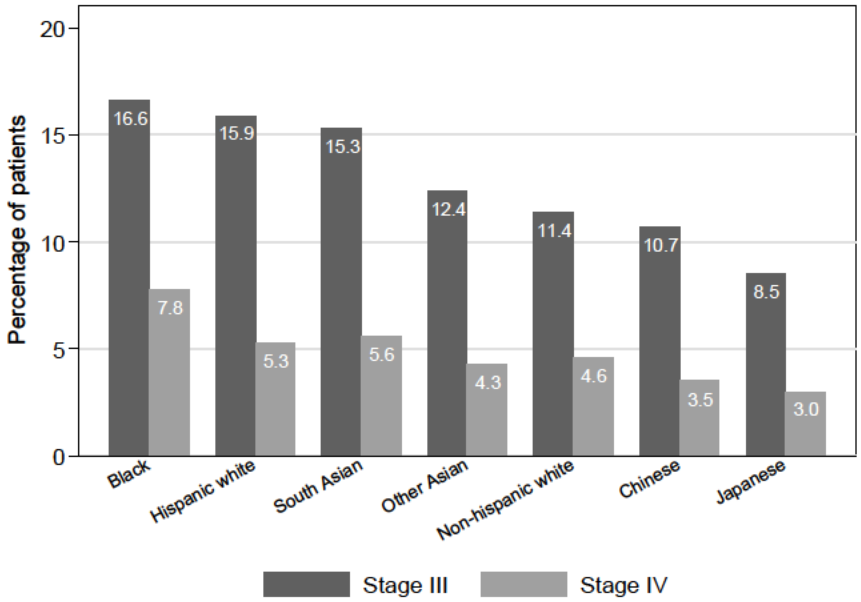
No clear trend across age groups is observed with respect to the incidence of HR-positive HER2-negative aBC with PIK3CA mutation among women in European countries. In Canada and the USA incidence increases with age while in Asia it appears that BC is more commonly diagnosed in younger age groups relative 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 July 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 February 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 March 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 July 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).

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
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%

Reference	Country	Relative survival according to stage	
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: Allemani 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

	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**
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
Cerebrovascular disease	12.53	11.31	94.29	109.35
Atrial fibrillation	8.07	7.9	130	172.74

	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**
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).

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

Table 3-1 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 subjects 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 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	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
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 subjects 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 subjects 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 CCI mg/kg/day in females and in most prematurely sacrificed animals of both sexes at CCI mg/kg/day. In the 13-week study, in the skin of females at CCI and CCI 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	No effect on epidermis (atrophy) in humans has been observed. 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 subjects recovered upon permanent

Key Safety findings (from non-clinical studies)	Relevance to human usage
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.	discontinuation of alpelisib and medical treatment. Severe cutaneous reactions are an important identified risk.
Genotoxicity	
No evidence of genotoxicity in vitro or in vivo.	There are no clinical data available regarding genotoxicity effects of alpelisib. Based on the current available data, there is no concern relevant to human usage.
Carcinogenicity	
No carcinogenicity, fertility or juvenile toxicity studies were conducted thus far with alpelisib.	There are no clinical data available regarding carcinogenic effects of alpelisib. 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 IC50 of CCI 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 CCI 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 CCI mg/kg/day. However, in a single dose invasive telemetry study in dogs, at doses of CCI CCI or CCI mg/kg, an increase in 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	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 ECG morphology, rhythm or P, PQ, QRS, QT and QTc duration. In the CBYL719C2301 study, hypertension events were generally mild to moderate in intensity and easily manageable with antihypertensive therapy.

Key Safety findings (from non-clinical studies)	Relevance to human usage
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.	No corneal events were reported in subjects 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.
Other toxicity-related information or data	
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.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Alpelisib is indicated for the treatment of postmenopausal women, and adult men with HR-positive, HER2-negative, advanced breast cancer with PIK3CA mutation in combination with fulvestrant after disease progression following an endocrine-based regimen. For the indication being sought, alpelisib data from pivotal Study CBYL719C2301 (SOLAR-1) is included in the RMP analyses to support the characterization and evaluation of the alpelisib safety profile. CBYL719C2301 is 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. The safety set included all subjects who received any study treatment. Data from the cohorts of subjects with PIK3CA mutation and without PIK3CA mutation were combined for a more robust safety evaluation. Data from subgroup analysis of subjects with PIK3CA mutation are also presented.

Table 4-1 Overview of study BYL719C2301 which contributed to safety data

Study design	Exposure	Exposure by mutation status		Data cut-off
	N=571	With PIK3CA mutation N= 340	Without PIK3CA mutation N=231	
Randomized, double-blind, placebo-controlled, international, multicenter Phase III study	Alpelisib plus fulvestrant : 284 Placebo plus fulvestrant : 287	Alpelisib plus fulvestrant: 169 Placebo plus fulvestrant: 171	Alpelisib plus fulvestrant: 115 Placebo plus fulvestrant: 116	12-Jun-2018

Table 4-2 Duration of exposure – Study BYL719C2301 (safety set)

	All subjects		Subjects with PIK3CA mutation	
Duration	**Alpelisib 300 mg qd+ Fulvestrant N= 284 n (%)**	**Placebo qd + Fulvestrant N= 287 n (%)**	**Alpelisib 300 mg qd+ Fulvestrant N= 169 n (%)**	**Placebo qd + Fulvestrant N= 171 n (%)**
Less than 1 month	15 (5.3)	9 (3.1)	9 (5.3)	5 (2.9)
at least 1 month	269 (94.7)	278 (96.9)	160 (94.7)	166 (97.1)
at least 2 months	246 (86.6)	223 (77.7)	150 (88.8)	129 (75.4)
at least 3 months	231 (81.3)	192 (66.9)	141 (83.4)	110 (64.3)
at least 4 months	205 (72.2)	161 (56.1)	129 (76.3)	89 (52.0)
at least 6 months	168 (59.2)	141 (49.1)	104 (61.5)	81 (47.4)
at least 12 months	101 (35.6)	83 (28.9)	63 (37.3)	51 (29.8)
at least 18 months	52 (18.3)	48 (16.7)	30 (17.8)	24 (14.0)
Subject-time (months)	**2847.3**	**2530.4**	**1733.1**	**1431.0**

Subject-time is the sum of each subject's treatment exposure in month.
Source: Annex 7 - Table 4-1.1

Table 4-3 Exposure by age group (≥65 years, <65 years) – Study BYL719C2301 (safety set)

		All subjects			Subjects with PIK3CA mutation			
		Alpelisib 300 mg qd+ Fulvestrant N=284		Placebo qd + Fulvestrant N=287	Alpelisib 300 mg qd+ Fulvestrant N=169		Placebo qd + Fulvestrant N=171	
Age	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)
Total	284 (100)	2847.3	287 (100)	2530.4	169 (100)	1733.1	171 (100)	1431.0
< 65 years	167 (58.8)	1762.4	153 (53.3)	1242.0	95 (56.2)	1005.7	88 (51.5)	707.4
≥ 65 years	117 (41.2)	1085.0	134 (46.7)	1288.4	74 (43.8)	727.5	83 (48.5)	723.6

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

Source: Annex 7 - Table 4-1.2

Table 4-4 Exposure by age group (≥75 years, <75 years) – Study BYL719C2301 (safety set)

		All subjects			Subjects with PIK3CA mutation			
		Alpelisib 300 mg qd+ Fulvestrant N=284		Placebo qd + Fulvestrant N=287	Alpelisib 300 mg qd+ Fulvestrant N=169		Placebo qd + Fulvestrant N=171	
Age	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)
Total	284 (100)	2847.3	287 (100)	2530.4	169 (100)	1733.1	171 (100)	1431.0
< 75 years	250 (88.0)	2572.6	248 (86.4)	2120.4	149 (88.2)	1584.9	145 (84.8)	1191.7
≥ 75 years	34 (12.0)	274.7	39 (13.6)	410.0	20 (11.8)	148.2	26 (15.2)	239.3

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

Source: Annex 7 - Table 4-1.3

Table 4-5 Exposure by race – Study BYL719C2301 (safety set)

		All subjects			Subjects with PIK3CA mutation			
		Alpelisib 300 mg qd+ Fulvestrant N=284		Placebo qd + Fulvestrant N=287	Alpelisib 300 mg qd+ Fulvestrant N=169		Placebo qd + Fulvestrant N=171	
Race	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)
Total	284 (100)	2847.3	287 (100)	2530.4	169 (100)	1733.1	171 (100)	1431.0
White	199 (70.1)	2032.6	177 (61.7)	1454.9	117 (69.2)	1215.6	108 (63.2)	811.6
Asian	59 (20.8)	602.0	66 (23.0)	696.8	34 (20.1)	344.6	40 (23.4)	401.7

			All subjects				Subjects with PIK3CA mutation	
Black or African American	2 (0.7)	21.0	6 (2.1)	48.8	1 (0.6)	15.3	3 (1.8)	39.3
Other	24 (8.5)	191.7	38 (13.2)	330.0	17 (10.1)	157.6	20 (11.7)	178.4

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

Source: Annex 7 - Table 4-1.4

Table 4-6 Exposure by region – Study BYL719C2301 (safety set)

					All subjects		Subjects with PIK3CA mutation	
		Alpelisib 300 mg qd+ Fulvestrant N=284		Placebo qd + Fulvestrant N=287	Alpelisib 300 mg qd+ Fulvestrant N=169		Placebo qd + Fulvestrant N=171	
Region	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)	Subjects n (%)	Subject-time (Month)
Total	284 (100)	2847.3	287 (100)	2530.4	169 (100)	1733.1	171 (100)	1431.0
Europe	153 (53.9)	1502.4	144 (50.2)	1222.2	86 (50.9)	874.8	86 (50.3)	665.9
North America	29 (10.2)	294.5	37 (12.9)	241.0	19 (11.2)	201.1	24 (14.0)	158.8
Asia	56 (19.7)	592.3	64 (22.3)	677.5	32 (18.9)	335.4	38 (22.2)	382.4
Latin America	17 (6.0)	158.9	26 (9.1)	266.4	14 (8.3)	142.0	17 (9.9)	173.9
Other	29 (10.2)	299.4	16 (5.6)	123.4	18 (10.7)	179.9	6 (3.5)	50.0

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

Source: Annex 7 - Table 4-1.5

Table 4-7 Exposure by PIK3CA mutation status in tissue - Study BYL719C2301 (safety set)

	Alpelisib 300 mg qd+ Fulvestrant N=284		**Placebo qd + Fulvestrant N=287**	
PIK3CA mutation status	**Subjects n (%)**	**Subject-time (Month)**	**Subjects n (%)**	**Subject-time (Month)**
Total	284 (100)	2847.3	287 (100)	2530.4
With PIK3CA mutation	169 (59.5)	1733.1	171 (59.6)	1431.0
Without PIK3CA mutation	115 (40.5)	1114.2	116 (40.4)	1099.4

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

Source: Annex 7 - Table 4-1.6

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

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

Table 5-1 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 chronic liver disease	As a standard precaution, subjects with chronic liver disease Child Pugh score B or C, active chronic disease, severe hepatic impairment were excluded from BYL719C2301 study. Also, fulvestrant is contraindicated in severe hepatic impairment subjects and dose adjustment is required in moderate hepatic impairment.	No	A dedicated study on hepatic impairment (CBYL719A2105) was conducted and results showed no impact of moderate or severe hepatic impairment on the clearance, elimination, or distribution of alpelisib, supporting that no dose adjustment of alpelisib is required in subjects with mild, moderate, or severe hepatic impairment.
Patients with severe renal impairment	These subjects were excluded from the clinical development program as a standard precaution. In addition, fulvestrant is contraindicated in severe renal impairment subjects.	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 subjects 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.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for non-inclusion as missing information
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 heart disease or a recent history of cardiac events	Preclinical Cardiac safety studies, in vitro and in vivo, indicated a negligible risk of an electrophysiological effect. This population was excluded as a precaution.	No	Preclinical cardiac safety studies, in vitro and in vivo, indicated a minimal risk of an electrophysiological effect. In the 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 embryofoetal 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. Reproductive toxicity is considered as an important potential risk.
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 embryofoetal developmental and teratogenic effects.	No	The targeted indication is for postmenopausal women.

5.2 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.

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

Table 5-2 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 hepatic impairment Patients with renal impairment Patients with cardiovascular impairment	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 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. 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 4-5).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Elderly patients (≥ 65 years)	Included in the clinical development program. (Table 4-3)
Paediatric patients (<18 years of age)	Not included in the clinical development program.
Male patients	Included in the clinical development program.

6 Part II Safety specification Module SV: Post-authorization experience

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

6.1.1 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).

6.1.2 Part II Module SV.1.2. Exposure

The estimated exposure is provided in the Table 6-1 below.

Table 6-1 Cumulative exposure from marketing experience

	EEA (PTY)	USA and Canada (PTY)	CCI	ROW* (PTY)	Total
Piqray FCT 150 mg	809	3780	[redacted]	1686	**6276**
Piqray FCT 200 mg	127	585	[redacted]	116	**828**
Piqray FCT 250 mg	350	771	[redacted]	341	**1463**
Total	**1287**	**5137**		**2144**	**8567**

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 30-May-2023.

*Sales from United Kingdom are included in Rest of the World (ROW) region.

Source of data: PSUR (24-Nov-2022 to 23-May-2023).

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

7.1 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.

8 Part II Safety specification Module SVII: Identified and potential risks

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

8.1.1 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 risk management plan (RMP) and the reasons for non-inclusion are provided below.

Table 8-1 Risks not considered important for inclusion in the list of safety concerns

Reason for non-inclusion as a safety concern	Adverse reactions	Rationale for non-inclusion as an RMP safety concern
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	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. Therefore, this risk is considered to have low impact on individual patients and to be manageable.
	Hypertension	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,

Reason for non-inclusion as a safety concern	Adverse reactions	Rationale for non-inclusion as an RMP safety concern
		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 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 only 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 (≥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 events were manageable and recovered with adequate therapy.

Reason for non-inclusion as a safety concern	Adverse reactions	Rationale for non-inclusion as an RMP safety concern
		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]. 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.
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	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

Reason for non-inclusion as a safety concern	Adverse reactions	Rationale for non-inclusion as an RMP safety concern
		practice. Therefore, hypersensitivity is not considered an important risk.

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

Table 8-2 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 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 four cases, alpelisib was administered as combination therapy with other drugs such as cetuximab, MEK162 (binimetinib), LJM716, and everolimus. Of these four 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 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 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].

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
	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 8-3 Important Potential risks:

There are no important potential risks for alpelisib.

Table 8-4 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.

8.2 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.

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

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

8.3.1.1 Important Identified Risk: Hyperglycaemia

Table 8-5 Clinical trial data of hyperglycaemia

	All subjects			Subjects with PIK3CA mutation		
	Alpelisib 300mg qd + Fulv N=284 n (%) 95% CI	**Placebo qd + Fulv N=287 n (%) 95% CI**	**Risk Difference 95% CI**	**Alpelisib 300mg qd + Fulv N=169 n (%) 95% CI**	**Placebo qd + Fulv N=171 n (%) 95% CI**	**Risk Difference 95% CI**
Number of subjects with at least one event	187 (65.8) (60.0 - 71.3)	30 (10.5) (7.2 - 14.6)	55.4 [48.2; 61.9]	113 (66.9) [59.2; 73.9]	17 (9.9) [5.9; 15.4]	56.9 [47.5; 65.0]
Maximum grade						
Grade 2 AEs	45 (15.8)	7 (2.4)		29 (17.2)	4 (2.3)	
Grade 3 AEs	95 (33.5)	1 (0.3)		54 (32.0)	0	
Grade 4 AEs	13 (4.6)	1 (0.3)		10 (5.9)	1 (0.6)	
SAEs	30 (10.6)	0		18 (10.7)	0	
AE outcome*						
Recovered/resolved	166 (58.5)	21 (7.3)		100 (59.2)	13 (7.6)	
Recovering/resolving	10 (3.5)	1 (0.3)		8 (4.7)	0	
Not recovered/not resolved	38 (13.4)	9 (0.3)		27 (16.0)	5 (2.9)	
Recovered/resolved with sequelae	6 (2.1)	1 (0.3)		2 (1.2)	0	
Unknown	3 (1.1)	0		2 (1.2)	0	
Missing	4 (1.4)	0		4 (2.4)	0	

* Only reported outcomes are presented. If an outcome is not reported in any arms, it is not presented in this table.

Numbers (n) represent counts of subjects.
MedDRA version 21.0, CTCAE version 4.03, Case Retrieval Strategy version 22-Jun-2018.
Source: Attachment to Annex 7 of RMP v 1.2 Table 1-3.1

Table 8-6 Important identified risk Hyperglycaemia: Other details

Name of the risk	Hyperglycaemia
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.
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:	• Hyperglycaemia was frequently observed with alpelisib plus fulvestrant treatment. In the alpelisib plus fulvestrant group, hyperglycaemia related events were reported in 65.8% of subjects, the maximum severity was grade 3 in 33.5% and grade 4 in 4.6%. Severe complications of hyperglycaemia, such as ketoacidosis, were reported rarely (two cases occurred in Study BYL719C2301, both cases resolved) [BYL719 SCS]. • Hyperglycaemia developed typically early (median time to first occurrence of grade ≥2 hyperglycaemia was 15 days (range: 5 days to 517 days)) during the treatment and was generally manageable with oral anti-diabetic agents (primarily metformin) and alpelisib dosing modification as needed; and 6.7% subjects discontinued alpelisib due to hyperglycaemia [BYL719 SCS]. • The median duration of a grade ≥2 hyperglycaemia was 10 days, and of grade ≥3 hyperglycaemia was 8 days, indicating that with appropriate intervention, the hyperglycaemia is manageable. The hyperglycaemia is manageable with oral antidiabetic medication (primarily metformin). In the vast majority of events, hyperglycaemia recovered at last available assessment [BYL719 SCS]. • In the alpelisib plus fulvestrant group, of the 187 subjects for whom a hyperglycaemia AEs were reported, anti-diabetic medication was given to 163 subjects. Among these 163 subjects, the most frequent medication used was metformin (142 subjects, 87.1%). Other, less frequently used medications included various types of insulin, dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. sitagliptin, linagliptin), sulfonylureas (e.g. gliclazide, glibenclamide, glimepiride) and others [BYL719 SCS]. • Subjects 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 subjects who were diabetic or pre-diabetic at baseline, compared to subjects with normal glucose tolerance at baseline. In pre-diabetic and diabetic subjects, mean FPG levels peaked within the first two weeks of treatment, and subsided thereafter towards baseline levels [BYL719 SCS]. • 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 subjects. • Severe hyperglycaemia, in some cases associated with HHNKS or ketoacidosis, has been observed in patients treated with alpelisib. Some

Name of the risk	Hyperglycaemia
	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	Subjects with diabetes mellitus or pre-diabetic conditions such as impaired fasting glucose and other risk factors such as BMI ≥30 and age ≥75. Subjects 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.

8.3.1.2 Important Identified Risk: Pneumonitis

Table 8-7 Clinical trial data of pneumonitis

	All subjects			Subjects with PIK3CA mutation		
	Alpelisib 300mg qd + Fulv N=284 n (%) 95% CI	Placebo qd + Fulv N=287 n (%) 95% CI	Risk Difference 95% CI	Alpelisib 300mg qd + Fulv N=169 n (%) 95% CI	Placebo qd + Fulv N=171 n (%) 95% CI	Risk Difference 95% CI
Number of subjects with at least one event	5 (1.8) [0.6; 4.1]	1 (0.3) [0.0; 1.9]	1.4 [-6.8; 9.6]	2 (1.2) [0.1; 4.2]	1 (0.6) [0.0; 3.2]	0.6 [-10.2; 11.4]
Maximum grade						
Grade 2 AEs	3 (1.1)	0		1 (0.6)	0	
Grade 3 AEs	1 (0.4)	1 (0.3)		0	1 (0.6)	
Grade 4 AEs	0	0		0	0	
SAEs	3 (1.1)	1 (0.3)		0	1 (0.6)	
AE outcome*						

	All subjects			Subjects with PIK3CA mutation		
	Alpelisib 300mg qd + Fulv N=284 n (%) 95% CI	Placebo qd + Fulv N=287 n (%) 95% CI	Risk Difference 95% CI	Alpelisib 300mg qd + Fulv N=169 n (%) 95% CI	Placebo qd + Fulv N=171 n (%) 95% CI	Risk Difference 95% CI
Recovered/resolved	4 (1.4)	0		1 (0.6)	0	
Recovering/resolving	1 (0.4)	1 (0.3)		1 (0.6)	1 (0.6)	
Not recovered/not resolved						

* Only reported outcomes are presented. If an outcome is not reported in any arms, it is not presented in this table.
Numbers (n) represent counts of subjects.
MedDRA version 21.0, CTCAE version 4.03, Case Retrieval Strategy version 22-Jun-2018.
Source: Attachment to Annex 7 of RMP v 1.2 Table 1-3.4

Table 8-8 Important identified risk Pneumonitis: Other details

Name of the risk	Pneumonitis
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 study CBYL719C2301, pneumonitis AEs occurred in five subjects (1.8%) in the alpelisib plus fulvestrant group (the PTs were pneumonitis in four subjects, and interstitial lung disease in one subject). None of these events had a fatal outcome. All cases were suspected to be related to study treatment except for one non-serious case of pneumonitis where the treatment was discontinued before onset of event. Out of four remaining cases, three were SAEs which all recovered completely and one was a non-serious grade 1 pneumonitis which did not recover by the clinical cutoff [BYL719 SCS].
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.

8.3.1.3 Important Identified Risk: Severe cutaneous reactions

Table 8-9 Clinical trial data of severe cutaneous reactions

	All subjects			Subjects with PIK3CA mutation		
	Alpelisib 300mg qd + Fulv N=284 n (%) 95% CI	Placebo qd + Fulv N=287 n (%) 95% CI	Risk Difference 95% CI	Alpelisib 300mg qd + Fulv N=169 n (%) 95% CI	Placebo qd + Fulv N=171 n (%) 95% CI	Risk Difference 95% CI
Number of subjects with at least one event	4 (1.4) [0.4; 3.6]	0 [0.0; 1.3]	1.4 [-6.8; 9.6]	3 (1.8) [0.4; 5.1]	0 [0.0; 2.1]	1.8 [-9.0; 12.5]
Maximum grade						
Grade 2 AEs	1 (0.4)	0		0	0	
Grade 3 AEs	3 (1.1)	0		3 (1.8)	0	
Grade 4 AEs	0	0		0	0	
SAEs	4 (1.4)	0		3 (1.8)	0	
AE outcome*						
Recovered/resolved	4 (1.4)	0		3 (1.8)	0	

* Only reported outcomes are presented. If an outcome is not reported in any arms, it is not presented in this table.

Numbers (n) represent counts of subjects.
MedDRA version 21.0, CTCAE version 4.03, Case Retrieval Strategy version 22-Jun-2018.
Source: Attachment to Annex 7 of RMP v 1.2 Table 1-3.6

Table 8-10 Important identified risk Severe cutaneous reactions: Other details

Name of the risk: 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	In studies for the combination of alpelisib and fulvestrant, two suspected cases of SJS and four suspected cases of EM have been reported. Cases of DRESS were reported in post-marketing setting.
Characterization of the risk:	In study CBYL719C2301, severe cutaneous reactions occurred in four subjects (1.4%) in the alpelisib plus fulvestrant group. The PTs were erythema multiforme in three subjects, and Stevens-Johnson syndrome in one subject. All were SAEs and were considered related to study drug by the Investigator, and three of the four events led to discontinuation. All four subjects recovered from the events without sequelae. One of the subjects with EM continued on study treatment. None of the events were Grade 4 or life threatening or fatal in nature. All four events were reported in subjects in Japan [BYL719 SCS].

Name of the risk: Severe cutaneous reactions	Details
	Two cases of DRESS were reported in patients treated with alpelisib. Corticosteroids were initiated and alpelisib was discontinued. The outcome was completely recovered in one case. In the second case, the outcome was condition improved. The latter was a well-documented DRESS case, in which though previous antineoplastic treatment with atezolizumab could have facilitated the development of the hypersensitivity reaction.
Risk factors and risk groups	There are no identified risk factors for the occurrence of severe cutaneous reactions in alpelisib treated subjects.
Preventability	Alpelisib treatment should not be initiated in subjects with history of SJS, EM, TEN or DRESS. 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.

8.3.1.4 Important Identified Risk: Osteonecrosis of the jaw

Table 8-11 Clinical trial data of Osteonecrosis of the jaw

	All subjects	Subjects with PIK3CA mutation	Risk Difference 95% CI	All subjects	Subjects with PIK3CA mutation	Risk Difference 95% CI
Number of subjects with at least one event	13 (4.6) [2.5; 7.7]	4 (1.4) [0.4; 3.5]	3.2 [-5.1; 11.3]	8 (4.7) [2.1; 9.1]	2 (1.2) [0.1; 4.2]	3.6 [-7.2; 14.3]
Grade 2 AEs	8 (2.8)	2 (0.7)		4 (2.4)	2 (1.2)	
Grade 3 AEs	4 (1.4)	2 (0.7)		4 (2.4)	0	
SAEs	5 (1.8)	1 (0.3)		5 (3.0)	0	
Recovered/resolved	1 (0.4)	1 (0.3)		0	0	
Recovering/ resolving	1 (0.4)	0		0	0	
Not recovered/not resolved	9 (3.2)	3 (1.0)		6 (3.6)	2 (1.2)	
Missing	3 (1.1)	0		2 (1.2)	0	

* Only reported outcomes are presented. If an outcome is not reported in any arms, it is not presented in this table.

Numbers (n) represent counts of subjects. A subject may be counted in several rows for action taken and outcome.

MedDRA version 21.0, CTCAE version 4.03, Case Retrieval Strategy version 03-Nov-2019
Source: Attachment to Annex 7 of RMP v 1.2 Table 8-2.21

Table 8-12 Important identified risk Osteonecrosis of the jaw: Other details

Name of the risk	Osteonecrosis of the jaw
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 study CBYL719C2301, in the alpelisib plus fulvestrant group, 4.6% of subjects had osteonecrosis of the jaw. In placebo plus fulvestrant group, 1.4% subjects experienced ONJ. All subjects with ONJ took bisphosphonates and/or denosumab before or concurrently during study treatment. Most of the events were grade 2. The outcome was not recovered or not resolved in 9/13 subjects at the last follow-up report. There were no fatal or life-threatening events.
Risk factors and risk groups	Subjects receiving bisphosphonates and/or denosumab before or during treatment with alpelisib are at a higher risk of developing ONJ.
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 ONJ is acceptable in the patient population being treated with alpelisib. In addition, ONJ 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 ONJ (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.

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

Table 8-13 Safety with long-term use

Name of missing information:	Safety with long-term use
Evidence source	The number of patients in alpelisib clinical studies who received the medicine for ≥ 12 months is limited.
Anticipated risk/ consequence of the missing information:	The available information on safety of alpelisib treatment beyond a duration of ≥ 12 months is limited.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table 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

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

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

A specific AE follow-up checklist will be used to collect further data to help further characterize and/or closely monitor each important identified risk of "Osteonecrosis of the jaw" and "Hyperglycaemia".

The targeted follow-up checklists are provided in Annex 4.

Other forms of routine pharmacovigilance activities for risks

There are no other forms of routine pharmacovigilance activities.

10.2 Part III.2. Additional pharmacovigilance activities

Additional pharmacovigilance activities for alpelisib are described below.

- Study CBYL719C2005 (HCP knowledge survey) (Category 3): Survey among healthcare professionals treating patients with metastatic breast cancer in selected European countries to evaluate their knowledge on management of hyperglycaemia when using alpelisib

10.2.1 Study CBYL719C2005 (HCP knowledge survey)

Study short name and title:

Survey among healthcare professionals treating patients with metastatic breast cancer in selected European Union countries to evaluate their knowledge on management of hyperglycaemia when using Alpelisib.

Rationale and study objectives:

Rationale:

In order to assess effectiveness of additional risk minimization measures for hyperglycaemia (prescriber's/HCP guide), Novartis will conduct the survey 12 to 18 months post Piqray (alpelisib) reimbursement among oncologists/ HCPs prescribing Piqray. The survey will establish whether oncologists/HCPs prescribing Piqray have received the educational material for hyperglycaemia, and if they demonstrate accurate understanding and implementation of relevant behaviors relating to hyperglycaemia when administering Piqray (alpelisib).

Objective:

The primary objective of this study is to measure physician knowledge and understanding of the key information included in the educational material. The following objectives will be addressed

- Investigate whether physicians have received any educational material related to Piqray (alpelisib).
- Assess physicians' knowledge and understanding of key safety information pertaining to the educational material
- Assess physicians' knowledge and understanding of key safety information pertaining to the following areas:
  - Risk factors for hyperglycaemia
  - Signs and symptoms of hyperglycaemia
  - Management of hyperglycaemia prior to starting and during treatment with Piqray (alpelisib).

Secondary objective:

The survey will assess as secondary objectives HCPs' self-reported risk minimization behaviors.

Study design:

This is a multinational, questionnaire-based, cross-sectional survey to be conducted among healthcare professionals prescribing Piqray.

Study population:

In order to be eligible to enroll and complete the survey, the HCP must have personally prescribed Piqray (alpelisib) within 3 months prior to the date of the survey. The level of experience of prescribing and thus their knowledge and experience of hyperglycaemia management in patients prior and during treatment with Piqray (alpelisib) will be assessed for each participating physician during the screening process.

Screening criteria proposed in the survey will require eligible physicians to have:
- Have more than 5 advanced breast cancer patients in their current caseload;
- Treated more than 15 patients with advanced breast cancer in the last three months prior to the survey date;
- Personally prescribed disease modifying therapies to patients, and;
- Have prescribed Piqray (alpelisib) ideally in at least 1 advanced breast cancer patient.

Milestones:

Final report submission: 31-May-2025

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

CBYL719C2005: Survey among healthcare professionals treating patients with metastatic breast cancer in selected European countries to evaluate their knowledge on management of hyperglycaemia when using Piqray (Alpelisib).
 	
Status: Ongoing
	The primary objective of this study is to measure physician knowledge and understanding of the key information included in the educational material. The following objectives will be addressed
	• Investigate whether physicians have received any educational material related to Piqray (alpelisib)
	• Assess physicians' knowledge and understanding of key safety information pertaining to the educational material
	• Assess physicians' knowledge and understanding of key safety information pertaining to the following areas:
	  • Risk factors for hyperglycaemia
	  • Signs and symptoms of hyperglycaemia
	  • Management of hyperglycaemia prior to starting and during treatment with Piqray (alpelisib).
	Secondary objective:
	• The survey will assess as secondary objectives HCPs' self-reported risk minimization behaviors.
		Hyperglycaemia	Final report submission	31-May-2025

11 Part IV: Plans for post-authorization efficacy studies

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

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

Risk Minimization Plan

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
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 PL Section 2 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.

Safety concern	Routine risk minimization activities
	• 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 Warnings and precautions PL Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** 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 Warnings and precautions 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

Safety concern	Routine risk minimization activities
	• 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 Warnings and precautions 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. • 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
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

12.2 Part V.2. Additional Risk minimization measures

Prescriber's guide

Objectives:

The objective of this educational program is to minimize the risk of hyperglycaemia while on Piqray therapy for metastatic breast cancer. Additional guidance/measures, prior and during treatment for the management of hyperglycaemia are included in the educational material for prescribers.

Rationale for the additional risk minimization measure

There is a need to mitigate the risk of serious (including life-threatening and fatal) hyperglycaemia events.

Target audience and planned distribution path

In addition to recommendations described in the SmPC, Oncologist/HCPs prescribing Piqray for treatment of advanced breast cancer will receive the Prescriber's Guide.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Novartis proposes to evaluate the effectiveness of the proposed additional risk minimisation measures based on outcome indicators that will define clinically relevant endpoints reflecting the success of the risk minimisation measures.

Information to assess outcome indicators will be obtained through the Novartis safety database (Argus). All hyperglycaemia events (serious and non-serious, including possible outcomes, e.g. ketoacidosis) will be analysed by seriousness. Relevant exposure for context will be estimated based on sales data.

Estimates of adverse event reporting rates will be presented with 95% confidence intervals overall, as well as by region. Changes in reporting rates over time between the group of EU countries and other countries (grouped by regions that have not implemented EM) will be compared graphically. Relevant AE rates from clinical trials will be presented for contextualization.

Analyses will be reviewed periodically and presented in the PSUR.

The effectiveness of the additional risk minimization measure will also be assessed through an HCP knowledge survey (Study CBYL719C2005) as an additional pharmacovigilance activity.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 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 and 4.8 PL Sections 2, 3, 4 Additional risk minimization measures: Prescriber's guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up checklist Additional pharmacovigilance activities: Study CBYL719C2005
Pneumonitis	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 PL Sections 2, 4 Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

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

13 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.

13.1 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 endocrine-therapy as monotherapy. 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*:* link to the EPAR summary landing page.

13.2 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 the case of Piqray, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

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.

13.2.1 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 13-1 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

13.2.2 Part VI - II B: Summary of important risks

Table 13-2 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 PL Section 2 Warnings and precautions PL Section 3 How to take Piqray PL Section 4 Possible side effects **Additional risk minimization measures**

	Prescriber's guide **Other routine risk minimization measures beyond the Product Information** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CBYL719C2005 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 13-3 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 Warnings and precautions PL Section 4 Possible side effects **Other routine risk minimization measures beyond the Product Information** None

Table 13-4 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 Warnings and precautions PL Section 4 Possible side effects **Other routine risk minimization measures beyond the Product Information** None

Table 13-5 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	Subjects receiving bisphosphonates and/or denosumab before or during treatment with alpelisib are at a higher risk of developing ONJ.

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 Warnings and precautions PL Section 4 Possible side effects **Other routine risk minimization measures beyond the Product Information** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Table 13-6 Missing information: Safety with long-term use

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

13.2.3 Part VI - II C: Post-authorization development plan

13.2.3.1 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.

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

Table 13-7 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives

CBYL719C2005	In order to assess effectiveness of additional risk minimization measures for hyperglycaemia (prescriber's/HCP guide), Novartis will conduct the survey 12 to 18 months post Piqray (alpelisib) reimbursement among oncologists/ HCPs prescribing Piqray.
	The primary objective of this study is to measure physician knowledge and understanding of the key information included in the educational material. The following objectives will be addressed
	• Investigate whether physicians have received any educational material related to Piqray (alpelisib)
	• Assess physicians' knowledge and understanding of key safety information pertaining to the educational material
	• Assess physicians' knowledge and understanding of key safety information pertaining to the following areas:
	  • Risk factors for hyperglycaemia
	  • Signs and symptoms of hyperglycaemia
	  • Management of hyperglycaemia prior to starting and during treatment with Piqray (alpelisib).

Study short name	Rationale and study objectives
	Secondary objective: The survey will assess as secondary objectives HCPs' self-reported risk minimization behaviors.

14 Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Osteonecrosis of the jaw

Targeted Follow-up Checklist: Alpelisib, Osteonecrosis of the Jaw (ONJ) (Version 1/ 2020)

ONJ is exposed bone or bone that can be probed through an intraoral or extra-oral fistula(e) in the maxillofacial region that has persisted for more than 6-8 weeks of appropriate evaluation and dental care in the absence of metastatic disease in the jaw or osteoradionecrosis and no history of radiation therapy to the jaws.

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

Information on event:

Diagnosis details of ONJ and duration (if recovered) and date/onset	Action taken with alpelisib	If Bisphosphonates (BP)/Denosumab (D) is received concomitantly, Action taken with BP/D	Surgical and/or medical treatment details and dates	Outcome
Diagnostic details and duration: _____ Onset date: _____ Latency (days) from start of alpelisib treatment: _____ Latency (days) from last dose of alpelisib treatment:	No action ☐ Dose reduced ☐ Dose interrupted ☐ Discontinuation ☐ Date: _____	No action ☐ Dose reduced ☐ Dose interrupted ☐ Discontinuation ☐ Date: _____		Complete recovery ☐ If recovered, event end date: _____ Recovered with sequelae ☐ Condition improved ☐ Condition unchanged ☐ Condition worsened ☐ Not resolved ☐ Death ☐ Not reported ☐ Unknown ☐

Event Description:

Did the patient present with any of the following signs or symptoms? ***Check all that apply***

☐ Area surrounding lesion red and/or swollen ☐ Suppuration (pus)

☐ Spontaneous pain
☐ Swollen/tender lymph nodes on same side as lesion
☐ Pain on palpation
☐ Unable to eat
☐ Paresthesia
☐ Anesthesia
☐ Dysesthesia
☐ Ulceration
☐ None of the above

Where was the jaw location of the observed lesion? *(Please include the overall size)*

☐ Upper left ☐ Lower left
☐ Upper front ☐ Lower front
☐ Upper right ☐ Lower right

Length (cm)	Width (cm)

Is bone exposed?
☐ **Yes** *(please specify the largest dimension below)* ☐ **No** ☐ **Unknown**
If Yes, largest dimension is: ☐ <0.5 cm ☐ 0.5-0.99 cm ☐ 1.0-1.99 cm ☐ >1.99 cm

NOTE: please contact the treating dentist / oral surgeon / periodontist to submit copies of the X-ray films/reports and dental notes describing the initial, follow-up and final presentations.

Is the event accompanied by a bone/soft tissue infection?
☐ **Yes** *(please specify including method of diagnosis (e.g. biopsy with isolated pathogen(s)))*

_____

☐ **No** ☐ **Unknown**

Has the patient experienced complications of the reported event(s) (e.g. pathological fracture, fistula, infection)?
☐ **Yes** *(please specify)*

_____

☐ **No** ☐ **Unknown**

Was treatment given for the condition/symptoms?

☐ **Yes** *(please specify)* ☐ **No** ☐ **Unknown**

Did the patient have a dental examination prior to treatment with alpelisib?
☐ Yes ☐ No ☐ Unknown

If yes, did the patient have ONJ before starting alpelisib treatment (at baseline)?

☐ Yes ☐ No ☐ Unknown

If yes, was ONJ resolved?
☐ Yes ☐ No ☐ Unknown

Did the patient receive BP/D/or other antiresorptive agents <u>before</u> treatment with alpelisib?

☐ Yes ☐ No ☐ Unknown

If yes, please provide details of therapy below:

Drug	Route of administration	Dosing regimen or daily dose	Dates of treatment (dd/mm/yyyy)	Indication for use

			Start date	Stop date	

If the answer is Yes to the previous question, did the patient experience ONJ under previous treatment with BP/D or other antiresorptive agents before starting alpelisib?

☐ Yes ☐ No ☐ Unknown

If yes, please provide details of ONJ

Diagnosis details of ONJ and duration (if recovered) and date/onset	Action taken with BP/D	Surgical and/or medical treatment details and dates	Outcome
Diagnostic details and duration: _____ Onset date: _____ Latency (days) from start of alpelisib treatment: _____ Latency (days) from last dose of alpelisib treatment:	No action ☐ Dose reduced ☐ Dose interrupted ☐ Discontinuation ☐ Date: _____		Complete recovery ☐ If recovered, event end date: _____ Recovered with sequelae ☐ Condition improved ☐ Condition unchanged ☐ Condition worsened ☐ Not resolved ☐ Death ☐ Not reported ☐ Unknown ☐

Did the patient receive BP/D or other antiresorptive agents <u>during</u> treatment with alpelisib?

☐ Yes ☐ No ☐ Unknown

If yes, please provide details of therapy below:

Drug	Route of administration	Dosing regimen or daily dose	Dates of treatment (dd/mm/yyyy)		Indication for use
			Start date	Stop date	

Use of antiangiogenic agents or other drugs increasing the risk:

Previous or concomitant use of drugs potentially increasing the risk of ONJ (eg chemotherapy, antiangiogenic agents):

☐ Yes ☐ No ☐ Unknown

Concomitant use of systemic glucocorticosteroids:

☐ Yes ☐ No ☐ Unknown

List details for the above drugs as appropriate:

Drug	Route of administration	Dosing regimen or daily dose	Dates of treatment (dd/mm/yyyy)		Indication for use
			Start date	Stop date	

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Does the patient have a history or did the patient experience during alpelisib treatment any of the following risk factors? ***Check all that apply and specify including dates***

☐ Cancer
☐ Radiotherapy to head and neck area
☐ Poor oral hygiene
☐ Impaired healing after dental procedure
☐ local bacterial infection/inflammation
☐ diabetes mellitus
☐ chronic maxillary sinusitis
☐ tobacco use
☐ renal dialysis
☐ None of the above
☐ Dental treatments (e.g. fillings, crowns, root canal treatments, routine cleanings, deep scaling, orthodontics)
☐ Dental-surgical procedures (e.g. routine/surgical tooth extractions, periodontal surgery, implants)
☐ Dental/oral problems (e.g. periodontal/ dental infections, toothache, stomatitis, oral ulcers)
☐ Trauma or fractures upper/lower jaw
☐ chronic inflammation
☐ stomatitis
☐ osteoporosis
☐ erythropoietin therapy
☐ cyclophosphamide therapy

Hyperglycaemia

Targeted Follow-up Checklist: Alpelisib, Hyperglycaemia (Life threatening and fatal) and Complications of Hyperglycaemia (serious cases only) (version 1 /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
- ☐ Cardiac arrhythmia
- ☐ Coma
- ☐ Confusion
- ☐ Dry mouth
- ☐ Dry or itchy skin
- ☐ Fatigue
- ☐ Weight loss
- ☐ None of the above
- ☐ Other relevant symptoms (please specify)
- ☐ Fever
- ☐ Hallucinations
- ☐ Impotence (male)
- ☐ Kussmaul hyperventilation
- ☐ Nausea
- ☐ Numbness in fingers and toes
- ☐ Polydipsia
- ☐ Weakness
- ☐ Polyphagia
- ☐ Polyurea
- ☐ Poor wound healing
- ☐ Recurrent infections
- ☐ Thick, dark patches around the neck, armpits, elbow pits and groin

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

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

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
- ☐ Cimetidine
- ☐ Herbals
- ☐ Insulin
- ☐ Lithium
- ☐ Oral hypoglycaemics
- ☐ OTCs
- ☐ Pentamidine
- ☐ Quinine
- ☐ Salicylates
- ☐ Steroids
- ☐ Sulfa drugs
- ☐ Other drugs known to cause hyperglycaemia

- ☐ 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)

Details of proposed Prescriber's Guide

Key Safety Messages

Severe hyperglycaemia, in some cases associated with hyperglycaemic hyperosmolar non-ketotic syndrome (HHNKS) or ketoacidosis, has been observed in patients treated with Piqray. Some cases of ketoacidosis with fatal outcome have been reported in the post-marketing setting.

Prior to initiating treatment

- Piqray is associated with an increased risk of hyperglycaemia.
- Patients at higher risk (diabetics, pre-diabetic, have FPG >250 mg/dL, have a BMI ≥30, or are of age ≥75 years) need consultation with a healthcare professional experienced in the treatment of hyperglycaemia.
- Test for FPG and HbA1c and optimise the patient's level of blood glucose before starting treatment with alpelisib.
- Counsel patients with regard to the risk of hyperglycaemia, need for lifestyle changes, signs and symptoms of hyperglycaemia (e.g. excessive thirst, urinating more often than usual or greater amount of urine than usual, increased appetite with weight loss, difficulty breathing, headache, nausea, vomiting) and the importance of immediately contacting healthcare professional if these symptoms occur.

During treatment

- Follow the schedule for monitoring fasting glucose according to the Piqray label. Please note there are different schedules for patients with and without risk factors
- In case of hyperglycaemia follow the hyperglycaemia-related dose modification and management table according to the Piqray label
- When initiating antidiabetic treatment consideration should be taken with regard to possible drug-drug interactions.

In addition, appropriate recommendations with regard to schedule of monitoring and dose modification will be included in this section of the Educational Material.