EU RISK MANAGEMENT PLAN FOR ITOVEBI / INAVOLISIB

RMP version to be assessed as part of this application:

RMP Version number: 1.3

Data lock point for this RMP: 27 February 2025

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
22-May-2025 15:58:58	Deputy QPPV	[redacted]
22-May-2025 16:02:17	Company Signatory (PV)	[redacted]

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Rationale for Submitting an Updated RMP

This Itovebi (inavolisib) European Union Risk Management Plan (EU RMP) Version 1.3 is based on the Marketing Authorisation Holder's responses to the Committee for Medicinal Products for Human Use (CHMP) third List of Outstanding issues.

Summary of Significant Changes in This RMP

Part I, Product Overview: Updated indication in the EEA.

Annex 3: Updated to include non-interventional study in Part A rather than Part C.

Annex 8: Updated to summarize the changes incorporated in this RMP version.

Other RMP Versions under Evaluation

Not applicable

Details of Currently Approved RMP

Not applicable

See page 1 for signature and date

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	inavolisib
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	Itovebi
Marketing authorization procedure	Centralized
Brief description of the product	Chemical Class: Inavolisib is a small-molecule inhibitor of the phosphatidylinositol 3-kinase (PI3K) catalytic subunit alpha isoform protein (p110α; encoded by the *PIK3CA* gene).
	Summary of mode of action: Inavolisib is a highly potent and selective inhibitor of p110α. In addition, inavolisib promotes the degradation of mutated p110α (mutant degrader).
	Important information about its composition: • Each 3 mg film-coated tablet contains 23 mg of lactose. • Each 9 mg film-coated tablet contains 69 mg of lactose.
Hyperlink to the Product Information	EU PI
Indication(s) in the EEA	Current: Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with *PIK3CA*-mutated, hormone receptor (HR)-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment (see section 5.1). Patients previously treated with a CDK 4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK 4/6 inhibitor treatment and the detection of recurrence.

	In pre- or perimenopausal women and in men, endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.
	Proposed: Not applicable
Dosage in the EEA	Current: Itovebi is administered at 9 mg orally (PO) once daily (QD) with or without food. Itovebi should be administered in combination with palbociclib and fulvestrant according to the respective dosing instructions. Treatment of pre/perimenopausal women and men with Itovebi should also include an LHRH agonist in accordance with clinical practice.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): 3 mg and 9 mg film-coated tablets
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the European Union?	Yes

EEA = European Economic Area; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; INN = International non-proprietary name; LHRH = luteinizing hormone-releasing hormone; PI3K = phosphatidylinositol 3-kinase; PO = orally; QD = once daily.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AKT	protein kinase B
AUC	area under the concentration-time curve
BMI	body mass index
CCOD	clinical cutoff date
CDK	cyclin-dependent kinase
C_{max}	maximum concentration observed
CVD	cardiovascular disease
ESMO	European Society for Medical Oncology
E.U. RMP	E.U. Risk Management Plan
GALT	gut-associated lymphoid tissues
HbA_{1C}	glycated hemoglobin
HCP	healthcare professional
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2-negative
HR	hormone receptor
HR+	hormone receptor-positive
ICH	International Conference for Harmonisation
LHRH	luteinizing hormone-releasing hormone
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	mammalian target of rapamycin
OR	odds ratio
PARP	poly (ADP-ribose) polymerase
PBRER	Periodic Benefit-Risk Evaluation Report
PI	Product Information
PI3K	phosphoinositide 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (gene name/acronym)
PO	Oral
PSUR	Periodic Safety Update Report
PT	preferred term
PV	Pharmacovigilance

Abbreviation	Definition
QD	once a day
QTc	corrected QT interval
RMP	Risk Management Plan
SAE	serious adverse event
SD	Sprague-Dawley
SEER	Surveillance, Epidemiology, and End Results
SMQ	Standardised MedDRA Query
SmPC	Summary of Product Characteristics
SOC	System Organ Class

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 *PIK3CA*-MUTATED, HR-POSITIVE, HER2-NEGATIVE METASTATIC BREAST CANCER

Incidence

Breast cancer is the most common cancer among females occurring worldwide with over 2.2 million incident cases (all ages) in 2020 (24.5% of all cancers) accounting for the age-standardized incidence of 47.8 cases per 100,000 women. In Europe and the United States, the age-standardized incidence of breast cancer is 74.3 per 100,000 women and 90.3 per 100,000 women, respectively, and is regarded as the most common cancer in the region (GLOBOCAN, WHO 2020). Table 2 describes the incidence of breast cancer worldwide, in the United States and Europe (GLOBOCAN, WHO 2020). In men, breast cancer is rare, accounting for less than 1% of all breast cancer cases in the US and an incidence of 1.2 cases per 100,000 men (Breast Cancer, Facts and Figures 2022-2024).

Hormone receptor (HR)-positive/ human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2-) breast cancer is the most common breast cancer subtype accounting for approximately 73% of all breast cancers (Breast Cancer, Facts and Figures 2022-2024). The annual 5-year (2016–2020) age-adjusted incidence of HR+/HER2- breast cancer (all stages) was 87.2 per 100,000 women respectively for all races in the United States (SEER 2023). The annual age-adjusted incidence of localized, regional, and metastatic HR+/HER2- was 60.2, 22.3, and 3.9 per 100,000 women, respectively (SEER 2023). The annual incidence from the Ontario (Canada) Cancer registry (2012–2016) was reported to be 97–105 cases per 100,000 women (Seung et al, 2020). The World age-standardized annual incidence of HR+/HER2- and HR+/HER2-positive breast cancer in France was estimated to be 75.21 and 10.3 per 100,000 women, respectively, in 2012 (Cortet et al, 2018).

The phosphatidylinositol 3-kinase (PI3K) pathway is the most frequently altered pathway in HR+ breast cancer and is associated with tumor development, disease progression, and endocrine resistance (Li et al, 2021). The frequency of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (*PIK3CA)* mutations varies across different breast cancer molecular subgroups. For patients with HR+/HER2- BC, *PIK3CA* mutations occur in approximately 35-40% of tumors, regardless of stage (i.e., early breast cancer vs metastatic breast cancer) (Anderson et al, 2020; Razavi et al, 2018; Miron et al, 2010; Bachman et al; 2005; Samuels et al; 2004). A systematic review of 37 studies identified between 1993 and 2019 reported that among all HR+/HER2- metastatic breast cancer patients, *PIK3CA* mutation ranged between 13.3% and 61.5% (median: 36.4%; interquartile range: 31.2-45.6%). More specifically, *PIK3CA*

mutation ranged from 20.8% to 61.5% among tissue biopsies in this subgroup (33 studies) and 43.4% to 46.8% among liquid biopsies (6 studies) (Anderson et al, 2020).

Prevalence

The global 5-year prevalence of breast cancer in 2020 was 201.6 per 100,000 women. In Europe and in the United States, the 5-year prevalence was 552.2 and 640.3 per 100,000 women respectively (GLOBOCAN, WHO). Table 2 describes the prevalence of breast cancer worldwide, in the United States, and in Europe (available from GLOBOCAN 2020 database and fact sheets, WHO).

Table 2 Estimates of Breast Cancer Incidence, Mortality, and 5-Year Prevalence in 2020 (all ages) in different geographic locations

Country	Incidence per 100,000 (World age-standardized rate)	Mortality per 100,000 (World age-standardized rate)	5-year Prevalence (proportion)
Worldwide	47.8	13.6	201.6
Europe	74.3	14.8	552.2
United States	90.3	12.4	640.3
Asia	36.8	11.9	142.0

Source: GLOBOCAN 2020.

Demographics

Age: Amongst women with breast cancer identified from the Surveillance, Epidemiology, and End Results (SEER) registries in the United States between 2000 and 2018, the age-adjusted incidence rate was 48.2, 208.4, and 376.5 per 100,000 women in 20–44-year, 45–54-year, and ≥55-year age-groups, respectively (Du et al, 2022).

HR+/HER2- breast cancer is slower-growing and less aggressive than other subtypes (Breast Cancer, Facts and Figures 2022-2024). A retrospective study in Italy identified 355 women with de novo HR+/HER2- metastatic breast cancer having a median age of 65 years. Crude incidence (per 100,000) distribution by age class showed an increase in estimation from 18–49 to 70–79 years [3 (18–49 years), 8.8 (50–59 years), 10.1 (60–69 years), 13.9 (70–79 years)], and then a decrease in women aged 80 or more (8.3 per 100,000) (Piccinni et al, 2019). According to the SEER Explorer database, in the United States, the median age at diagnosis for HR+/HER2- breast cancer patients is 64 years. The age-specific 5-year (2016-2020) incidence of HR+/HER2- breast cancer increases with advancing age among all racial groups and reported to be 28.4 per 100,000 women (in <50 years age group), 183.4 per 100,000 women (in 50-64 years age group), and 309.9 per 100,000 (in 65 years and older age group) (SEER 2023). In patients with de novo metastatic HR+/HER2- breast cancer (diagnosed at presentation), the age-adjusted incidence rates were 1.3, 8.0, and 14.2 per 100,000 women for age groups<50 years, 50-64 years, and 65+ respectively (SEER 2023).

In the SOLAR-1 trial, 341 patients with *PIK3CA*-mutated HR+/HER2- advanced breast cancer were recruited with a median age of 63 years (André et al, 2019), while in the

SANDPIPER trial, 516 patients with *PIK3CA*-mutated HR+/HER2- advanced breast cancer were enrolled with a median age of approximately 61 years (Dent et al, 2021). Among all patients with *PIK3CA* mutations, 71% were ≤ 65 years and 29% were > 65 years (Mosele et al, 2020).

Race and ethnicity: Racial disparities are significant contributors of breast cancer incidence and survival rate. In the United States, the age-adjusted incidence rate of HR+ breast cancer (from 2000-2018) was reported to be 146.6 per 100,000 for non-Hispanic Whites, 114.1 for non-Hispanic Blacks, and 109.5 per 100,000 for non-Hispanic Asians (Du et al, 2022). From SEER explorer database, in the United States, the age-adjusted annual incidence of HR+/HER2- breast cancer was highest among non-Hispanic Whites (97.7 per 100,000 women), followed by non-Hispanic Blacks (74.4 per 100,000), Non-Hispanic Asian/Pacific Islanders (72.0 per 100,000), and lowest for Hispanics (63.6 per 100,000 women). However, for incident/de novo metastatic HR+/HER2- breast cancer, the annual incidence was observed to be highest for non-Hispanic Blacks (5.1 per 100,000 women), followed by non-Hispanic Whites (4.0 per 100,000), Hispanics (3.0 per 100,000), and Asian/Pacific Islanders (2.8 per 100,000 women) (SEER 2023).

There have been mixed reports on the influence of race on *PIK3CA* mutation prevalence. In studies of Asian and Hispanic patients, the mutation prevalence range (i.e., 35-40%) was similar to non-Hispanic Whites (Li et al, 2021; Blesinger et al, 2018). For African American patients and those with African ancestry, some data suggest *PIK3CA* mutation prevalence may be up to 10% lower in these women (Chen et al. 2022; Pitt et al. 2018; Baselga et al, 2017). The application of this prevalence across all race/ethnicity sub-groups, including Native American and Alaskan Native women, are limited and one should consider the level of uncertainty in race-ethnicity specific prevalence for the *PIK3CA* mutation. It is possible that both genetic and environmental factors play a role in driving these apparent tumor biology differences by race among patients with HR+/HER2- breast cancer harboring *PIK3CA* mutations (Pitt et al, 2018).

The Main Existing Treatment Options

Locally advanced and metastatic breast cancer remains a virtually incurable disease, with the 5-year survival of locally advanced/metastatic breast cancer patients with advanced stage at diagnosis of 31.1 months, with 29.2% of these patients likely to survive at least 5 years from the time of diagnosis. The 5-year survival of distant disease also remains low for HR-positive, HER2-negative locally advanced/metastatic breast cancer at 34% (SEER 2023). Current treatments for advanced or metastatic breast cancer focus on prolonging life and improving or maintaining quality of life. Preventing resistance to therapy and ultimately achieving a cure remain unmet needs in this disease setting.

First-line treatment: According to the European Society for Medical Oncology (ESMO 2023; Gennari et al, 2021) and the National Comprehensive Cancer Network guidelines for breast cancer (NCCN 2024), the gold standard first-line treatment option

for HR+/HER2- metastatic breast cancer patients is cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) combined with endocrine therapy. CDK4/6 inhibitors are effective in de novo or recurrent locally advanced/metastatic breast cancer, in endocrine sensitive and endocrine resistant settings, in postmenopausal or premenopausal women (the latter being treated with a LHRH agonist) and in men. Endocrine monotherapy in the first-line setting is recommended for a small group of patients with poorer performance status and/or comorbidities, while chemotherapy is reserved for those patients with visceral crisis. Fulvestrant has demonstrated efficacy when combined with PI3K inhibitors for the treatment of *PIK3CA*-mutated HR+/HER2- metastatic breast cancer patients who received aromatase inhibitors treatment in the context of neo-adjuvant or adjuvant therapy or for advanced disease and progressed (André et al, 2019). The combination of fulvestrant with alpelisib has been approved for use in this setting (Piqray E.U. Summary of Product Characteristics [SmPC]); however, ESMO treatment guidelines recommend the use of fulvestrant with alpelisib as second line treatment (ESMO 2023; Gennari et al, 2021).

Second-line treatment: The selection of second-line therapy is based on biological/molecular (e.g. targetable aberrations), clinical (e.g. extent of disease and organ function), and patient characteristics (e.g. fitness/frailty). For patients with *PIK3CA*-mutated tumors who are candidates for endocrine-based therapy, the combination of alpelisib and fulvestrant is a recommended treatment option. Other treatment options include the combination of everolimus with exemestane and for patients with germline pathogenic BRCA1/2 mutations, poly (ADP-ribose) polymerase (PARP) inhibitor monotherapy (olaparib or talazoparib). In patients with imminent organ failure (visceral crisis), and/or endocrine refractory disease, chemotherapy is a preferred option.

Beyond second-line treatment: For patients with endocrine-sensitive tumors, continuation of endocrine therapy-based treatments with agents not previously received in the metastatic setting is a recommended option. Otherwise, patients with tumors that are endocrine refractory should be considered for chemotherapy. Sequential single-agent chemotherapy is generally preferred over combination strategies.

Risk Factors for the Disease

Increased age is a known risk factor for breast cancer, and it is estimated that about one-third of postmenopausal breast cancers are linked to potentially modifiable factors, including, postmenopausal obesity, physical inactivity, use of combined estrogen and progestin menopausal hormones, alcohol consumption, no full-time pregnancies, not breastfeeding and having benign breast disorders.

Many risk factors (early menarche, late menopause, obesity, and hormone use) affect lifetime exposure of breast tissue to hormones. Hormones are thought to influence breast cancer risk by increasing cell division, thereby increasing the likelihood of DNA damage, as well as facilitating cancer growth. Although exposures that influence risk

accumulate throughout a woman's life, research suggests that early-life exposures during breast development may be particularly critical. The most common germline mutations associated with breast cancer occur in the *BRCA1* and *BRCA2* genes, with an average cumulative lifetime risk of about 70% (Breast Cancer, Facts and Figures 2022-2024).

Information on risk factors specific to *PIK3CA*-mutated HR+/HER2- breast cancer was limited in the literature.

Natural History of the Indicated Condition in the (Untreated) Population

Morbidity and Mortality: Breast cancer ranks as the fifth most prevalent cause of death from cancer overall (both sexes), while in females it is the most common cause of cancer-related death worldwide. An estimated 685,000 deaths were attributed to breast cancer in 2020, with an age-standardized mortality rate of 13.6 per 100,000 women accounting for 6.9% of all cancer deaths. It is the third most common cause of cancer associated death (both sexes) in Europe and fourth most common in the United States with an age-standardized rate of 14.8 and 12.4 per 100,000 women in 2020 respectively (GLOBOCAN, WHO 2020). Table 2 describes the mortality due to breast cancer worldwide, in the United States, and in Europe (available from GLOBOCAN 2020 database and fact sheets, WHO).

The 5-year relative survival rates for HR+/HER2- breast cancer in the United States were 94.8% for all stages and 34% for de novo metastatic stage between 2013 and 2019 (SEER 2023). The 5-year relative survival rate for metastatic HR+/HER2- breast cancer varied slightly among different races with lowest recorded for non-Hispanic black women (23.7%), followed by Hispanics (34.0%), and highest for non-Hispanic Whites (35.8%) and non-Hispanic Asians / Pacific Islanders (37.3%) (SEER 2023). In metastatic HR+/HER2- breast cancer, the median survival is approximately 2 years and may extend to 33 months. Site of metastatic disease greatly affects survival outcomes. Patients with bone-only disease have superior survival, whereas those with brain metastases have inferior survival (Daily et al, 2021). In Italy, survival analysis performed on 355 women with HR+/HER2- metastatic breast cancer found that during the whole follow-up, 80 women (22.5% of the cohort) experienced a disease progression; in particular, 1, 2, and 3 disease progression events were recorded in 18.0%, 2.7%, and 0.8% of patients, respectively. First disease progression occurred, on average, 13 ± 6 months after diagnosis (Piccinni et al, 2019).

A pooled analysis of 33 study arms across 11 trials included 1,386 patients with *PIK3CA*-mutated HR+/HER2- metastatic breast cancer. Across all included studies, the median progression-free survival was 5.4 months for the *PIK3CA*-mutated cohort compared to 6.2 months for the *PIK3CA* wild-type cohort. Median overall survival was

reported to be 26.9 months in eight *PIK3CA*-mutated cohorts compared to 37.8 months for the six *PIK3CA* wild-type cohorts (Fillbrunn et al, 2022).

Information on pregnancy outcomes specifically in patients with *PIK3CA*-mutated HR+/HER2- breast cancer was limited in the literature.

Important Co-Morbidities

The presence of concurrent medical conditions in patients with breast cancer has been shown to correlate with reduced survival, greater treatment-related toxicities and complications from standard of care management, and diminished quality of cancer related treatment (Sogaard et al, 2013). Pre-existing medical conditions in patients with breast cancer are common, particularly in those who are older, or those that have received previous cancer treatment (Keesari et al, 2024; Kim et al, 2022; Greenlee et al 2022). Studies have shown that women with breast cancer had increased incidence of prediabetes, cardiovascular disease (CVD) events, CVD-related mortality, and all-cause mortality compared with women without breast cancer (Keesari et al, 2024; Greenlee et al, 2022).

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical safety of inavolisib has been assessed in a comprehensive battery of toxicology studies that include single-dose and repeat-dose general toxicology studies (once a day [QD] oral [PO] dosing) of up to 3 months' duration in rats and dogs; in vitro and in vivo genetic toxicology studies; in vitro phototoxicity study; in vitro and in vivo secondary pharmacology and safety pharmacology studies; and embryofetal development (Segment II) studies in rats. In addition, RO7533297 (M5), which was initially identified as a degradant in the drug product, has been assessed in the in vitro bacterial reverse mutation assay and in the 28-day rat *Pig-a* gene mutation assay with inavolisib. Impurities in inavolisib drug product have been evaluated for their mutagenicity potential using the standard in silico structure activity relationship software programs in combination with expert review. One impurity, RO7304383, was tested in the bacterial mutagenesis assay.

The PI3K/AKT/mTOR pathway (hereinafter referred to as the PI3K pathway) is involved in several important cellular functions including its role in regulating normal growth and development as well as maintaining organ homeostasis and function. The majority of findings identified in nonclinical toxicology studies were consistent with the anticipated pharmacologic effects of PI3K inhibition, including hyperglycemia and body weight loss in rats and dogs, inflammation in dogs, bone marrow hypocellularity, atrophy of glandular and reproductive tissues and eye lens degeneration in rats; and lymphoid depletion and swelling of the lens fibers in the eye in dogs. Findings were generally dose-dependent and reversible, and considered to be clinically monitorable and/or manageable. Lens fiber degeneration observed in some rats (≥ 3.6 times the area under the concentration-

time curve [AUC] exposure of 1060 ng • hr/mL at 9 mg [Study GO39374]) was considered irreversible.

Key safety findings from nonclinical studies and relevance to human usage are summarized below. Unless otherwise indicated, exposure multiples provided represent the fold difference between the AUC exposure in nonclinical species where the findings were observed relative to that at the clinical 9 mg QD PO dose (1060 ng • hr/mL [Study GO39374]).

Key Safety Findings:

- **Metabolic Effects**

Dose dependent and reversible, minimal to marked, increases in glucose were observed in rats and dogs (≥ 0.2x), consistent with the pharmacologic effect of PI3K inhibition on insulin signaling (Fritsch et al, 2014). Hyperglycemia was accompanied by increases in cholesterol and urine glucose at higher doses of inavolisib. Correlative microscopic adaptive changes in the pancreas included islet hypertrophy with vascular ectasia (angiectasia) in rats and diffuse hypertrophy/vacuolation of islet cells in dogs. Other microscopic findings consistent with hyperglycemia-related metabolic disturbances observed in one dog with persistent hyperglycemia included centrilobular vacuolation/degeneration of the hepatocytes in the liver, diffuse bilateral micro vesicular vacuolation in the straight proximal tubules of the kidney, and vacuolation at the equatorial region of the lens cortex of the eyes.

Relevance to human usage: Yes

Discussion:

The PI3K pathway plays a central role in cell physiology by transmitting diverse extracellular stimuli through a signaling cascade (Hoxhaj 2020).

Among the most frequently observed events are mutations in *PIK3CA*, which encodes the p110α catalytic subunit of the PI3K complex, and loss of function mutations in *PTEN*, which encodes a phosphatase that degrades the phosphoinositide lipids generated by PI3K complex activation. As p110α mediates virtually all cellular responses to insulin, targeted inhibition of this enzyme disrupts glucose metabolism in multiple tissues. For example, blocking insulin signaling promotes glycogen breakdown in the liver and prevents glucose uptake in the skeletal muscle and adipose tissue, resulting in transient hyperglycemia within a few hours of PI3K pathway inhibition. Glucose transport capacity, glycogen synthesis, and glycolysis have been reported to be reduced (Hernandez-Aya and Gonzalez-Angulo 2011). The effect is usually transient because compensatory insulin release from the pancreas (insulin feedback) restores normal

glucose homeostasis. Hyperglycemia may be exacerbated or prolonged in patients with any degree of insulin resistance, which may necessitate discontinuation of therapy.

Hyperglycemia is an important identified risk for inavolisib and is an on-target toxicity known to occur with PI3K inhibitors. Hyperglycemia events were reported in both the pivotal and supportive study. The majority of hyperglycemia events occurred within the first two months of treatment with inavolisib (see SVII.3.1).

Hyperglycemia is included in the Special warnings and precautions for use section of the Itovebi Summary of Product Characteristics (SmPC) (Section 4.4), and as an adverse drug reaction (ADR) in the Undesirable effects section (Section 4.8) of the Itovebi SmPC.

- **Inflammation**

In dogs, dose-dependent and reversible inflammation was observed in multiple organs (≥ 0.8x). These findings correlated with changes in clinical pathology markers of inflammation, including increased neutrophils and fibrinogen, decreased red cell mass, albumin and albumin/globulin ratio; increased globulins, leukocytes, lymphocyte, and monocyte counts.

Relevance to human usage: Yes

Discussion:

Immune dysregulation results in diverse pathologies including autoimmune disease, chronic inflammatory disorders, allergies as well as immune deficiencies and cancer. The PI3K signaling pathway plays a complex role in orchestrating both pro-inflammatory and anti-inflammatory pathways to maintain effective immunity while protecting host tissues (Stark et al, 2015).

Preclinical and early clinical trials show great potential in therapeutic targeting of this pathway, however, isoform specific serious adverse drug reactions from PI3K inhibitors related to inflammation have been observed including pneumonitis, diarrhea, colitis, stomatitis, rash, and elevated transaminases that are mostly associated with PI3Kδ inhibition (Curigliano and Shah, 2019). PI3Kα inhibitors may also cause adverse events (AEs) including pneumonitis, diarrhea, and colitis but at a lower frequency than that observed in PI3Kδ inhibitors (Yu et al, 2023).

In patients treated with inavolisib in clinical trials, the most common inflammation associated AEs were stomatitis/oral mucositis (see SVII.1.1).

Stomatitis/oral mucositis is listed in the Special warnings & precautions for use section (Section 4.4) of the Itovebi SmPC. Additionally, stomatitis/oral mucositis and diarrhea are listed as ADRs in the Undesirable effects section (Section 4.8) of the Itovebi SmPC.

- **Hematopoietic Effects and Lymphoid Depletion**

Dose-dependent and reversible decreases in all circulating hematopoietic cell lineages were observed in rats (≥ 0.2x). These hematologic changes were correlated with a slight increase in activated partial thromboplastin and decreases in cellularity in the bone marrow and splenic red pulp.

Dose-dependent decreases in lymphocytes in lymphoid tissues, including thymus, gut-associated lymphoid tissues (GALT)/Peyer's patch, mesenteric lymph node, mandibular lymph node and spleen, were observed in dogs (≥ 0.2x) and showed a trend toward recovery.

Relevance to human usage: Yes

Discussion:

Myelosuppression is a common adverse effect of antitumor drugs. Likewise, pathologic alterations and suppression in the PI3K pathway may result in disruption of cellular homeostasis leading to clinical adverse effects such as anemia, thrombocytopenia, and neutropenia (Zhang et al, 2019).

Anemia associated with PI3Kα and PI3Kβ inhibitors is not frequent and symptoms are usually mild with most patients suffering from grade 1 severity (Zhang et al, 2019). However, for HR+ breast cancer patients the risk of bone metastases that can induce anemia was relatively high (Liu et al, 2021).

Nakao et al, 2008 illustrated a significant role for the PI3K signaling pathway in thrombopoietin-induced proliferation of primary megakaryocytes. Suppression of PI3K pathway signaling induces apoptosis in normal human megakaryocytes and this is more commonly observed with PI3Kδ/γ inhibitors (Zhang et al, 2019).

PI3K/AKT/mTOR inhibitor-induced bone marrow suppression has been frequently associated with PI3Kδ/γ inhibitors (Zhang et al, 2019). The immunosuppressant effects observed with the alpha-specific inhibitor alpelisib were minimal (Piqray E.U. SmPC).

In patients treated with inavolisib in clinical trials, hematologic effects including lymphopenia, anemia, neutropenia, thrombocytopenia were observed primarily in combination with palbociclib. Blood counts are monitored in patients enrolled in inavolisib clinical studies. In pivotal study WO41554, thrombocytopenia and anemia were assessed as ADRs and are both listed as ADRs in the Undesirable effects section (Section 4.8) of the Itovebi SmPC (see SVII.1.1).

- **Ocular Lens Findings**

Minimal-to-slight lens fiber degeneration of the eye was observed (including one recovery animal) in rats (≥ 3.6x) in the 1-month study. No ocular findings were noted in the 3-month study up to 1.4x (the highest dose tested).

Bilateral, reversible, very slight swelling of the fibers at the equatorial region of the lens was observed (≥ 0.2x) in the 3-month study in dogs. The minimal nature and distribution

of this finding is not expected to affect lens function. Lens opacity at the posterior capsule/cortex noted during ophthalmology evaluations in two animals (1.2x) did not have histopathologic correlates.

Relevance to human usage: Yes

Discussion:

The PI3K pathway plays a role in the proliferation, migration, and apoptosis of corneal and lens epithelial cells (Chen et al, 2022; Liegl et al, 2014). Corneal diseases (diabetic keratopathy, dry eye disease, and keratitis) (Chen et al, 2022) and cataract development are associated with the PI3K/AKT signaling pathway (Liegl et al, 2014). In general, a sustained high glucose state can manifest persistent ocular conditions that may cause impaired or permanent vision loss (Shah et al, 2021). Ocular effects have been observed with PI3K inhibitors in preclinical and clinical studies, including blurred vision and dry eye (Piqray E.U. SmPC).

In patients treated with inavolisib in clinical trials, low grade eye disorder events (defined as Preferred Terms [PTs] in Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class [SOC] Eye disorders) have been reported (see SVII.1.1).

In the Itovebi SmPC list of ADRs in the Undesirable effects section (Section 4.8), only the ADR of dry eye is listed within the Eye disorders SOC.

- **Reproductive and Developmental Toxicity**

In male rats, dose-dependent atrophy of the prostate and seminal vesicle and decreased organ weights without microscopic correlate in the epididymis and testis were observed (≥ 0.4x). In the 1-month toxicity study in dogs, focal inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed (≥ 2.0x). However, there were no inavolisib-related microscopic findings in the testes or epididymides or effects on sperm concentration, motility, or morphology in the 3-month dog toxicity study at similar exposures.

In female rats, minimal to mild and reversible atrophy in the uterus and vagina and decreased ovarian follicles were observed (≥ 1.1x) in the 4-week rat toxicity study; and findings suggestive of an interruption/alteration of the estrus cycle were observed (≥ 1.5x) in the 3-month rat toxicity study. Potential effects on female reproductive system cycling are expected to be reversible in a clinical setting.

The embryo-fetal development study in Sprague-Dawley (SD) rats identified inavolisib-related dose-dependent effects on embryo-fetal development (≥ 0.8x) that included decreases in fetal body weight and placental weight, post-implantation loss, lower fetal viability, and teratogenicity (fetal external, visceral, and skeletal malformations).

Relevance to human usage: Yes

Discussion:

No clinical studies assessing the reproductive and developmental toxicity of inavolisib have been conducted to date and there are no available data regarding the use of inavolisib during pregnancy.

Based on animal studies, inavolisib may cause fetal harm when administered to pregnant women, therefore, comprehensive contraception guidance is provided in the Fertility, pregnancy and lactation (Section 4.6) section of the Itovebi SmPC wherein female patients of childbearing potential and male patients with female partners of childbearing potential or pregnant female partners should use effective contraception while receiving inavolisib and for 1 week following the last dose of inavolisib. Embryo-fetal toxicity is included in the Preclinical safety data (Section 5.3) section of the Itovebi SmPC.

- **Genotoxicity**

Inavolisib does not pose a genotoxic risk in humans. Inavolisib was not mutagenic in the bacterial mutagenesis assay. Inavolisib showed clastogenicity in vitro; however, there was no evidence of inavolisib-induced in vivo genotoxicity (clastogenicity, aneugenicity, or DNA damage) in the micronucleus and comet study in rats (up to maximum tolerated dose at 16.1x exposure of the clinical dose of 9 mg).

RO7533297 (M5) is a degradant in the drug product. It was also detected in rats in vivo as a minor metabolite. RO7533297 was mutagenic in the bacterial mutagenesis assay. However, in the 28-day rat *Pig-a* gene mutation assay with inavolisib, there were no biologically relevant increases in *Pig-a* gene mutation in either mature erythrocytes or immature reticulocytes in the peripheral blood. The use of inavolisib in the rat *Pig-a* assay is justified, as the AUC ratio of RO7533297 to inavolisib was approximately 2.5% in rat plasma. In contrast, in the human mass balance study GP42652, circulating metabolites were minimal with the majority (99.5%) of drug-related material being inavolisib. Thus, inavolisib and RO7533297 (at clinically relevant circulating exposure) do not pose biologically relevant mutagenic risks in mammals in vivo.

Impurities were evaluated using standard in silico models (Derek for Nexus and Leadscope Statistical model). Five impurities were classified as non-mutagenic based on expert review and structural similarity to inavolisib. One alerting impurity was non-mutagenic in the bacterial reverse mutation assay. Remaining impurities are controlled in accordance with International Conference for Harmonisation (ICH) M7(R2).

Relevance to human usage: No

Discussion:

Inavolisib is not genotoxic and does not pose any genotoxic risk in humans.

- **Carcinogenicity**

No carcinogenicity studies with inavolisib have been conducted.

Relevance to human usage: No

Discussion:

No carcinogenicity studies are currently planned because such studies are not required for drugs intended for advanced cancer patients per ICH-S9.

- **Cardiovascular Effects**

Inavolisib-related cardiovascular effects were limited to minor findings in the single-dose cardiovascular safety pharmacology study in dogs, including generally dose-dependent, reversible, and non-adverse decreases in heart rate, increases in arterial pressure and contractility, lengthening of PR and QT intervals (likely driven by the decreased heart rates), and minimally lengthened corrected QT interval (QTc) at ≥ 9x the maximum concentration observed (C_{max}) total of 75.1 ng/mL at 9 mg clinical dose.

Relevance to human usage: No

Discussion:

No cardiovascular studies are currently planned for inavolisib.

Based on the Concentration-QTc analysis from study GO39374, it would not be expected that inavolisib would have a clinically relevant QTc prolongation effect (Report 1128819).

No clinically significant trends in post-baseline versus baseline mean electrocardiogram parameters were identified in both pivotal and supportive studies (Report 1126696, Report 1125233).

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

The exposure and safety data included in this E.U. Risk Management Plan (E.U. RMP) are primarily derived from the pivotal Phase III study WO41554 (INAVO120; clinical cutoff date [CCOD] of 29 September 2023; N=325; 162 patients were treated with inavolisib). In addition, safety data from Arm B (n=27), Arm E (n=20), and Arm F (n=19), as well as the aggregate safety data (Arms A through F) of the Phase I Study GO39374 (CCOD of 27 March 2023) from patients treated with 9 mg QD inavolisib as a single agent (Arm A), or inavolisib in combination (Arm B, C, D, E and F) are provided to support a comprehensive evaluation of the safety profile of inavolisib (N=165). Patients treated at doses other than 9 mg QD are not deemed relevant for the E.U. RMP.

Study WO41554 is a Phase III, randomized, double-blind, placebo-controlled, multicenter, global study designed to compare the efficacy, safety, and tolerability of the

triplet combination of inavolisib plus palbociclib and fulvestrant (Inavo+Palbo+Fulv) versus placebo plus palbociclib and fulvestrant (Pbo+Palbo+Fulv) in patients with *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease.

Study GO39374 is a Phase I, open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of inavolisib as a single agent in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumors and in combination with endocrine and targeted therapies in patients with locally advanced or metastatic *PIK3CA*-mutated breast cancer. Arm B of the study evaluated inavolisib in combination with palbociclib and letrozole; Arm E and Arm F evaluated inavolisib in combination with palbociclib and fulvestrant. In Arm F, patients were required to have a body mass index (BMI) $\geq$ 30 kg/m^2 and/or glycosylated hemoglobin (HbA_{1C}) $\geq$ 5.7% (i.e., risk factors for hyperglycemia). Patients enrolled in Arm F began metformin on Cycle 1, Day 1 along with palbociclib and fulvestrant and initiated inavolisib on Cycle 1, Day 15.

An overview of the key design features of the studies contributing to safety data in the RMP is provided in Table 3.

Table 3 Summary of Studies Contributing to Safety Evaluation

Study No (Phase)	Population	Study Design	Number of Patients Evaluable for Safety	Dose, Route, and Regimen	CCOD
Pivotal Study					
WO41554 (Phase III)	Patients ≥ 18 years of age with locally advanced or metastatic *PIK3CA*-mutated, HR-positive, HER2- negative breast cancer	Multicenter, randomized, double blinded, placebo-controlled	N = 324 (Inavo + Palbo + Fulv: 162 patients; Pbo + Palbo + Fulv: 162 patients)	Inavolisib 9 mg/placebo QD PO + palbociclib 125 mg QD PO (21/7) + fulvestrant 500 mg Q4wk IM (Days 1 and 15 of first 28-day cycle, and then Day 1 of each following 28-day cycle)	Primary analysis: 29 Sep 2023
Supportive Study					
Study GO39374 (Phase I)	Patients ≥ 18 years of age with locally advanced or metastatic *PIK3CA*-mutated solid tumors, including breast cancer	Multicenter, first-in-human, open-label, dose-escalation and expansion	Stage I: Dose escalation (N=50): Arm A=20; Arm B=13; Arm C=17 Stage II: Dose expansion[a]: (N = 140) Arm B=20 Arm C=20 Arm D=60 Arm E=20; Arm F = 20[a] Patients evaluable for safety = 190 Patients who received 9mg QD PO (N = 165) [b]	**Dose Escalation:** Arm A: inavolisib QD PO (6-, 9-, 12 mg) Arm B: inavolisib QD PO (3-, 6-, 9 mg) + letrozole 2.5 mg QD PO + palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm C: inavolisib QD PO (6-, 9 mg) + letrozole 2.5 mg QD PO **Dose Expansion:** Arm B: inavolisib 9mg QD PO + letrozole 2.5 mg QD PO + palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm C: inavolisib 9mg QD PO + letrozole 2.5 mg QD PO Arm D: inavolisib 9mg QD PO+ fulvestrant 500 mg IM Arm E: inavolisib 9mg QD PO+ fulvestrant 500 mg IM ± palbociclib 125 mg QD PO (3 weeks on/1 week off) Arm F[a]: inavolisib 9mg QD PO+ fulvestrant 500 mg IM± palbociclib 125 mg QD PO (3 weeks on/1 week off)+ metformin up to 2000 mg PO	Interim analysis: 27 Mar 2023

Table 3 Summary of Studies Contributing to Safety Evaluation (cont.)

CCOD=clinical cutoff date; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IM=intramuscular; IV=intravenous; PO=orally; QD=once daily.
Note: Phase I Study GO39374 Stage II Arm G (inavolisib in combination with trastuzumab and pertuzumab) is not included in the dossier as this arm was still enrolling at the time of CCOD, and the treatment combination studied and the population enrolled differ from the proposed indication in the application.

[a] A total of 21 patients were enrolled in Arm F of Study GO39374, one patient withdrew consent and discontinued from the study prior to receiving any study treatment.

[b] Patients who received 9mg QD PO (N =165): Arm A=9, Arm B=27, Arm C=30, Arm D=60, Arm E=20; Arm F=19.

Duration of Exposure

Pivotal Study WO41554:

As of the CCOD of 29 September 2023, a total of 162 patients with *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced or metastatic breast cancer in Study WO41554 received inavolisib (9 mg PO QD) in combination with palbociclib and fulvestrant (see Table 4). Of those patients, the largest proportion received inavolisib for >12 months (65 patients [40.1%]) in comparison to other treatment duration categories.

Table 4 Inavolisib Exposure by Duration, Study WO41554

Inavolisib Exposure by Duration, Safety Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

Duration of exposure	Number of Patients (N=162)	Person time* (N=162)
Total patients numbers/person time	162 (100.0%)	163.54
<= 3 months	31 (19.1%)	3.41
> 3 months to <= 6 months	21 (13.0%)	8.06
> 6 months to <= 12 months	45 (27.8%)	33.18
> 12 months	65 (40.1%)	118.89

n= number of patients exposed to Inavolisib
* Person time is the sum of exposure across all patients in unit: years
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

GitLab repository: https://gitlab-ci-token:64_qH1Lk6iqzjzWNL6ML7N1@code.roche.com/studies/clinicalreporting/WO41554_SCS_RMP_2023_897070U
Git hash: 72f8765f7ebac3b2055100a26a10590844b1bb69
14 DEC 2023 15:35 GMT
Output:/ocean/harbour/CDT70123/WO41554/SCS_RMP_2023/prod/output/t_rmp01_RMP_SAS_29SEP2023_41554.out

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Supportive Study GO39374:

As of the CCOD of 27 March 2023, a total of 165 patients with locally advanced or metastatic *PIK3CA*-mutated solid tumors in Study GO39374 received inavolisib (9 mg PO QD) in combination with endocrine and targeted therapies. Of those patients, 62 patients (37.6%) in Arms A–F received inavolisib (9 mg PO QD) for >12 months. (Annex 7B.1).

Exposure By Age Group and Gender

Pivotal Study WO41554:

Of the 162 patients in Study WO41554 who received inavolisib (9 mg PO QD) in combination with palbociclib and fulvestrant, the majority were female (96.9% [157/162 patients]) and were <65 years of age (84.7% [133/157 patients]) (see Table 5).

Table 5 Inavolisib Exposure by Age Group and Gender, Study WO41554

Inavolisib Exposure by Age Group and Gender, Safety Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

	Female		Male	
Age group (years)	Number of Patients (N=157)	Person time* (N=157)	Number of Patients (N=5)	Person time* (N=5)
Total patients numbers/person time	157 (100.0%)	154.97	5 (100.0%)	8.57
<65	133 (84.7%)	133.28	5 (100.0%)	8.57
65-74	19 (12.1%)	18.1	0 (0.0%)	0
>=75	5 (3.2%)	3.59	0 (0.0%)	0

n= number of patients exposed to Inavolisib
* Person time is the sum of exposure across all patients in unit: years
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

GitLab repository: https://gitlab-ci-token:64_qH1Lk6iqzjzWNL6ML7N1@code.roche.com/studies/clinicalreporting/WO41554_SCS_RMP_2023_8970700
Git hash: 72f8765f7ebac3b2055100a26a10590844b1bb69
14 DEC 2023 15:34 GMT
Output:/ocean/harbour/CDT70123/WO41554/SCS_RMP_2023/prod/output/t_rmp03_RMP_SAS_29SEP2023_41554.out Page 1 of 1

Supportive Study GO39374:

Of the 165 patients who received inavolisib (9 mg PO QD) in Arms A-F of Study GO39374, 66.1% (109/165 patients) were <65 years of age and 29.1% (48/165 patients) were 65–74 years of age. All patients enrolled in study GO39374 were female. (Annex 7B.2).

Exposure by Dose

Pivotal Study WO41554:

A total of 162 patients received inavolisib (9 mg PO QD) in combination with palbociclib and fulvestrant in Study WO41554 (see Table 6).

Table 6 Exposure by Dose, Study WO41554

Inavolisib Exposure by Dose, Safety Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

	Number of Patients (N=162)	Person time* (N=162)
9 mg	162 (100.0%)	163.54

n= number of patients exposed to Inavolisib
* Person time is the sum of exposure across all patients in unit: years
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

GitLab repository: https://gitlab-ci-token:64_qH1Lk6iqzjzWNL6ML7N1@code.roche.com/studies/clinicalreporting/WO41554_SCS_RMP_2023_8970700
Git hash: 72f8765f7ebac3b2055100a26a10590844b1bb69
14 DEC 2023 15:35 GMT
Output:/ocean/harbour/CDT70123/WO41554/SCS_RMP_2023/prod/output/t_rmp02_RMP_SAS_29SEP2023_41554.out Page 1 of 1

Supportive Study GO39374:

In study GO39374 (Arms A–F), 165 patients received at least one dose of inavolisib (9 mg PO QD) (189.9 patient-years of exposure) (Annex 7B.3).

Exposure by Race

Pivotal Study WO41554:

Of the 162 patients that received inavolisib (9 mg PO QD) in combination with palbociclib and fulvestrant, 58.0% were White (94/162 patients) and 38.3% were Asian 62/162) (see Table 7).

Table 7 Inavolisib Exposure by Race, Study WO41554

Inavolisib Exposure by Race, Safety Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

Race	Patients (N=162)	Person time* (N=162)
Total patients numbers/person time	162 (100.0%)	163.54
ASIAN	62 (38.3%)	61.71
BLACK OR AFRICAN AMERICAN	1 (0.6%)	0.63
UNKNOWN	5 (3.1%)	3.59
WHITE	94 (58.0%)	97.61

n= number of patients exposed to Inavolisib
* Person time is the sum of exposure across all patients in unit: years
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

GitLab repository: https://gitlab-ci-token:64_qH1Lk6iqzjzWNL6ML7N1@code.roche.com/studies/clinicalreporting/WO41554_SCS_RMP_2023_8970700
Git hash: 72f8765f7ebac3b2055100a26a10590844b1bb69
14 DEC 2023 15:34 GMT
Output:/ocean/harbour/CDT70123/WO41554/SCS_RMP_2023/prod/output/t_rmp05_RMP_SAS_29SEP2023_41554.out Page 1 of 1

Supportive Study GO39374:

Of the 165 patients that received at least one dose of inavolisib (9 mg PO QD), the majority were White (123 patients [74.5%]) (Annex 7B.4).

Exposure by Ethnicity

Pivotal Study WO41554:

Of the 162 patients that received inavolisib (9 mg PO QD) in combination with palbociclib and fulvestrant, the majority were Not Hispanic or Latino (145/162 patients [89.5%]) (see Table 8).

Table 8 Inavolisib Exposure by Ethnicity, Study WO41554

Inavolisib Exposure by Ethnic Origin, Safety Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

Ethnicity	Number of Patients (N=162)	Patient Time* (N=162)
Total patients numbers/person time	162 (100.0%)	163.54
HISPANIC OR LATINO	11 (6.8%)	8.32
NOT HISPANIC OR LATINO	145 (89.5%)	150.94
NOT REPORTED	2 (1.2%)	1.35
UNKNOWN	4 (2.5%)	2.93

n= number of patients exposed to Inavolisib
* Person time is the sum of exposure across all patients in unit: years
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

GitLab repository: https://gitlab-ci-token:64_qH1Lk6iqzjzWNL6ML7N1@code.roche.com/studies/clinicalreporting/WO41554_SCS_RMP_2023_8970700
Git hash: 72f8765f7ebac3b2055100a26a10590844b1bb69
14 DEC 2023 15:34 GMT
Output:/ocean/harbour/CDT70123/WO41554/SCS_RMP_2023/prod/output/t_rmp04_RMP_SAS_29SEP2023_41554.out

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Supportive Study GO39374:

Of the 165 patients that received at least one dose of inavolisib (9 mg PO QD), the majority were Not Hispanic or Latino (122/165 patients [73.9%]) (Annex 7B.5).

PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 9 Important Exclusion Criteria in Pivotal Studies in the Development Program [a]

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Metaplastic breast cancer	This type of breast cancer is predominately triple negative and as such standard of care treatment is chemotherapy.	No	This exclusion criterion was not related to the safety of the patient. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Any prior systemic therapy for metastatic breast cancer (including prior treatment with fulvestrant or any selective estrogen-receptor degrader [b], any PI3K, AKT, or mTOR inhibitor, chemotherapy, radiotherapy, any other anti-cancer therapy, or an investigational drug[s])	These patients were excluded as prior therapy could confound study results.	No	Given the life-threatening nature of the proposed indication, treatment with inavolisib should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes	Minimize the identified risk of inavolisib that is known to cause hyperglycemia.	Yes	See S.VII.3.2 for more details.

Table 9 Important Exclusion Criteria in Pivotal Studies in the Development Program [a] (cont.)

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Patients with creatinine clearance < 50 mL/min on the basis of the Cockcroft–Gault glomerular filtration rate estimation (i.e., patients with moderate to severe renal impairment) [c]	The major clearance pathways for inavolisib were found to be urinary excretion and metabolism. An increase in exposure is expected in patients with moderate to severe renal impairment who may potentially be unable to tolerate inavolisib therapy.	No	Based on the results from Study GP44944, the objective of which is to evaluate the effect of moderate to severe renal impairment on the PK and safety of inavolisib, dose adjustment recommendations have been added to the SmPC for moderate renal impairment. Additional results for patients with severe renal impairment from Study GP44944 are awaited.
Serious infection requiring IV antibiotics within 7 days prior to Day 1 of Cycle 1	This comorbidity could affect compliance with the protocol or interpretation of results, potentially confounding safety assessments.	No	Given the life-threatening nature of the proposed indication, treatment with inavolisib should be an option for such patients. No specific warning or exclusion is included in the SmPC as there has been no evidence that inavolisib worsens any viral or bacterial infections.
Known and untreated, or active CNS metastases, leptomeningeal disease or carcinomatous meningitis	Such patients were excluded because it is unlikely they would have a successful outcome on inavolisib. Inavolisib does not cross an intact blood-brain barrier and therefore would not benefit patients with CNS disease.	No	Patients with CNS disease requiring treatment are indicated for treatments that are effective within the CNS.

Table 9 Important Exclusion Criteria in Pivotal Studies in the Development Program [a] (cont.)

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results.	Such patients were excluded because these other comorbidities could affect the compliance with study treatment or interpretation of safety results.	No	Given the life-threatening nature of the proposed indications, treatment with inavolisib should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Chronic corticosteroid therapy of $\geq$10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease	These patients were excluded as they have a severe inflammatory condition and inavolisib use is associated with inflammation risks (e.g., pneumonitis, stomatitis). These patients were also excluded due to the tendency for high-dose corticosteroids to raise blood sugar level, and to minimize effects of possible early and late complications of long-term treatment with immunosuppressive drugs that could confound study results.	No	Given the life-threatening nature of the proposed indications, treatment with inavolisib should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.
Allergy or hypersensitivity to components of the inavolisib/placebo, palbociclib, or fulvestrant formulations	Patients with hypersensitivity to inavolisib, palbociclib, fulvestrant, any excipient and/or component of the placebos cannot be treated or continue treatment	No	Hypersensitivity is listed as a contraindication in the SmPC.

Table 9 Important Exclusion Criteria in Pivotal Studies in the Development Program [a] (cont.)

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or within 60 days after the final dose of study treatment (patients may be advised to use an effective means of contraception for up to 2 years after the last dose of fulvestrant)	No clinical data is available to confirm whether inavolisib can cross the placenta or cause harm to the fetus when administered to pregnant women, or whether it affects reproductive capacity. The available nonclinical data for inavolisib and the known risks associated with the drug class indicate an overall risk to embryo-fetal development and teratogenicity.	No	Section 4.6 (Fertility, pregnancy, and lactation) of the SmPC advises women of childbearing potential to avoid pregnancy, and women to discontinue breastfeeding while receiving inavolisib, and for 1 week after the last dose. It also includes recommendations for pregnancy testing prior to treatment initiation.
Major surgical procedure, or significant traumatic injury, within 28 days prior to Day 1 of Cycle 1 or anticipation of the need for major surgery during the course of study treatment	These patients were excluded to minimize risks the therapy may have to surgical healing and to the risk of infection in an acutely post-surgical patient. In addition, post-surgical recovery may limit ability to comply with study requirements and complications may confound interpretation of results.	No	Given the life-threatening nature of the proposed indication, treatment with inavolisib should be an option for such patients. No specific warning or exclusion is included in the SmPC as it is considered part of routine oncology practice to assess a patient's fitness for treatment.

AKT = protein kinase B; CNS = central nervous system; HbA_{1C} = glycosylated hemoglobin; IV=intravenous; mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol 3-kinase; SmPC = Summary of Product Characteristics.

[a] Exclusion criteria are from Study WO41554.

[b] With the exception of patients who received this prior treatment as part of neoadjuvant therapy only and with treatment duration of no longer than 6 months.

[c] For inclusion in study WO41554, patients were required to have a creatinine clearance ≥50 mL/min.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical trial development program for inavolisib was unable to detect adverse drug reactions that are:

- rare adverse reactions
- caused by prolonged exposure
- caused by cumulative exposure
- or that have a long latency

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Use in Pregnancy and Lactation

Based on animal studies (see Module SII), inavolisib may cause fetal harm when administered to pregnant women, therefore, inavolisib is not recommended during pregnancy, and comprehensive contraception guidance is provided wherein female patients of childbearing potential and male patients with female partners of childbearing potential or pregnant female partners should use effective contraception while receiving inavolisib and for 1 week following the last dose of inavolisib.

No clinical studies of inavolisib in pregnant women have been performed, and there are no available data regarding the use of inavolisib during pregnancy. The use of inavolisib during labor and delivery has not been established.

No studies have been conducted to assess the impact of inavolisib/metabolites on milk production or its presence in breast milk. Because of the potential for serious adverse reactions in the breastfed infant, it is recommended that women should not breastfeed during inavolisib treatment and for 1 week after the last dose of inavolisib.

Table 10 Exposure of Special Populations Included or Not in Clinical Trial Development Program

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	Mild hepatic impairment [a]: n = 100 [b] Moderate hepatic impairment [a]: n = 0 [b] Severe hepatic impairment [a]: n = 0 [b]
Patients with renal impairment	Mild renal impairment [a]: n = 117 [b] Moderate renal impairment [a]: n = 24 [b] Severe renal impairment [a]: n = 0 [b]
Patients with cardiovascular impairment	Not included in the clinical development program
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Very limited
Population with relevant different ethnic origin	Refer to Table 8
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other:	Not included in the clinical development program

[a] Hepatic impairment categories:
Normal: total bilirubin (TB) and AST ≤ upper limit of normal (ULN).
Mild hepatic impairment: TB > ULN to 1.5 × ULN or AST > ULN and total bilirubin ≤ ULN.
Moderate hepatic impairment: TB > 1.5–3 × ULN, any AST.
Severe hepatic impairment: TB > 3–10 × ULN, any AST.
Renal impairment category is based on estimated creatinine clearance per FDA guidance:
Normal: ≥ 90 mL/min.
Mild: 60–89 mL/min.
Moderate: 30–59 mL/min.
Severe: 15–29 mL/min.
[b] Patients from studies WO41554 or GO39374 who received at least one dose of inavolisib (9 mg).
Source: Annex 7B.6; Annex 7B.7; Annex 7B.8; Annex 7B.9.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

This section is not applicable, as this is the initial marketing application in the EEA.

SV.1 POST-AUTHORIZATION EXPOSURE

This section is not applicable, as this is the initial marketing application in the EEA.

SV.1.1 Method used to calculate exposure

This section is not applicable, as this is the initial marketing application in the EEA.

SV.1.2 Exposure

This section is not applicable, as this is the initial marketing application in the EEA.

PART II: MODULE SVI— ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Drugs that have a potential for misuse for illegal purposes are expected to share general characteristics such as psychoactive, stimulant, or sedative effects, or less commonly, anabolic effects or enhancement of hemoglobin levels.

For inavolisib, there is neither nonclinical nor current clinical evidence supporting psychostimulatory effects or dependency, which would induce misuse for illegal purposes.

A review of safety information obtained in patients exposed to inavolisib concluded that there was no indication of abuse or dependence-related AEs.

Therefore, the potential for inavolisib to be misused for illegal purposes is low.

PART II: MODULE SVII— IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1Risks 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:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- **Nausea & Vomiting**

When treating cancer patients with PI3K/AKT pathway inhibitors, nausea and vomiting are among the common impending side-effects (Nunnery et al, 2019). These are not

usually serious or severe enough to discontinue therapy and are clinically easily managed using standard of care approaches (Curigliano and Shah, 2019).

Nausea

A total of 45/162 inavolisib-treated patients (27.8%) from pivotal study WO41554 reported a nausea AE. Grade 1 events were reported in 30 patients (18.5%), Grade 2 events were reported in 14 patients (8.6%), and 1 patient (0.6%) reported a Grade 3 event (Annex 7B.10).

In inavolisib-treated patients, no nausea event led to withdrawal of any study drug. Nausea events led to dose reduction of inavolisib in 1 patient (0.6%), and dose interruption of inavolisib in 4 patients (2.5%) (Annex 7B.11, Annex 7B.12, Annex 7B.13).

In supportive study GO39374, 108 patients out of 190 patients (56.8%) who received any dose of inavolisib experienced a nausea AE. The majority of the nausea events were Grade 1 (78 patients, 41.1%), with Grade 2 and Grade 3 events reported in 22 patients (11.6%) and 8 patients (4.2%), respectively. No Grade 4 or Grade 5 nausea events were reported (Annex 7B.14).

In Arm B (Inavo+Palbo+Letro), Arm E (Inavo+Palbo+Fulv), and Arm F (Inavo+Palbo+Fulv+Met) of study GO39374, the majority of nausea events were Grade 1-2 (51.5%, 65.0% and 57.9%, respectively). In each of Arm E (Inavo+Palbo+Fulv) and Arm F (Inavo+Palbo+Fulv+Met), one patient reported a Grade 3 event, respectively. No Grade 3–4 events were reported in Arm B (Annex 7B.14).

Vomiting

A total of 24/162 inavolisib-treated patients (14.8%) from pivotal study WO41554 reported a vomiting AE. Grade 1 events were reported in 19 patients (11.7%), Grade 2 events were reported in 4 patients (2.5%), and 1 patient (0.6%) reported a Grade 3 event (Annex 7B.10).

In inavolisib-treated patients, no vomiting event led to withdrawal of any study drug. Vomiting events led to dose reduction of inavolisib in 2 patients (1.2%), and dose interruption of inavolisib in 3 patients (1.9%) (Annex 7B.11, Annex 7B.12, Annex 7B.13).

In supportive study GO39374, 77 patients out of 190 patients (40.5%) who received any dose of inavolisib experienced a vomiting event. Grade 1 events were reported in 54 patients (28.4%), Grade 2 events were reported in 19 patients (10.0%), and Grade 3 events reported in 4 patients (2.1%) (Annex 7B.14).

In Arm B (Inavo+Palbo+Letro), Arm E (Inavo+Palbo+Fulv), and Arm F (Inavo+Palbo+Fulv+Met) of study GO39374, the majority of vomiting events were Grade 1-2 (51.9%, 55.0% and 25.0%, respectively). In Arm B (Inavo+Palbo+Letro) and Arm F (Inavo+Palbo+Fulv+Met), one patient and 2 patients reported a Grade 3 event, respectively. No Grade 3–4 events were reported in Arm E (Annex 7B.14).

The risk of nausea and vomiting is expected due to the mechanism of action of inavolisib, and the management of nausea and vomiting is well understood by oncology healthcare professionals. Therefore, the risk of nausea and vomiting will be followed up

via routine pharmacovigilance and routine risk communication messages in the product information.

- **Diarrhea**

Diarrhea is one of the most common immune-mediated AEs reported for different PI3K inhibitors (Esposito et al, 2019) (Pan-PI3K: buparlisib, pilaralisib, pictilisib; p110 isoform-specific inhibitors: alpelisib [p110α-specific], taselisib [p110β-sparing], and idelalisib and duvelisib [p110δ-specific]) (Nunnery et al, 2019). It is due to the impairment of colon macrophage functionality (Uno et al. 2010) and modulation of immune activity (Gadkar et al. 2022) associated with isoform inhibitions. Severe diarrhea has been associated with PI3Kδ isoform inhibition (Uno et al. 2010). In patients taking alpelisib, diarrhea was observed in over 50% of patients and was usually Grade 1-2.

In pivotal study WO41554, a total of 78/162 inavolisib-treated patients (48.1%) reported a diarrhea AE. The majority of the diarrhea events reported were Grade 1-2 events (72 patients, 44.4%), with Grade 3 events reported in 6 patients (3.7%). No Grade 4 or Grade 5 diarrhea events were reported (Annex 7B.10).

In inavolisib-treated patients, no diarrhea event led to withdrawal of any study drug. Diarrhea events led to dose reduction of inavolisib in 2 patients (1.2%), and dose interruption of inavolisib in 11 patients (6.8%) (Annex 7B.11, Annex 7B.12, Annex 7B.13).

In supportive study GO39374, 123 patients out of 190 patients (64.7%) experienced a diarrhea AE. The majority of the diarrhea events were Grade 1-2 (118 patients, 62.1%), with Grade 3 events reported in 5 patients (2.6%). No patient experienced a Grade 4 or 5 AE of diarrhea (Annex 7B.14).

In Arm B (Inavo+Palbo+Letro), Arm E (Inavo+Palbo+Fulv), and F of study GO39374, the majority of diarrhea events were Grade 1-2 (77.8%, 80.0%, and 55.0%, respectively), with one patient reporting a Grade 3 event in all three arms (Annex 7B.14).

The risk of diarrhea is expected due to the mechanism of action of inavolisib, and the management of diarrhea is well understood by oncology healthcare professionals. Therefore, the risk of diarrhea will be followed up via routine pharmacovigilance and risk-minimization measures.

- **Rash**

The PI3K pathway plays a vital role in keratinocyte differentiation and inhibition of this pathway results in modulation of certain growth factors and differentiation markers leading to epidermal cellular death (Calautti et al, 2005). PI3K inhibitors have been associated with mild-to-severe cutaneous AEs, including exfoliative dermatitis, erythematous rash, generalized rash, macular rash, maculopapular rash, pruritic rash, and exfoliative rash (Baselga et al, 2017; Powles et al. 2016). More specifically, inhibition of the PI3K delta and PI3K gamma isoforms are identified as key contributors

to this toxicity as these isoforms play important roles in immune responses and inflammation (Fritsch et al, 2014).

In pivotal study WO41554, a total of 41/162 inavolisib-treated patients (25.3%) reported a rash AE, of which 34 patients (21.0%) reported a Grade 1 event, and 7 patients (4.3%) reported a Grade 2 event. No Grade 3–4 rash events were reported (Annex 7B.10).

In inavolisib-treated patients, no rash event led to withdrawal of any study drug. Rash events led to dose reduction of inavolisib in 1 patient (0.6%), and dose interruption of inavolisib in 2 patients (1.2%) (Annex 7B.11, Annex 7B.12, Annex 7B.13).

In supportive study GO39374, 47 patients out of 190 patients (24.7%) who received any dose of inavolisib experienced a rash AE. The majority of rash events were Grade 1 (43 patients, 22.6%), with Grade 2 and Grade 3 events reported in 3 patients (1.6%) and 1 patient (0.5%), respectively (Annex 7B.14).

In Arm B (Inavo+Palbo+Letro) of study GO39374, the majority of rash events were Grade 1 (40.7%), with Grade 2 rash events reported in 2 patients (7.4%). In Arm E (Inavo+Palbo+Fulv) and Arm F (Inavo+Palbo+Fulv+Met) of study GO39374, all rash events were Grade 1 (Annex 7B.14).

The high PI3K α selectivity of inavolisib, sparing the PI3K γ and δ isoforms, supports the observed nonclinical and clinical data on the incidence and severity of rash observed to date with inavolisib.

The known risk of rash and its management is well understood by oncology healthcare professionals. Therefore, this risk will be followed up via routine pharmacovigilance which, together with routine risk communication messages in the product information, are considered sufficient for this risk.

- **Ocular Toxicities**

The PI3K/AKT signaling pathway, when activated, promotes anti-apoptotic, anti-inflammatory, proliferative, and migratory functions and wound healing in the corneal epithelium (Chen et al, 2022). However, under the influence of other factors such as hyperglycemia, both the corneal epithelium homeostasis and the normal expression of the signaling pathway are disrupted resulting in associated ocular diseases. It is difficult to distinguish potential ocular toxicities that may be specifically due to inavolisib from symptoms of hyperglycemia (e.g., blurred vision). Chronic exposure to high blood glucose levels can lead to several ocular complications such as diabetic retinopathy, diabetic papillopathy, glaucoma, cataract, and ocular surface diseases characterized by blurred vision and dry eyes (Sayin et al, 2015; Threatt et al, 2013).

A total of 36/162 inavolisib-treated patients (22.2%) in pivotal study WO41554 reported an event under the ocular toxicities grouped term which included all PTs captured under the SOC “eye disorders” as a primary SOC. The most commonly reported PTs were dry eye (8.6%) and vision blurred (3.7%). Grade 1 events were reported in 29 patients (17.9%) and Grade 2 events were reported in 7 patients (4.3%) (Annex 7B.10). In inavolisib-treated patients, ocular toxicity events did not lead to withdrawal, dose

reduction, or dose interruption of any study drug (Annex 7B.11, Annex 7B.12, Annex 7B.13).

In supportive study GO39374, 60 patients out of 190 patients (31.6%) who received any dose of inavolisib experienced an event under the ocular toxicities grouped term. Ocular toxicities included all PTs captured under the SOC “eye disorders” as either a primary or secondary SOC. The most commonly reported PT was dry eye (2.1%). The majority of ocular toxicity events were low grade, with 59 patients (31.1%) experiencing Grade 1-2 events and one patient (0.5%) experiencing a Grade 3 event. No patient experienced a Grade 4 or Grade 5 AE of ocular toxicities (Annex 7B.14).

In Arm B (Inavo+Palbo+Letro) of study GO39374, Grade 1–2 ocular toxicity events were reported in 14 patients (42.4%), with a Grade 3 event reported in 1 patient, and no Grade 4 events were reported. In Arm E (Inavo+Palbo+Fulv) and Arm F (Inavo+Palbo+Fulv+Met), all ocular toxicities events were Grade 1-2 (55.0% and 30.0%, respectively) (Annex 7B.14).

The risk of ocular toxicity will be followed up via routine pharmacovigilance which, together with routine risk communication messages in the product information, are considered sufficient for this risk (see Module SII, Ocular Lens Findings).

- **Hematologic Effects (Neutropenia, Thrombocytopenia, Anemia, Lymphopenia)**

Inhibiting the PI3K/AKT/mTOR signaling pathway induces bone marrow suppression potentially causing anemia, thrombocytopenia, neutropenia, and lymphopenia.

mTOR is crucial for hematopoiesis and the regulation of growth and proliferation of red blood cells, therefore, its inhibition induces anemia. Though anemia is frequently reported, symptoms are usually mild and low grade in severity (Zhang et al, 2019).

Megakaryocyte population depletion is the main reason for nonimmune drug-induced thrombocytopenia (Swisher et al, 2009). Suppression of PI3K pathway signaling induces apoptosis in normal cells, which may lead to the development of thrombocytopenia that is usually mild and does not require hospitalization and platelet transfusion (Zhang et al, 2019).

The main mechanism underlying neutropenia is failure to produce neutrophils, owing to bone marrow suppression or peripheral destruction (Bhatt and Saleem, 2004). PI3K/AKT/mTOR inhibitor-induced bone marrow suppression further inhibits production of neutrophils (Sarkar et al, 2012; Vier et al, 2016). The less potent immunosuppressive effects of PI3K inhibition are primarily ascribed to the delta isoform, which is predominantly expressed in B-cells (Uhlén et al. 2015). In clinical settings, PI3K inhibitors have been shown to increase the incidence of neutropenia, but these are mild events, and treatment can be resumed in most patients after adjusting the dose (Zhang et al, 2019). Treatment-emergent severe neutropenia events have been observed with PI3Kδ-specific inhibitors such as idelalisib (Zydelig E.U. SmPC), while the

immunosuppressant effects observed with the alpha-specific inhibitor alpelisib were minimal (Piqray E.U. SmPC).

In study WO41554 and study GO39374 (Arms B, E, and F), neutropenia events were mostly Grade 3–4 in severity, and no fatal events were reported (Annex 7B.10, Annex 7B.15, Annex 7B.16, Annex 7B.17). This was consistent with the known safety profile of palbociclib, as the majority of neutropenia events were reported in patients receiving combination therapies with palbociclib. The majority of thrombocytopenia events were Grade 1–2 in severity and reversible; no thrombocytopenia events were associated with bleeding events or study treatment withdrawals. In pivotal study WO41554, thrombocytopenia events were reported as ADRs in 78 inavolisib-treated patients (48.1%) (Annex 7B.18). The majority of patients who developed anemia experienced Grade 1–2 events. Anemia events were reported as ADRs in 60 inavolisib-treated patients (37.0%) (Annex 7B.18). The majority of lymphopenia events were Grade 1–2 in severity (Annex 7B.10, Annex 7B.15, Annex 7B.16, Annex 7B.17).

Hematologic effects are expected as these are known risks associated with palbociclib with some contribution due to the mechanism of action of inavolisib, and the management of hematologic effects is well understood by oncology healthcare professionals. Therefore, the risk of neutropenia, thrombocytopenia, anemia, and lymphopenia will be followed up via routine pharmacovigilance.

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:

- **Pneumonitis**

Pneumonitis, including interstitial lung disease and acute interstitial pneumonitis, is rare and was observed with the similar in-class drug, alpelisib, in clinical settings (André et al, 2019).

Pneumonitis occurred with a low frequency in inavolisib-treated patients in studies WO41554 and GO39374 (3 patients [1.9%] and 2 patients [1.1%], respectively). All events of pneumonitis were Grade 1-2 in severity (Annex 7B.10, Annex 7B.14). It is worth noting that pneumonitis is a known risk associated with palbociclib (Ibrance E.U. SmPC).

While pneumonitis can be a serious adverse event (SAE), the impact on the benefit-risk profile of inavolisib is considered low. This risk is well-characterized and understood by oncology healthcare providers.

- **Colitis**

Colitis is a recognized immune-mediated class effect of PI3K inhibitors mainly related to defects in the number and function of Treg cells associated with a histopathological picture of increased inflammation with architectural disturbance (apoptosis and/ or

attenuation of glands). It is labelled with PI3Kδ inhibitors such as idelalisib, and duvelisib, as well as the PI3Kα inhibitor alpelisib (Zydelig E.U. SmPC; Copiktra E.U. SmPC; Piqray E.U. SmPC). Gadkar et al, 2022 showed that inhibition of both PI3Kα and δ is required to initiate an inflammatory process with epithelial damage, while PI3Kδ inhibition increases the GI toxicity risk. Inavolisib is a highly potent (picomolar) and selective inhibitor of the p110α isoform with less potent inhibition of other isoforms including p110δ (inavolisib selectivity is more than 300-fold over the other p110 isoforms, and is approximately 26 times more selective for PI3Kα over PI3Kδ than alpelisib [fold difference]) (Song et al, 2022). Some risk of colitis with the drug is plausible albeit reduced versus all prior cited PI3K inhibitors.

In study WO41554, no instances of treatment-emergent colitis were reported in the study (Annex 7B.10).

In supportive study GO39374, one patient (0.5%) experienced a colitis event (Annex 7B.14). The one patient (1.7%) was in Arm D (Inavo+Fulv). No colitis events were reported in the other Arms of supportive study GO39374. Following medical review, the Grade 3 non-serious colitis AE occurred concurrently with Grade 2 SAE of diarrhea. The diagnosis of colitis was confirmed with sigmoidoscopy (findings included diffuse moderate inflammation characterized by edema and geographic ulcerations) and infectious etiology was ruled out. The patient received several concomitant GI toxic medications and the positive dechallenge for diarrhea was confounded by event treatment, yet, the causal role of inavolisib cannot be ruled out since GI toxicities are also associated with the drug. The patient's bowel motions returned to normal within a day of starting oral steroids. Eventually the patient discontinued the study due to rapid disease progression.

While colitis can be a SAE, the impact on the benefit-risk profile of inavolisib is considered low. This risk is well characterized and understood by oncology healthcare providers.

Known risks that require no further characterization and are followed up via routine pharmacovigilance—namely, through signal detection and adverse reaction reporting—and for which the risk-minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized):

- **Reproductive Toxicity**

Inavolisib can cause fetal harm when administered to a pregnant woman based on findings from nonclinical studies and its mechanism of action. During early embryonic development, PI3Kα is important to embryo implantation, placental development and resource utilization, fetal organogenesis, and the proximal-distal gradient

(López-Tello et al, 2019; Laplante and Sabantini 2012; Vanhaesebroeck et al, 2012; Manning and Cantley 2007).

No clinical studies assessing the reproductive and developmental toxicity of inavolisib have been conducted to date and there are no available data regarding the use of inavolisib during pregnancy.

There were no pregnancies reported in patients treated with inavolisib in clinical studies.

Pregnancy is unlikely to occur in patients with metastatic breast cancer, as the vast majority of HR+ breast cancer occurs in post-menopausal women, and any pre- or peri-menopausal patients will be on ovarian function suppression (i.e., LHRH agonists). Moreover, the chance of conception and overall fertility in this patient population is reduced given prior chemotherapy, advanced stage of the disease and poor prognosis. Given the life-threatening nature of the proposed indication, patients will be closely monitored during treatment and female patients of childbearing potential and male patients with female partners of childbearing potential or pregnant female partners will be advised to use effective contraception while receiving inavolisib and for 1 week following the last dose of inavolisib. This known risk of reproductive toxicity will be followed up via routine pharmacovigilance which, together with adherence by prescribers to risk-minimization messages in the product information (routine risk-minimization measures), are considered sufficient for this risk (see Module SII, Reproductive and Developmental Toxicity).

- **Stomatitis or Mucosal Inflammation**

Stomatitis is considered to be a clinically important known risk for inavolisib and is subject to routine PV activities and will be presented in each scheduled PBRER for inavolisib. It is a relatively common side-effect of PI3K pathway inhibitors and is usually low grade (Grade 1). It is most strongly associated with mTOR inhibition and was observed with the similar-in-class drug, alpelisib, in clinical settings (Mayer et al, 2019). Therefore, the MAH is not proposing any additional PV or ARMM activities for this important risk.

A total of 83/162 inavolisib-treated patients (51.2%) in pivotal study WO41554 reported an event of stomatitis or mucosal inflammation. The majority of events were Grade 1–2 (74 patients [45.7%]) and 9 patients (5.6%) reported Grade 3 events. No Grade 4 stomatitis or mucosal inflammation events were reported (Annex 7B.10).

In inavolisib-treated patients, one patient (0.6%) experienced a stomatitis/ mucosal inflammation event which led to withdrawal of inavolisib. Stomatitis /mucosal inflammation events led to dose reduction of inavolisib in 6 patients (3.7%), and dose interruption of inavolisib in 16 patients (9.9%) (Annex 7B.11, Annex 7B.12), in supportive study GO39374, 92 patients out of 190 patients (48.4%) who received any dose of inavolisib experienced a stomatitis/mucosal inflammation event. The majority of stomatitis/mucosal inflammation events were low grade, with 87 patients (45.8%)

experiencing Grade 1-2 events and 5 patients (2.6%) experiencing Grade 3-4 events. No patient experienced a Grade 5 AE of stomatitis/mucosal inflammation (Annex 7B.14).

In Arm B (Inavo+Palbo+Letro), Arm E (Inavo+Palbo+Fulv), and Arm F (Inavo+Palbo+Fulv+Met) of study GO39374, the majority of stomatitis/mucosal inflammation events were Grade 1-2 (63.6%, 80.0%, and 50.0%, respectively) and Grade 3 events were reported in one patient, 2 patients, and one patient, respectively. No Grade 4 events were reported (Annex 7B.14).

The known risk of stomatitis or mucosal inflammation is associated with PI3K-AKT-mTOR pathway inhibitors and its management with steroid mouthwash is well understood by oncology healthcare professionals (Rugo et al., 2017). Therefore, the risk of stomatitis or mucosal inflammation will be followed up via routine pharmacovigilance which, together with routine risk communication messages on treatment and prophylaxis in the product information, are considered sufficient for this risk.

SVII.1.2Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk of Hyperglycemia and Associated Complications (including Diabetic Ketoacidosis)

Risk-benefit impact:

Hyperglycemia is a known reversible on-target toxicity associated with PI3K α inhibitors due to temporary disruption of the insulin signaling pathway. Increased blood glucose levels were observed in rat and dog toxicology studies with inavolisib at all doses tested and appeared to be dose dependent.

The frequency of hyperglycemia in the pivotal clinical trial WO41554 was 58.6% in inavolisib-treated patients. Hyperglycemia events were mostly Grade 1 (26 patients [16.0%]) and Grade 2 (60 patients [37.0%]) in severity, with 9 patients (5.6%) reporting a Grade 3 hyperglycemia event. There were no Grade 4, Grade 5, or serious hyperglycemia events reported. In inavolisib-treated patients, 95 patients experienced 218 events of hyperglycemia out of which 75 patients (78.9%) had at least 1 event of hyperglycemia reported resolved, 18 patients (18.9%) had at least 1 event of hyperglycemia reported unresolved, and 9 patients (9.5%) had at least 1 event of hyperglycemia reported resolving at the CCOD (Table 11). Hyperglycemia events led to withdrawal of inavolisib in 1 patient (0.6%), dose reduction of inavolisib in 4 patients (2.5%), and dose interruption of inavolisib in 44 patients (27.2%) (Annex 7B.11, Annex 7B.12, Annex 7B.13).

The frequency of hyperglycemia in the supportive clinical trial GO39374 was 67.3% in inavolisib-treated patients, and ranged from 66.7%–73.7% in Arms B, E, and F. Overall, the majority of hyperglycemia events were low grade, with 70 patients (42.4%) experiencing Grade 1–2 events and 41 patients (24.8%) experiencing Grade 3–4 events. No patient experienced a Grade 5 hyperglycemia AE. A total of 3 patients (1.8%)

experienced a serious AE of hyperglycemia. In inavolisib-treated patients, 111 patients experienced 257 events of hyperglycemia out of which 100 patients (90.1%) had at least 1 event of hyperglycemia reported resolved, 27 patients (24.3%) had at least 1 event of hyperglycemia reported unresolved, 4 patients (3.6%) had at least 1 event of hyperglycemia reported resolved with sequelae, and 1 patient (0.9%) had at least 1 event of hyperglycemia reported resolving at the CCOD (Annex 7B.19). Hyperglycemia events led to withdrawal of inavolisib in 1 patient (0.5%), dose reduction of inavolisib in 18 patients (9.5%), and dose interruption of inavolisib in 58 patients (30.5%) (Annex 7B.20, Annex 7B.21, Annex 7B.22).

There is the potential for hyperglycemia to result in complications. While there have been no events of complications from hyperglycemia observed in studies WO41554 and GO39374, complications of hyperglycemia can be life-threatening, and require early detection, careful monitoring, and timely medical intervention (Annex 7B.15, Annex 7B.17). Cases of hyperglycemia, including complications such as life-threatening ketoacidosis have been reported in the post-marketing setting.

The risk-minimization measures proposed include comprehensive glucose monitoring and hyperglycemia management guidance via labeling. The proposed risk-minimization measures are aimed at the patient/caregivers to enhance their awareness of the signs and symptoms of hyperglycemia and the best course of action to be taken should any of those signs and symptoms occur.

Important Potential Risks

Not applicable

Missing Information

- **Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment)**
- **Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)**

Risk-benefit impact:

Hyperglycemia is an expected on-target and reversible toxicity associated with PI3K inhibitors. Patients with underlying glycemic metabolic disorders, such as Type 1 and Type 2 diabetes, may be at higher risk for PI3K inhibitor-induced hyperglycemia due to their underlying insulin resistance. Hence, diabetic patients and patients with elevated fasting glucose at baseline (fasting glucose $\geq$126 mg/dl [$\geq$7.0 mmol/L] or $HbA_{1C}\geq$6.0% [$\geq$42 mmol/mol]) were excluded from the pivotal study WO41554. Additionally, patients with diabetes requiring anti-hyperglycemic medication and $HbA_{1C}\geq$7% and fasting blood glucose of > 140mg/dL were also excluded from the supportive study GO39374. Thus, further characterization of the safety profile of inavolisib in this patient population is

required and will be addressed by the planned studies that aim to assess the overall safety of inavolisib in patients with Type 1 and Type 2 diabetes.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

This section is not applicable as this is the first RMP for inavolisib.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Information on Important Identified Risks

Hyperglycemia and Associated Complications (including Diabetic Ketoacidosis)

Potential mechanisms:

p110α is important for insulin-mediated blood glucose control. Inhibition of p110α modulates signaling from the insulin receptor, reduces active transport of glucose into adipose tissue and muscles and increases the breakdown of glycogen in the liver, which results in increased blood glucose levels and a compensatory release of insulin (Świderska et al, 2018; Huang et al, 2018).

Hyperglycemia is an on-target effect of PI3K inhibition, and therefore its occurrence in inavolisib-treated patients is considered related to the pharmacological activity of the compound. If left untreated, or in the case of poor blood sugar control in high-risk patients (e.g., those with medical history of type 1 or 2 diabetes, concurrent infections, those receiving concomitant systemic corticosteroids, or other conditions requiring more intensified glycaemia management), hyperglycemia can potentially lead to complications.

Evidence source(s) and strength of evidence:

- Nonclinical studies, showing dose dependent and reversible, minimal to marked, increases in glucose observed in rats at ≥1 mg/kg and in dogs at ≥0.5 mg/kg (see Module SII),
- Clinical trial data from studies WO41554 and GO39374,
- Class effect: As observed with other PI3Kα inhibitors such as alpelisib, changes in glucose metabolism may lead to hyperglycemia (Piqray E.U. SmPC, Truqap E.U. SmPC),
- Complications due to hyperglycemia have not been reported in studies WO41554 and GO39374. Cases of hyperglycemia, including complications such as life-threatening ketoacidosis have been reported in the post-marketing setting.

Characterization of the risk:

The frequency of hyperglycemia in the pivotal clinical trial WO41554 was 58.6% in inavolisib-treated patients (Table 11). Hyperglycemia events were mostly Grade 1 (26 patients [16.0%]) and Grade 2 (60 patients [37.0%]) in severity, with 9 patients (5.6%) reporting a Grade 3 hyperglycemia event. There were no Grade 4, Grade 5, or serious hyperglycemia events reported. In inavolisib-treated patients, 95 patients experienced 218 events of hyperglycemia out of which 75 patients (78.9%) had at least 1 event of hyperglycemia reported resolved, 18 patients (18.9%) had at least 1 event of hyperglycemia reported unresolved, and 9 patients (9.5%) had at least 1 event of hyperglycemia reported resolving at the CCOD. Hyperglycemia events led to withdrawal of inavolisib in 1 patient (0.6%), dose reduction of inavolisib in 4 patients (2.5%), and dose interruption of inavolisib in 44 patients (27.2%) (Annex 7B.11, Annex 7B.12, Annex 7B.13).

Among the inavolisib-treated patients who had hyperglycemia events, the median time to first onset was 7 days (range: 2.0 to 955.0 days) (Annex 7B.23). The rate of new onset of hyperglycemia events was highest during the first 2 months of receiving inavolisib (Annex 7B.24).

Of the inavolisib-treated patients who had hyperglycemia events, 66 patients (40.7%) received treatment for hyperglycemia AEs. The most commonly used (≥10% of patients) concomitant medications for management of hyperglycemia events were metformin (62 out of 66 patients [93.9%] and insulin (8 out of 66 patients [12.1%]) (Annex 7B.25).

Table 11 Hyperglycemia: Frequency, Severity, Seriousness and Outcomes (Study WO41554)

Seriousness, Outcomes, Severity, Frequency with 95% CI for Adverse Events, Hyperglycemia Group term, Safety
Analysis Set
Protocol: WO41554, CCOD: 29SEP2023, Data Snapshot: 23NOV2023

	Inavo+Palbo+Fulv (N=162)
Number of patients with at least one adverse event	95 (58.6%)
95% CI for % of patients with at least one AE (Clopper-Pearson)	(50.6, 66.3)
Total number of AEs	218
Number of patients with at least one AE by worst grade	
Grade 1	26 (16.0%)
Grade 2	60 (37.0%)
Grade 3	9 (5.6%)
Grade 4	0
Grade 5	0
Number of patients with at least one serious AE	0
Number of patients with at least one AE by outcome	
Fatal outcome	0
Unresolved	18 (18.9%)
Recovered/Resolved	75 (78.9%)
Resolved with sequelae	0
Recovering/Resolving	9 (9.5%)
Unknown outcome	1 (1.1%)

Investigator text for AEs encoded using MedDRA version 26.1. Grading displayed is based on numeric thresholds only in NCI CTCAE version 5.
AE = adverse event; CI = Confidence Interval; 95% CI were computed using Clopper-Pearson. Multiple occurrences of qualifying events in a patient are counted only once at the patients worst grade.
N= number of patients exposed to Inavolisib.
Inavo = Inavolisib, Pbo = Placebo, Palbo = Palbociclib, Fulv = Fulvestrant

GitLab repository: https://gitlab-ci-token:64_9bPPTieA5jXDs1v_yxbm@code.roche.com/studies/clinicalreporting/WO41554_SCS_RMP_2023_8970700
Git hash: 5860cfb3559a2c4f6af911c5e8b08f4f1d6b74bf
19 DEC 2023 11:52 GMT
Output:/ocean/harbour/CDT70123/WO41554/SCS_RMP_2023/prod/output/t_rmp06_RMP_AEHYP_SAS_29SEP2023_41554.out Page 1 of 1

The frequency of hyperglycemia in the supportive clinical trial GO39374 was 67.3% in inavolisib-treated patients, and ranged from 66.7%-73.7% in Arms B, E, and F (Annex 7B.19). Overall, the majority of hyperglycemia events were low grade, with 70 patients (42.4%) experiencing Grade 1-2 events and 41 patients (24.8%) experiencing Grade 3-4 events. No patient experienced a Grade 5 hyperglycemia AE. A total of 3 patients (1.8%) experienced a serious AE of hyperglycemia. In inavolisib-treated patients, 111 patients experienced 257 events of hyperglycemia out of which 100 patients (90.1%) had at least 1 event of hyperglycemia reported resolved, 27 patients (24.3%) had at least 1 event of hyperglycemia reported unresolved, 4 patients (3.6%) had at least 1 event of hyperglycemia reported resolved with sequelae, and 1 patient (0.9%) had at least 1 event of hyperglycemia reported resolving at the CCOD. Hyperglycemia events led to withdrawal of inavolisib in 1 patient (0.5%), dose reduction of inavolisib in 18 patients (9.5%), and dose interruption of inavolisib in 58 patients (30.5%) (Annex 7B.20, Annex 7B.21, Annex 7B.22).

Among all patients who had hyperglycemia AEs, the median time to onset of the first occurrence of hyperglycemia was 7 days (range: 2.0–955.0 days) (Annex 7B.26). Out of a total of 295 hyperglycemia events, 254 events (86.1%) were recovered/resolved, 35 events (11.9%) were not recovered/not resolved, 5 events (1.7%) were recovered/resolved with sequelae, and 1 event (0.3%) was recovering/resolving at the

CCOD (Annex 7B.27). Of the 84 patients (44.2%) who experienced an event of hyperglycemia that was Grade ≥2, 83 patients reported one grade improvement or resolution with a median time of 8 days (range: 1–64 days) (Annex 7B.28).

A total of 88 patients (46.3%) received at least one treatment for hyperglycemia (Annex 7B.29). The most commonly used (≥5% patients) concomitant medications for hyperglycemia events were metformin (40.5%), empagliflozin (15.8%), sitagliptin (15.3%), pioglitazone (9.5%), and insulin (6.3%). Overall, 12 patients received insulin for the treatment of hyperglycemia, with the median duration of insulin use of 4.5 days (range: 1–282 days) (Annex 7B.30).

Complications due to hyperglycemia have not been reported in studies WO41554 and GO39374 (Annex 7B.15, Annex 7B.17). Life-threatening cases of ketoacidosis have been reported in the post-marketing setting.

Risk factors and risk groups:

There are several risk factors for developing hyperglycemia, including (pre)diabetes, $HbA_{1C} \geq 5.7\%$, BMI ≥ 30 kg/m^2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus.

No specific risk factors for the development of complications of hyperglycemia in Itovebi-treated patients have been identified. However, high-risk patients (e.g., pre-diabetes, patients with a medical history of type 1 or 2 diabetes, concurrent infections, those receiving concomitant systemic corticosteroids, or other conditions requiring more intensified glycemia management), may be at greater risk of experiencing hyperglycemia leading to associated complications.

Preventability:

Preventability measures are described in the Itovebi SmPC, Section 4.4 Special warnings and precautions for use. As described in the Itovebi SmPC and PL, prior to the start of inavolisb treatment, patients should be advised of the signs and symptoms of hyperglycemia and to immediately contact a healthcare professional if these symptoms occur. High-risk patients, including patients with a history of diabetes mellitus, require more frequent monitoring of fasting glucose, HbA1C, blood ketones and other metabolic parameters may be necessary in line with the local standard of care. Patients with a history of diabetes mellitus may require intensified anti-hyperglycemic therapy and consultation with a healthcare professional experienced in the treatment of hyperglycemia should be considered before initiating treatment with Itovebi.

Monitoring or self-monitoring of fasting glucose levels more frequently as clinically indicated should be considered in patients with risk factors for hyperglycemia. Monitoring of HbA_{1C} and ketones (preferably in blood), in addition to fasting glucose, is recommended in these patients. Anti-hyperglycemic treatment should be initiated or

adjusted as required (see Itovebi SmPC, section 4.2 Posology and method of administration, Dose Modification).

Based on the severity of hyperglycemia, Itovebi dosing may be interrupted, reduced, or discontinued, and provision of appropriate medical intervention (in accordance with local practice) should help to prevent complications.

Impact on the benefit-risk balance of the product:

The majority of hyperglycemia events were non-serious, manageable with oral anti-hyperglycemic agents and dose reductions/interruptions, and no Grade 4 or 5 events were reported. No SAEs were reported in pivotal study WO41554.

Guidance regarding careful blood glucose monitoring or self-monitoring, lifestyle changes (e.g., dietary modifications, physical activity), dose modification, and management with anti-hyperglycemic treatment provided in the product information reduce the risk of hyperglycemia. Poorly controlled hyperglycemia can lead to complications, which may be life-threatening. This may also disproportionately impact morbidity and quality of life in the target patient population. Complications of hyperglycemia can be life-threatening, and require early detection, careful monitoring, and timely medical intervention.

Comprehensive product labeling, together with routine and additional pharmacovigilance activities are considered adequate to manage the risk of hyperglycemia and associated complications (including diabetic ketoacidosis).

Public health impact:

There is no potential public health impact beyond that within the treated population.

Information on Important Potential Risks

Not applicable

SVII.3.2. Presentation of the Missing Information

Information on Missing Information

- **Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment)**
- **Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)**

Hyperglycemia is an expected on-target and reversible toxicity associated with PI3K inhibitors and is an identified risk for inavolisib. Patients with underlying glycemic metabolic disorders, such as Type 1 or Type 2 diabetes, may be at higher risk for PI3K inhibitor-induced hyperglycemia due to their underlying insulin dysregulation. Hence, diabetic patients and patients with elevated fasting glucose at baseline (fasting glucose $\geq$ 126 mg/dl [$\geq$ 7.0 mmol/L] or $HbA_{1C} \geq 6.0\%$ [$\geq$ 42 mmol/mol]) were excluded from the pivotal study WO41554. Additionally, patients with diabetes requiring anti-

hyperglycemic medication and $HbA_{1C} \geq 7\%$ and fasting blood glucose of > 140 mg/dL were also excluded from the supportive study GO39374. Thus, further characterization of the safety profile of inavolisib in this patient population is required and will be addressed by the planned studies that aim to assess the overall safety of inavolisib in patients with Type 1 and Type 2 diabetes.

Refer to Annex 7B.31, Annex 7B.32.

Evidence source:

Population in need of further characterization.

The assessment of the impact of Type 1 and Type 2 diabetes on the safety profile of inavolisib is not fully understood and ongoing analysis of future safety information in this patient population is needed.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 12 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Hyperglycemia and Associated Complications (including Diabetic Ketoacidosis)
Important potential risks	None
Missing information	• Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment) • Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

ROUTINE PHARMACOVIGILANCE ACTIVITIES BEYOND ADVERSE REACTIONS REPORTING AND SIGNAL DETECTION

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are as follows:

Specific adverse reaction follow-up questionnaires: A targeted follow-up safety questionnaire is in place to enable comprehensive data collection for the important identified risk of Hyperglycemia and Associated Complications (including Diabetic Ketoacidosis) in a standardised way across regions and prescribers. The information received will facilitate ongoing surveillance activities in the post-marketing setting, and will enable more complete collection of data, thereby optimizing risk evaluation.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Study GO45322

Study GO45322 is a planned Phase II prospective, multicenter, open-label study to assess the safety of the use of inavolisib and inavolisib-associated hyperglycemia in Type 2 diabetic patients with PIK3CA-mutated, HR-positive, HER2-negative advanced breast cancer treated with a combination of inavolisib plus palbociclib and endocrine therapy (Table 13).

These data will support further evaluating the following:

- Missing Information: Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment)
- Important Identified Risk: Hyperglycemia and Associated complications (including diabetic ketoacidosis)

Table 13 Planned PASS (Study GO45322) Summary: Safety in Patients with Type 2 Diabetes Mellitus (requiring non-insulin anti-hyperglycemic treatment)

Study/activity short name and title:
A Phase II Prospective, Open-Label, Safety Study of Inavolisib and Fulvestrant with or without Palbociclib in Patients with *PIK3CA*-Mutated, Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer and Type 2 Diabetes Mellitus.
Rationale and Study Objectives:
This study will evaluate the safety and tolerability of the use of inavolisib and fulvestrant, with or without palbociclib in well-controlled Type 2 diabetic patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative advanced breast cancer treated with a combination of inavolisib plus palbociclib and endocrine therapy.
Study design:
A Phase II, prospective, open-label, safety study.
Study populations:
Approximately 40 participants with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment) and *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer.
Milestones:
Final protocol availability: Q2/Q3 2025 Final report submission: TBD

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; PASS = post-authorization safety study; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; TBD = to be determined.

Non-Interventional Study

A planned non-interventional study to assess the safety of the use of inavolisib and inavolisib-associated hyperglycemia in Type 1 or Type 2 diabetic patients (requiring insulin treatment) with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer treated with a combination of inavolisib plus palbociclib and endocrine therapy (Table 14).

These data will support further evaluating the following:

- Missing Information: Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)
- Important Identified Risk: Hyperglycemia and Associated complications (including diabetic ketoacidosis)

Table 14 Planned PASS Summary: Safety in Patients with Type 1 and Type 2 Diabetes Mellitus (requiring insulin treatment)

Study/activity short name and title: A Non-interventional study of Inavolisib and Fulvestrant with or without a CDK inhibitor in Patients with *PIK3CA*-Mutated, Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer and Type 1 or Type 2 Diabetes (requiring insulin treatment).
Rationale and Study Objectives: This study will evaluate the safety of the use of inavolisib and fulvestrant, with or without a CDK inhibitor in Type 1 or Type 2 diabetic patients (requiring insulin treatment) with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative advanced breast cancer treated with a combination of inavolisib plus palbociclib and endocrine therapy.
Study design: A non-interventional, retrospective, cohort study.
Study populations: Approximately 30-50 participants with Type 1 and Type 2 diabetes (requiring insulin treatment) and *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer.
Milestones: Final protocol availability: Q4 2025 Final report submission: TBD

CDK = cyclin dependent kinase; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; PASS = post-authorization safety study; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; TBD = to be determined.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 15 Ongoing and Planned Additional Pharmacovigilance Activities

Study (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
There are no Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
There are no Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk-minimization activities				
Study GO45322: A Phase II Prospective, Open-Label, Safety Study of Inavolisib and Fulvestrant with or without Palbociclib in Patients with *PIK3CA*-Mutated, Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer and Type 2 Diabetes. **(Planned)**	To evaluate the safety and tolerability of the use of inavolisib and fulvestrant with or without palbociclib in well-controlled Type 2 diabetic patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative advanced breast cancer.	Missing Information: safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment) Important Identified Risk: Hyperglycemia and Associated complications (including diabetic ketoacidosis)	Final report submission	TBD

Table 15 Ongoing and Planned Additional Pharmacovigilance Activities (cont'd)

Study (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk-minimization activities				
Planned: A Non-interventional study of Inavolisib and Fulvestrant with or without a CDK inhibitor in Patients with *PIK3CA*-Mutated, Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer and Type 1 or Type 2 Diabetes (requiring insulin treatment). **(Planned)**	To evaluate the safety of of inavolisib and fulvestrant, with or without a CDK inhibitor in Type 1 or Type 2 diabetic patients (requiring insulin treatment) with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative advanced breast cancer.	Missing Information: safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment). Important Identified Risk: Hyperglycemia and Associated complications (including diabetic ketoacidosis)	Final report submission	TBD

CDK = cyclin dependent kinase; CHMP = Committee for Medicinal Products for Human Use; HER2 = human epidermal growth factor receptor 2; NCA = National Competent Authority; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; PK = pharmacokinetic; PRAC = Pharmacovigilance Risk Assessment Committee; TBD = to be determined.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No post-authorization efficacy studies are currently proposed for inavolisib.

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN
V.1 ROUTINE RISK-MINIMIZATION MEASURES

Table 16 Description of Routine Risk-Minimization Measures by Safety Concern

Safety concern	Routine risk-minimization activities
Hyperglycemia and Associated Complications (including Diabetic Ketoacidosis)	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration, Dose Modification SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 and 4.4 Recommendation on dose modification and management advice for hyperglycemia is included in SmPC section 4.2. Recommendations on monitoring and management of hyperglycemia, including diabetic ketoacidosis, is included in SmPC section 4.4. **Other routine risk-minimization measures beyond the Product Information:** Pack size Medicine's legal status: Inavolisib is a prescription only medicine

Table 16 Description of Routine Risk-Minimization Measures by Safety Concern (cont.)

• Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment) • Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use: Hyperglycemia **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Information on use in patients with diabetes is provided in SmPC Section 4.4 **Other routine risk-minimization measures beyond the Product Information:** Pack size Medicine's legal status: Inavolisib is a prescription only medicine

SmPC = Summary of Product Characteristics.

V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

Not applicable.

REMOVAL OF ADDITIONAL RISK-MINIMIZATION ACTIVITIES

Not applicable

V.3 SUMMARY OF RISK-MINIMIZATION MEASURES

Table 17 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety concern	Risk-minimization measures	Pharmacovigilance activities
Hyperglycemia and Associated Complications (including Diabetic Ketoacidosis)	**Routine risk-minimization measures:** SmPC section 4.2, and 4.4, and 4.8 Dose modification and management advice for hyperglycemia is included in SmPC section 4.2. Recommendations on monitoring and management of hyperglycemia, including diabetic ketoacidosis is included in SmPC section 4.4. **Other routine risk-minimization measures beyond the Product Information:** Pack size Medicine's legal status: Inavolisib is a prescription only medicine **No additional risk-minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** Planned Studies to evaluate inavolisib-associated hyperglycemia in Type 1 or Type 2 diabetic patients
• Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment) • Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)	**Routine risk-minimization measures:** SmPC section 4.4 Information pertaining to the use of inavolisib in patients with Type 1 and Type 2 diabetes is included in Section 4.4. **Other routine risk-minimization measures beyond the Product Information:** Pack size Medicine's legal status: Inavolisib is a prescription only medicine **No additional risk-minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** No activities beyond routine PSUR/PBRER reporting **Additional pharmacovigilance activities:** Planned Studies to evaluate inavolisib-associated hyperglycemia in Type 1 or Type 2 diabetic patients

PBRER = Periodic Benefit-Risk Evaluation Report, PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Itovebi (inavolisib)

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

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

This summary of the RMP for Itovebi 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 Itovebi's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Itovebi is indicated in combination with palbociclib and fulvestrant for the treatment of adult patients with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment. It contains inavolisib as the active substance, and it is given by oral route.

Further information about the evaluation of Itovebi's benefits can be found in *Itovebi*'s EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Itovebi, together with measures to minimize such risks and the proposed studies for learning more about Itovebi's 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 authorized pack size—The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
- The medicine's legal status—The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk-minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, 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 Itovebi is not yet available, it is listed under “missing Information” below.

II.A List of Important Risks and Missing Information

Important risks of Itovebi 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 Itovebi. 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 about 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).

List of Important Risks and Missing Information	
Important identified risks	Hyperglycemia and Associated Complications (including Diabetic Ketoacidosis)
Important potential risks	None
Missing information	• Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment) • Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)

II.B Summary of Important Risk

Important Identified Risk: Hyperglycemia and Associated Complications (including Diabetic Ketoacidosis)	
Evidence for linking the risk to the medicine	• Nonclinical studies, showing dose dependent and reversible, minimal to marked, increases in glucose observed in rats at ≥1 mg/kg and in dogs at ≥0.5 mg/kg • Clinical trial data from studies WO41554 and GO39374 • Class effect: As observed with other PI3Kα inhibitors such as alpelisib, changes in glucose metabolism may lead to hyperglycemia • Complications due to hyperglycemia, including diabetic ketoacidosis have not been reported in studies WO41554 and GO39374. Cases of hyperglycemia, including complications such as life-threatening ketoacidosis have been reported in the post-marketing setting.
Risk factors and risk groups	There are several risk factors for developing hyperglycemia, including (pre)diabetes, $HbA_{1C} \geq 5.7\%$, BMI ≥ 30 kg/m^2, ≥ 45 years of age, history of gestational diabetes, and family history of diabetes mellitus. No specific risk factors for the development of complications of hyperglycemia in Itovebi-treated patients have been identified. However, high-risk patients (e.g., patients with a medical history of Type 1 or 2 diabetes, concurrent infections, those receiving concomitant systemic corticosteroids, or other conditions requiring more intensified glycemia management), may be at greater risk of experiencing hyperglycemia leading to associated complications.
Risk-minimization measures	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration, Dose Modification SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable Effects **Routine risk-minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 – Posology and method of administration

	contains instructions about dose modification and management advice for hyperglycemia SmPC Section 4.4 – Special warnings and precautions for use provide recommendations on monitoring and management of hyperglycemia, including diabetic ketoacidosis **Other routine risk-minimization measures beyond the Product Information:** Pack size Medicine's legal status: Inavolisib is a prescription only medicine **Additional risk-minimization measures:** No additional risk-minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study GO45322 to evaluate inavolisib-associated hyperglycemia in Type 2 diabetic patients (requiring non-insulin anti-hyperglycemic treatment). A non-interventional, retrospective, cohort study in patients with Type 1 or Type 2 Diabetes (requiring insulin treatment). See Section II.C of this summary for an overview of the post-authorization development plan.

BMI = body mass index; HbA_{1c} = glycosylated hemoglobin; SmPC = Summary of Product Characteristics.

Missing Information: • **Safety in patients with Type 2 diabetes mellitus (requiring non-insulin anti-hyperglycemic treatment)** • **Safety in patients with Type 1 or Type 2 diabetes mellitus (requiring insulin treatment)**	
Risk-minimization measures	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use **Routine risk-minimization activities recommending specific clinical measures to address the risk:** Information on use in patients with diabetes is provided in SmPC Section 4.4 **Other routine risk-minimization measures beyond the Product Information:** Pack size Medicine's legal status: Inavolisib is a prescription only medicine **Additional risk-minimization measures:** No additional risk-minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study GO45322 to evaluate inavolisib-associated hyperglycemia in Type 2 diabetic patients (requiring non-insulin anti-hyperglycemic treatment). Retrospective, non-interventional study in patients with Type 1 or Type 2 Diabetes (requiring insulin treatment). See Section II.C of this summary for an overview of the post-authorization development plan.

SmPC = Summary of Product Characteristics.

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation of inavolisib.

II.C.2 Other Studies in Post-Authorization Development Plan

Study short name:

Study GO45322

A planned phase II prospective, open-label safety study of inavolisib and fulvestrant with or without palbociclib in patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer and Type 2 diabetes.

Purpose of the study:
This study will evaluate the safety of the use of inavolisib and inavolisib-associated hyperglycemia in Type 2 diabetic patients (requiring non-insulin anti-hyperglycemic treatment) with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative advanced breast cancer and metastatic breast cancer treated with a combination of inavolisib plus palbociclib and endocrine therapy.

Study short name: To be confirmed
A planned non-interventional study of inavolisib and fulvestrant with or without a CDK inhibitor in patients with *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer and Type 1 or Type 2 diabetes (requiring insulin treatment).

Purpose of the study:
This study will evaluate the safety of the use of inavolisib and inavolisib-associated hyperglycemia in Type 1 or Type 2 and diabetic patients requiring insulin treatment with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer treated with a combination of inavolisib and endocrine therapy with or without CDK inhibitor.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Specific Adverse Reactions Follow-Up Forms/Questionnaires

Guided Questionnaire – Complications of Hyperglycemia, including Diabetic Ketoacidosis

Roche	**Guided Questionnaire Inavolisib - Severe Complications of Hyperglycaemia**	Version: 1.0 (Mar/2025) Page X / X AER: *[to be completed internally]*

We are sending you this follow-up questionnaire because we have received a report on a patient who developed a severe complication of hyperglycemia whilst receiving inavolisib. If this report was not initially provided by yourself, it may have been forwarded to us by the patient, a sales representative, a medical communications department, or a patient support program. Please provide additional information below, if available to you.

By providing this, you are actively participating in safety monitoring and enabling comprehensive data collection that will facilitate ongoing safety surveillance activities, thereby optimizing the evaluation and understanding of the risk factors for severe complications of hyperglycemia, which will benefit your patients.

Severe complications of hyperglycemia in patients with Type I and Type II diabetes (HbA_{1C} >8%), including ketoacidosis and hyperglycemia hyperosmolar nonketotic state have been reported in patients treated with medicinal products targeting the PI3K/AKT/mTOR signaling pathway, including PI3K inhibitors.

Your responses are confidential and used for pharmacovigilance purposes only. Personal identifiers will not be disclosed beyond regulatory requirements.

Patient Information			
Patient ID/ Initials/Name:		Sex:	Male ☐ Unknown ☐ Female ☐ Undifferentiated ☐
		or Age at time of the event:	..... Year(s)
Date of Birth (DD/MMM/YYYY):		Height:	..... cm
Ethnic Origin/Race:		Weight:	..... kg

Adverse Event Details		
Reported Term *(please provide final diagnosis)*:		
Symptoms *(please provide the accompanying symptoms the patients experienced with the reported term above)*:		
AE Onset Date (DD/MMM/YYYY) (first symptom):	☐ Unknown	
Hospital Admission ☐ Yes	Admission Date (DD/MMM/YYYY):	☐ No
	Discharge Date (DD/MMM/YYYY):	☐ Unknown
AE End Date (DD/MMM/YYYY):	☐ Unknown	

Was treatment for the AE provided? □ Yes □No □ Unknown	If yes, please specify (drug name, dose, frequency, route, start date, stop date):
Was Diabetologist/Endocrinologist consulted? □ Yes □No	If yes, please provide relevant consultation details (e.g. details of assessment/diagnosis including tests and results and interventions):

AE related to inavolisib (Itovebi)?	□ Yes	□ No	□ Unknown
AE related to palbociclib?	□ Yes	□ No	□ Unknown
AE related to fulvestrant?	□ Yes	□ No	□ Unknown
AE related to other *(please specify)*:			

Outcome of the event:	□ Recovered/Resolved □ Recovering/Resolving □ Recovered with sequelae Specify sequelae: □ Not recovered/Not resolved □ Death □ Outcome unknown
	Date of Outcome (DD/MMM/YYY):

Medical History, Concurrent Conditions, and Risk Factors

Please provide any relevant medical history, concurrent conditions, and any other contributing risk factors to the reported AE, if available

Relevant medical history, concurrent conditions, and other contributing risk factors	**Start Date** (DD/MMM/YYYY)	**Stop Date** (DD/MMM/YYYY)	**If yes, please provide details**
Previous episodes of ketoacidosis □ Yes □ No			If more than one episode, please provide details of latest episode and # of episodes previously experienced if more than one:

Hyperosmolar Hyperglycemic State	□ Yes □ No			
Reduced caloric/carbohydrate intake	□ Yes □ No			
Surgery	□ Yes □ No			
Infection	□ Yes □ No			
Excessive alcohol intake	□ Yes □ No			
Recent Cardio/Cerebro/Vascular Episode	□ Yes □ No			
High dose corticosteroid	□ Yes □ No			
Renal impairment	□ Yes □ No			
Previous complication of hyperglycemia	□ Yes □ No			Please describe the complication:
Other (*please specify*):				
Other (*please specify*):				
Other (*please specify*):				
Other (*please specify*):				

Medical History/Concurrent Condition: Diabetes

If the patient has diabetes, please specify the diagnosis.

Type 1 diabetes mellitus	□ Yes	□ No
Type 2 diabetes mellitus	□ Yes	□ No
Pre-diabetes	□ Yes	□ No
Ketosis-prone diabetes	□ Yes	□ No
Latent autoimmune diabetes	□ Yes	□ No
History of gestational diabetes	□ Yes	□ No
Other (*please specify*):		

Duration of prediabetes/diabetes since time of diagnosis

< 1 Year □	1-3 Year □	3-5 Year □	5-10 Year □	>10 Year □

Test results prior to start of treatment with inavolisib

Please indicate if any of the following tests have been performed, and the result:

Test	Date (DD/MMM/YYY)	Result	Not Done
Fasting Glucose			□
HbA_{1c}			□
Ketones			□

Drug Therapy Details:

Inavolisib

Indication:	**Dosing Schedule:**	**Start Date** (DD/MMM/YYYY):	**Stop Date** (DD/MMM/YYYY) **(if applicable):**

Details of most recent inavolisib administration prior to adverse event (AE)

Date (DD/MMM/YYYY)	**Dose**	**Action Taken with next dose in response to AE?**
		□ Dose maintained □ Dose decreased □ Dose interrupted □ Dose increased □ Dose discontinued

Palbociclib

Indication:	**Dosing Schedule:**	**Start Date** (DD/MMM/YYYY):	**Stop Date** (DD/MMM/YYYY) **(if applicable):**

Details of most recent palbociclib administration prior to adverse event (AE)

Date (DD/MMM/YYYY)	**Dose**	**Action Taken with next dose in response to AE?**
		□ Dose maintained □ Dose decreased □ Dose interrupted □ Dose increased □ Dose discontinued

Fulvestrant

Indication:	**Dosing Schedule:**	**Start Date** (DD/MMM/YYYY):	**Stop Date** (DD/MMM/YYYY) **(if applicable):**

Details of most recent fulvestrant administration prior to adverse event (AE)

Date (DD/MMM/YYYY)	**Dose**	**Action Taken with next dose in response to AE?**
		□ Dose maintained □ Dose decreased □ Dose interrupted □ Dose increased □ Dose discontinued

Concomitant Medications

Antihyperglycemic Medication
(Please list any antihyperglycemic medications the patient received 3 months prior to the onset of the reported AE)

Drug Name (generic or trade name)	**Indication**	**Dosing Regimen & Frequency of Dosing**	**Route**	**Start Date (DD/MMM/YYYY)**	**Stop Date (DD/MMM/YYYY)**	**Was the reported AE above related to this medication?**
						□ Yes □ No
						□ Yes □ No
						□ Yes □ No
						□ Yes □ No
						□ Yes □ No

Please add additional details of any known missed or changed doses of the antihyperglycemic medications listed above:

Other Medications

Please add any other relevant concomitant medications the patient is taking excluding drugs used to treat the reported AE.

Drug Name (generic or trade name)	Indication	Dosing Regimen & Frequency of Dosing	Route	Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)	Was this a suspect medication?
						□ Yes □ No
						□ Yes □ No
						□ Yes □ No
						□ Yes □ No

Please add additional details of any known missed or changed doses of the antihyperglycemic medications listed above:

Laboratory Results

Please indicate by selecting "yes" or "no" if any of the following tests listed below have been performed, and provide the results on the table below: Alternatively, the laboratory results of the tests that you have selected "yes" can be attached with the follow-up questionnaire after completion and sent back to us. Please ensure that privacy law requirements have been adhered to when sending these reports by redacting sensitive information.

□ ***Laboratory Results Attached*** *(please tick if you prefer to send copies of the results rather than completing the table below)*

Laboratory Test	Was the test performed?	Baseline Value/ Peak Value (include units)	Date of Baseline Test (DD/MMM/YYYY)	Lab Results at time of AE	Date of Test at the time of AE (DD/MMM/YYYY)	Reference Range (include units)
Blood/Plasma Fasting Glucose	□ Yes □ No					
Blood/Plasma Random Glucose	□ Yes □ No					
HbA_{1C}	□ Yes □ No					
Serum Osmolality	□ Yes □ No					
Anion Gap	□ Yes □ No					
Arterial/ Blood pH	□ Yes □ No					
PCO2	□ Yes □ No					
Serum Bicarbonate	□ Yes □ No					
Serum Potassium (K)	□ Yes □ No					
Serum Sodium (Na)	□ Yes □ No					
Blood/Serum Ketones	□ Yes □ No					
Urine Ketones	□ Yes □ No					
c-Peptide	□ Yes □ No					
Lactate	□ Yes □ No					
Beta-hydroxybutyrate	□ Yes □ No					
eGFR	□ Yes □ No					
Serum Creatinine	□ Yes □ No					
Urea	□ Yes □ No					
Other *(please specify)*						
Other *(please specify)*						

Laboratory Results

Please indicate by selecting "yes" or "no" if any of the following tests listed below have been performed, and provide the results on the table below: Alternatively, the laboratory results of the tests that you have selected "yes" can be attached with the follow-up questionnaire after completion and sent back to us. Please ensure that privacy law requirements have been adhered to when sending these reports by redacting sensitive information.

□ ***Laboratory Results Attached*** *(please tick if you prefer to send copies of the results rather than completing the table below)*

Laboratory Test	**Was the test performed?**	**Baseline Value/ Peak Value (include units)**	**Date of Baseline Test** (DD/MMM/YYYY)	**Lab Results at time of AE**	**Date of Test at the time of AE** (DD/MMM/YYYY)	**Reference Range (include units)**
Other *(please specify)*						
Other *(please specify)*						
Other *(please specify)*						
Other *(please specify)*						
Other *(please specify)*						
Other *(please specify)*						
Other *(please specify)*						
Other *(please specify)*						
Other *(please specify)*						

Other Relevant Information

Please provide any further relevant information about the Adverse Event (e.g., patient's diet and lifestyle, how was the patient's hyperglycemia monitored).

If you were the reporter for the initial report, please provide any significant updates since the time of the initial report.

Completed by:
Name of the reporter completing the form:
Are you a Healthcare Provider?: □ Yes □ No, please specify:
Complete Address:
Contact Details:

Thank you for completing this follow-up questionnaire.

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

Not applicable