EU Risk Management Plan (Version 0.4)

Global Patient Safety
Signatory information is available on request.

EU Risk Management Plan for Imlunestrant (LY384356)

RMP version to be assessed as part of the application: 0.4

Data lock point for this RMP: 24 June 2024

Date of final sign off: Refer to Page 1 for the approval date

Rationale for submitting an updated RMP: This updated EU Risk Management Plan (RMP) is submitted in response to the Committee for Medicinal Products for Human Use's (CHMP's) oral explanation discussion at Day 208, as part of Procedure No. EMEA/H/C/006184/0000.

Summary of significant changes in this RMP: Removal of the indication of imlunestrant proposed in combination with abemaciclib.

Other RMP versions under evaluation

RMP version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP

Version number: Not applicable

Approved with procedure: Not applicable

Date of approval (opinion date): Not applicable

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's Qualified Person for Pharmacovigilance (QPPV). The electronic signature is available on file.

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List of Abbreviations

Term	Definition
AI	aromatase inhibitor
AUC_{0-24}	area under the concentration versus time curve from zero to 24 hours
BC	breast cancer
CDK	cyclin-dependent kinase
CDK4/6i	CDK4/6 inhibitor
CHMP	Committee for Medicinal Products for Human Use
CYP	cytochrome p450
ER	oestrogen receptor
ET	endocrine treatment
GI	gastrointestinal
HER2-	human epidermal growth factor receptor 2-negative
HR+	hormone receptor-positive
MBC	metastatic breast cancer
NCCN	National Comprehensive Cancer Network
RMP	Risk Management Plan
SmPC	summary of product characteristics
SEER	Surveillance, Epidemiology, and End Results
SERD	**s**elective oestrogen receptor degrader
SSRI	serotonin-specific reuptake inhibitor
UGT	uridine diphospho-glucuronosyltransferase

Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Imlunestrant
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	Eli Lilly and Company
Medicinal products to which this RMP refers	Imlunestrant
Invented name(s) in the European Economic Area (EEA)	Inluriyo
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Selective oestrogen receptor degrader (SERD)
	Summary of mode of action: Selective pure antagonist of wild type and mutant oestrogen receptor α (ERα or ESR1). Imlunestrant potently inhibits transcription of ERα target genes, selectively inhibiting the proliferation of ER+ cancer cells.
	Important information about its composition: Orally bioavailable, non-covalent binding.
Hyperlink to the Product Information	See eCTD Module 1.3.1
Indication(s) in the EEA	**Current:** Not applicable
	Proposed: Inluriyo is indicated as a monotherapy for the treatment of adult patients with (ER)-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation, who have disease progression following prior treatment with an endocrine based regimen.
Dosage in the EEA	**Current:** Not applicable
	Proposed: The recommended dose of inluriyo monotherapy is 400 mg orally, once daily. Pre or perimenopausal women and men should receive a concomitant luteinising hormone-releasing hormone agonist according to current clinical practice standards. It is recommended that treatment be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.
Pharmaceutical form(s) and strengths	**Current:** Not applicable

	Proposed: Film-coated tablet, 200 mg
Is/will the product be subject to additional monitoring in the EU?	Yes At initial marketing authorisation application conclusion.

Abbreviations: ATC = anatomical therapeutic chemical class; ER = oestrogen receptor; ER+ = oestrogen receptor positive; ESR1 = oestrogen receptor 1; HER2- = human epidermal growth factor receptor 2-negative; INN = international non-proprietary name; N/A = not applicable; RMP = risk management plan; SmPC = summary of medicinal product characteristics.

Part II: Safety Specification

Module SI - Epidemiology of the Indications and Target Populations

SI.1 Breast Cancer

The target population of imlunestrant comprises patients with ER+, HER2- locally advanced or metastatic BC. Most BC statistics include all BCs, regardless of molecular subtype or stage at diagnosis. Clinically relevant differences in the target population distinct from the general epidemiology of overall BC are highlighted where relevant.

SI.1.1 Incidence

BC is the most common cancer in women in almost all countries (Cardoso et al. 2018). Globally, BC is on the rise, and industrialised nations see the highest rates, where developed countries account for nearly half of all global cases (Smolarz et al. 2022). According to the GLOBOCAN 2022 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, an estimated 2.3 million new cases of female BC were reported in 2022 (Ferlay et al. 2024). As per Sung et al. (2021), the 2022 age-standardised annual incidence rates of BC among females (per 100 000) globally and across different regions were as follows:

- 47.1 (world)
- 34.5 (Asia)
- 40.6 (Africa)
- 52.0 (Latin America)
- 76.3 (Europe)
- 91.5 (Oceania), and
- 95.9 (North America).

Males are disproportionately less affected, accounting for approximately 1% of all BCs. The male/female ratios of incident BC were reported to range from 1/83.9 globally to 1/105.5 in the US and 1/141 in the UK (Cancer Research UK 2016; Siegel et al. 2017; Li et al. 2019).

SI.1.2 Prevalence

Almost 8.2 million women worldwide were living with BC in 2022. As per Sung et al. (2021), the estimated 5-year female BC prevalence across different regions (in millions) were as follows:

- 3.2 (Asia)
- 2.3 (Europe)
- 1.3 (North America)
- 0.7 (Latin America)
- 0.5 (Africa), and
- 0.1 (Oceania).

Direct estimates of BC prevalence among males are not available. However, given that male patients with BC have a higher mortality rate across stages compared with their female

counterparts (Wang et al. 2019), prevalence of male BC cases is estimated as 0.6% to 1% of all BC cases.

ESR1 mutations rarely exist in primary tumours (approximately 1%) but are relatively common (10 to 50%) in metastatic, endocrine therapy-resistant ER+ HER2- BCs and increase with metastatic recurrences across treatment lines, secondary to selective pressure due to previous endocrine therapy (most commonly AI treatment). (Zundelevich et al. 2020).

SI.1.3 Demographics of the Population in the proposed Indication – [age, racial and/or ethnic origin] and Risk Factors for the Disease

Age

The median age at diagnosis was 63 years in female and 68 years in male patients (SEER*Explorer 2024). BC is most frequently diagnosed in women aged 55 to 64 years. The age distribution of new BC cases in females in Europe and the US are presented in Table SI.1.

Table SI.1 Age Distribution (%) of Incident Cases for Female Breast Cancer

Age at Diagnosis, Years	<20	20-34	35-44	45-54	55-64	65-74	75-84	>84
CI-5, 2003-2007	0.0	1.7	9.7	21.0	24.6	21.6	15.5	5.8
SEER 21, 2013-2017	0.0	1.9	8.3	19.7	25.7	25.5	13.6	5.6

Abbreviations: CI-5 = World Health Organization's IARC Cancer Incidence in Five Continents Volume X; IARC = International Agency for Research on Cancer; SEER 21 = Surveillance, Epidemiology, and End Results 2013-2017 All races, females.

The HR+, HER2- subtype is more common with increasing age. According to 2010 US SEER 18 data, 78% of women aged 65 to 74 years had cancers of the HR+, HER2- subtype compared to 65% of women up to 50 years of age (Howlader et al. 2014).

Breast cancer disproportionately affects women aged 50 and older, with over 70% of new cases and 81% of deaths occurring in this age group worldwide. However, the age distribution of cases and deaths varies significantly across different regions (Arnold et al. 2022). For example, in the US, 17% of BCs are diagnosed in women younger than 50 years, and 10% of deaths due to BC occur in this age group. (Giaquinto et al. 2022). In the Asia-Pacific region, the estimated percentage of patients with BC younger than 50 years is 42% (Youlden et al. 2014) and is almost 50% in the Middle East (El Saghir et al. 2007) and Latin America (Rodríguez-Cuevas S et al. 2001). In Western and Northern Europe, as well as North America, over 80% of cases and 90% of deaths occur in women aged 50 and older, and these regions continue to carry the highest age-standardised incidence rate for underage 50 (greater than 30 per 100 000) and 50 and older BC greater than 300 per 100 000) (Arnold et al. 2022).

Race/Ethnicity

Racial and ethnic disparities in BC outcomes persist. While the incidence rate is highest among white women, black women experience significantly higher mortality rates and lower survival rates (Łukasiewicz et al. 2021).

HR+, HER2- BC is the most common subtype among women of all races or ethnicities, accounting for 76% and 61% of BCs in White women and Black women, respectively (ACS 2019).

SI.1.4 Main Existing Treatment Options

Metastatic or Advanced BC

The European School of Oncology-European Society of Medical Oncology (ESO-ESMO) 4th International Consensus Guidelines for Advanced Breast Cancer (ABC4) and the NCCN guidelines specify that treatment for women with Stage IV or recurrent HR+, HER2-tumours without visceral crisis or endocrine resistance should include ET with or without targeted agents (ESMO Guidelines 2019; NCCN Guidelines 2020). For post-menopausal women with HR+, HER2-recurrent/Stage IV BC, preferred regimens include a CDK4/6i with an AI, fulvestrant with or without a CDK4/6i, or fulvestrant with a non-steroidal AI. Other recommended regimens include non-steroidal AIs (anastrozole and letrozole), exemestane, and tamoxifen or toremifene. For pre-menopausal women, first-line ET includes ovarian suppression or ablation with any of the previously listed ET for post-menopausal women or with a selective ER modulator.

For HR+, HER2- BC, ET remains an important backbone of treatment, either as monotherapy or in combination with other agents, even after recurrence, and is often preferred over cytotoxic chemotherapy. Choice of ET as backbone includes AI or SERD depending on prior ET received (AI or tamoxifen) and duration of response to the prior ET.

The NCCN preferred recommendation for second-line treatment of HR+, HER2- MBC in post-menopausal women includes fulvestrant with a CDK4/6i. The other treatment options are as follows:

- everolimus with either an AI, tamoxifen, or fulvestrant
- monotherapy with fulvestrant
- nonsteroidal or steroidal AI, or
- selective oestrogen receptor modulator.

Alpelisib is an option for tumours with PIK3CA mutations. Cytotoxic chemotherapy is recommended for ET-refractory tumours, or patients with symptomatic visceral disease, or both (NCCN 2020).

For patients with chemotherapy-naive tumours, when deemed appropriate, anthracycline- or taxane-based regimens are preferred. For patients previously treated with chemotherapy, anthracyclines, taxanes, capecitabine, vinorelbine, or eribulin are preferred with gemcitabine and platinum as additional choices.

With minor variations, BC in men is treated in the same way as BC in women.

Recently, elacestrant, an orally administered SERD, demonstrated a significant progression-free survival improvement compared to standard-of-care ET (majority fulvestrant) in the Phase 3 EMERALD trial. The current US FDA and EU European Medicines Agency marketing

approvals are limited to post-menopausal women and adult men with *ESR1*-mutated, ER+/HER2- ABC or MBC following disease progression on

- at least 1 line of ET, in the US (ORSERDU package insert), or
- at least 1 line of ET with a CDK4/6i, in the EU (ORSERDU summary of product characteristics).

Elacestrant is not approved for use in pre-menopausal women, patients without detected tumour *ESR1* mutation, and in combination with CDK4/6 inhibitors. Elacestrant has unknown efficacy in patients who are CDK4/6i naive.

SI.1.5 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

There is limited literature regarding the natural history of untreated BC.

Most patients present with a palpable mass or tumour detected as part of routine screening (Malherbe et al. 2022). If untreated, tumour infiltration into the skin with potential ulceration may develop. The primary tumour may metastasise into the axillary lymph nodes, the other breast, and ultimately to more distant sites, including brain, bones, and liver. Primary tumours may also extend directly into the chest wall musculature. Only 1 in 20 (5%) of untreated patients survived more than 5 years (Baum 2013). Without systemic therapy, only 25% of patients survived 10 years with radical mastectomy (Baum 2013).

Most patients in developed countries present with early stage (Stage 1 or 2) disease. Approximately 10% presented with advanced (Stage 3) disease with axillary lymph node involvement. Distant metastasis at diagnosis is rare (5%; Lousdal et al. 2014; Akinyemiju et al. 2015; Cancer Research UK 2016).

In less developed countries, disease is frequently more advanced at diagnosis. Approximately 20% to 25% of newly diagnosed BCs in some countries in Africa, Central and South America, and West Asia are already metastatic (Benitez Fuentes et al. 2023).

BC survival is strongly related to disease stage at diagnosis. In England, between 2016 and 2020, the 5-year relative survival rates rapidly decreased with increasing stage: Stage 1 (almost 100%), Stage 2 (90%), Stage 3 (more than 70%), and Stage 4 (more than 25%) (Cancer Research UK 2024). A similar relationship was observed in the US. Between 2013 and 2019, the 5-year survival rates were: localised (99%), regional (86%), and distant disease (31%) (SEER*Explorer 2024).

MBC is incurable; however, the presence or absence of hormone and epidermal growth factor receptors in breast tumours affects survival (SEER 2024). BC subtypes were also shown to be associated with notable differences in survival after relapse (Kennecke 2010). For example, the 5-year relative survival was most favourable among women with the HR+/HER2- subtype (95.1%), followed by the HR+/HER2+ subtype (91.5%) and the HR-/HER2+ subtype (85.7%). The HR-/HER2- subtype had the worst survival with 78.0% (SEER 2024).

Patients with MBC having tumours harbouring an ESR1 mutation have been shown to have worse outcomes (PFS and OS) compared to patients with wild-type ESR1 (Reinert et al. 2017; Turner et al. 2020).

Symptoms of MBC depend on the location of spread and can include pain, swelling, headache, vision disturbances, seizures, nausea, vomiting, anorexia leading to weight loss, jaundice, pruritus, rash, fatigue, cough, and dyspnoea. Based on primary care records from 80 patients with MBC from 11 general practices in the UK between 2002 and 2009, the common signs and symptoms included the following:

- groin pain (10%)
- pleurisy/pleural effusion (6%)
- shoulder pain (17%)
- loss of appetite (20%)
- vomiting (25%)
- low back pain (24%)
- flank/loin pain (11%)
- chest pain: musculoskeletal (23%)
- oedema (22%), and
- abnormal liver enzyme tests (38%).

A statistically significant association ($p<0.05$) between vomiting, low back pain, flank or loin pain, chest pain: musculoskeletal, oedema, and abnormal liver enzyme tests was observed when comparing patients with MBC to matched non-cancer controls (Hamilton et al. 2015).

Patients with MBC may also experience long-term disease complications or late effects of treatment. A meta-analysis of over 40 000 patients with early BC comparing women randomly assigned to radiotherapy versus no radiotherapy, showed an increased cardiac death and secondary cancers (lung and contralateral BC) more than 10 years after the breast radiotherapy (Taylor et al. 2017). Anthracyclines increase the risk of congestive heart failure (Afifi et al. 2020). AIs are associated with increased cardiovascular risks (Davezac et al. 2023). Tamoxifen reduces levels of antithrombin and protein S, proteins involved in blood clotting, potentially increasing venous thrombosis risk (Cushman et al. 2003). Venous thromboembolism risk also increases with metastatic disease, as demonstrated in a UK study of 13 202 participants which showed that the venous thromboembolism incidence rate (per 1000 person-years) was 6.8 for local, 9.9 for regional, and 18.2 for distant disease (Walker et al. 2016).

Worldwide in 2022, the age-standardised BC mortality was 12.7 per 100 000 with highest annual rates (per 100 000) in Africa (19.2), Oceania (15.4), Europe (14.6), South America (13.9), North America (12.3), and Asia (10.5) (Cancer Today 2024).

SI.1.6 Important Co-morbidities

As BC is associated with advancing age, co-morbidities are common (Patnaik et al. 2011). Older adults often have multiple additional health conditions, which significantly impact treatment decisions, outcomes, and survival. Older patients are more likely to die from causes unrelated to cancer. This “competing risk” can confound the assessment of BC-specific outcomes (Kiderlen

et al. 2014). In contrast, younger patients typically present with fewer co-morbidities, reducing the complexity of their co-morbidity management compared to older patients. However, younger patients have unique concerns related to fertility, body image, and career disruptions that can impact psychological well-being and overall experience (Tesch and Partridge 2022). Table SI.2 summarises important co-morbidities and their treatments in older adults (greater than or equal to 65 years), providing an illustration of the disease and the complex interplay of multiple health conditions.

Table SI.2 Important Comorbidity Prevalence and Expected Co-medications

Co-morbidity	Invasive and In Situ Breast Cancer ≥65 years (Netherlands 1997-2004)[a]	Invasive Breast Cancer ≥66 years (US 1992-2005)[b]	Expected Co-medications of Co-morbidity
	N = 3672	N = 123 680	
Cardiovascular disorders			
Cardiac arrhythmias	11.6%	NA	Aspirin Antiarrhythmics Anticoagulants
Cardiac valve disorders	4.3%	NA	NA[c]
Congestive heart failure	5.2%	6.9%	Aspirin Beta-blockers Diuretics Digoxin ACE inhibitors Angiotensin II receptor blockers Aldosterone antagonists
Myocardial infarction	6.7%	0.8%	Aspirin Antiplatelet therapy Beta blockers Nitrates Statins ACE inhibitors Angiotensin II receptor blockers
Cerebrovascular accident/stroke	7.7%	4.6%	Aspirin Antiplatelet therapy Anticoagulants Statins
Hypertension	32.1%	NA	ACE inhibitors Angiotensin II receptor blockers Beta blockers Calcium channel blockers Diuretics
Peripheral arterial disease	2.3%	NA	Aspirin Antiplatelet therapy Statins
Peripheral vascular disease	NA	2.7%	Aspirin Antiplatelet therapy Statins
DVT	3.0%	NA	Anticoagulants

Co-morbidity	Invasive and In Situ Breast Cancer ≥65 years (Netherlands 1997-2004)[a]	Invasive Breast Cancer ≥66 years (US 1992-2005)[b]	Expected Co-medications of Co-morbidity
	N = 3672	N = 123 680	
Endocrine disorders			
Hypercholesterolaemia	2.5%	NA	Statins
Diabetes	NA	14.5%	Insulin Metformin Sulphonylureas Meglitinides **Thiazolidinediones** Dipeptidyl peptidase-4 inhibitors Glucagon-like peptide-1 agonists Sodium-glucose co-transporter-2 inhibitors
Other disorders			
COPD	8.9%	9.5%	Bronchodilators Corticosteroids Theophylline Phosphodiesterase-4 inhibitors
Liver disease	NA	0.1%	NA[c]
Renal disease	NA	1.2%	NA[c]

Abbreviations: ACE = angiotensin converting enzyme; COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; N = number of patients in the analysis population; NA: not applicable.

[a] Kiderlen et al. 2014.

[b] Edwards et al. 2014.

[c] Diagnosis dependent, therefore treatment can involve a range of therapeutic modalities.

Module SII – Non-clinical Part of the Safety Specification

SII.1 Toxicity

Repeat-dose toxicity studies

In repeat-dose studies, the following important effects were observed:

- reproductive tract effects in rats and monkeys
- urinary tract effects in rats, and
- ocular effects in rats.

Reproductive tract effects

The primary imlunestrant-associated adverse effect in clinically relevant exposures from repeat-dose toxicity studies was female reproductive tract toxicity in rats and monkeys. Imlunestrant caused reversible cessation of oestrous cycling in rats, and in studies of 3 months or longer, male reproductive tissues were affected. Reproductive effects were consistent with exaggerated pharmacology of imlunestrant at the ER and have been observed with other drugs known to antagonise or degrade the ER, including tamoxifen and fulvestrant (Plouffe and Siddhanti 2001; Geiser et al. 2005; Sinkevicius et al. 2009). Importantly, with the exception of ovarian cysts, reproductive tract effects were reversible. Because pre-/peri-menopausal women with BC are required to use luteinising hormone-releasing hormone agonist with imlunestrant for ovulation prevention, the risk of ovarian cysts is greatly diminished.

Urinary tract effects

Imlunestrant was associated with urinary tract effects, including renal tubular degeneration or regeneration, hyperplasia of transitional epithelium in the bladder, and ascending inflammatory urinary tract pathology in rats. These findings occurred at systemic $AUC_{0\text{-}24}$ exposures that exceed those in humans by at least 4-fold and were not observed in monkeys.

Ocular effects

Ocular effects were limited to rats after chronic dosing and consisted of minimal to mild lens fibre degeneration, with or without increased cortical lens opacity. At tolerated doses in rats, lens degeneration was minimal, reversible, and occurred at systemic $AUC_{0\text{-}24}$ exposures that exceed those in humans by at least 4-fold. Additionally, lens fibre degeneration was not associated with increased corneal opacity. At doses that were not tolerated, microscopic lens degeneration was adverse, non-reversible, and was associated with increases in focal and central cortical lens opacity.

Developmental toxicity

When administered to pregnant rats during organogenesis, clinically relevant imlunestrant exposures caused embryo-foetal lethality and malformations. Similar toxicities were identified with other oestrogen-modulating treatments. These can be addressed through label requirements for the use of contraception and ovarian suppression with luteinising hormone-releasing hormone agonist by women of childbearing potential.

Genetic toxicity

Imlunestrant does not pose a biologically relevant genetic toxicity risk. Imlunestrant was not mutagenic in the bacterial reverse mutation (Ames) assay. In the in vitro micronucleus assay, imlunestrant caused chromosomal damage by a mixed aneugenic and clastogenic mechanism. However, this risk was discharged by the findings of 2 in vivo genotoxicity assays.

Carcinogenicity

In accordance with ICH S9 guidelines, carcinogenicity studies are not required for the proposed advanced cancer indication. The carcinogenicity assessment of imlunestrant to support the planned adjuvant indication is ongoing and will be updated following the completion of the 2-year rat carcinogenicity study. In a 6-month rasH2 transgenic mouse study, imlunestrant caused an increased incidence of benign and malignant sex cord stromal tumours at 2 times the human AUC at the recommended dose. The induction of such tumours is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-oestrogen and does not alter risk-benefit for the indicated patient population.

SII.2 Safety Pharmacology

Imlunestrant had no effects on the cardiovascular, respiratory, or central nervous systems when evaluated non-clinically.

SII.3 Other Toxicity-related Information or Data

Phototoxicity

At high doses that are not clinically relevant, imlunestrant was mildly phototoxic, producing barely perceptible redness in rats following exposure to ultraviolet radiation only with exposures exceeding those observed in humans at 400 mg by 36-fold. Imlunestrant was non-phototoxic at systemic exposures 11-fold higher than those observed in humans at 400 mg, providing a sufficient margin of safety. No imlunestrant-related phototoxic effects were noted in the eyes by ophthalmologic and histologic examination at any dose. Due to the low severity of effect and high safety margins, the clinical relevance of this risk is considered low.

Module SIII - Clinical Trial Exposure

Imlunestrant has been investigated in patients with ER+ locally advanced or metastatic BC and HER2-negative locally advanced or metastatic BC.

Clinical trial exposure summaries below include data from all completed studies. In these studies, imlunestrant has been used alone or in combination with other therapies.

Table SIII.1. Duration of Exposure

Cumulative for all tumour types[a]: Safety Population		
Duration of exposure[a]	**Patients**	**Person time (months)**
All imlunestrant treated patients (monotherapy and combination therapy)		
<1 month (30 days)	124	64.5
1 to <3 months (91 days)	249	484.3
3 to <6 months (183 days)	175	803.7
6 to <12 months (365 days)	227	2051.3
≥12 months	241	4289.8
Total	**1016**	**7693.6**
Imlunestrant monotherapy[b]		
<1 month (30 days)	101	54.5
1 to <3 months (91 days)	169	327.7
3 to <6 months (183 days)	103	472.4
6 to <12 months (365 days)	115	1051.5
≥12 months	94	1823.3
Total	**582**	**3729.4**
Imlunestrant + abemaciclib[c]		
<1 month (30 days)	18	7.9
1 to <3 months (91 days)	51	102.2
3 to <6 months (183 days)	47	219.3
6 to <12 months (365 days)	78	703.6
≥12 months	89	1506.7
Total	**283**	**2539.8**
Imlunestrant +Other Combinations[d]		
<1 month (30 days)	5	2.1
1 to <3 months (91 days)	29	54.4
3 to <6 months (183 days)	25	112
6 to <12 months (365 days)	34	296.2
≥12 months	58	959.7
Total	**151**	**1424.4**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_all.rtf		
Exposure in Advanced breast cancer: Safety Population		
<1 month (30 days)	28	13.8
1 to <3 months (91 days)	225	441.9
3 to <6 months (183 days)	160	734.7

6 to <12 months (365 days)	215	1939.9
≥12 months	231	4076.9
Total	**859**	**7207.1**
Imlunestrant monotherapy[e]		
<1 month (30 days)	12	6.8
1 to <3 months (91 days)	155	303.4
3 to <6 months (183 days)	93	427.4
6 to <12 months (365 days)	110	1006.6
≥12 months	88	1684.0
Total	**458**	**3428.1**
Imlunestrant + abemaciclib[f]		
<1 month (30 days)	11	4.9
1 to <3 months (91 days)	41	84.1
3 to <6 months (183 days)	42	195.4
6 to <12 months (365 days)	71	637.1
≥12 months	85	1433.1
Total	**250**	**2354.7**
Imlunestrant + Other Combinations[d]		
<1 month (30 days)	5	2.1
1 to <3 months (91 days)	29	54.4
3 to <6 months (183 days)	25	112.0
6 to <12 months (365 days)	34	296.2
≥12 months	58	959.7
Total	**151**	**1424.4**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_mbc.rtf		
Exposure for all tumour types[a]: ESR1-Mutation-Detected Safety Population		
All imlunestrant treated patients (monotherapy and combination therapy)		
<1 month (30 days)	10	4.8
1 to <3 months (91 days)	74	147.8
3 to <6 months (183 days)	68	315.6
6 to <12 months (365 days)	86	783.2
≥12 months	64	1117.3
Total	**302**	**2368.7**
Imlunestrant monotherapy[g]		
<1 month (30 days)	7	3.8
1 to <3 months (91 days)	58	115.4
3 to <6 months (183 days)	45	211.9
6 to <12 months (365 days)	48	431.0
≥12 months	33	597.3
Total	**191**	**1359.4**
Imlunestrant + abemaciclib[c]		
<1 month (30 days)	2	0.5
1 to <3 months (91 days)	11	21.7
3 to <6 months (183 days)	13	57.7

6 to <12 months (365 days)	25	234.4
≥12 months	18	298.3
Total	**69**	**612.6**
Imlunestrant + Other Combinations[d]		
<1 month (30 days)	1	0.5
1 to <3 months (91 days)	5	10.7
3 to <6 months (183 days)	10	45.9
6 to <12 months (365 days)	13	117.8
≥12 months	13	221.7
Total	**42**	**396.7**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_all_esr1_d.rtf		
Exposure in Advanced breast cancer ESR1-Mutation-Detected Safety Population		
All imlunestrant treated patients (monotherapy and combination therapy)		
<1 month (30 days)	10	4.8
1 to <3 months (91 days)	73	146.0
3 to <6 months (183 days)	68	315.6
6 to <12 months (365 days)	86	783.2
≥12 months	64	1117.3
Total	**301**	**2366.9**
Imlunestrant monotherapy[h]		
<1 month (30 days)	7	3.8
1 to <3 months (91 days)	57	113.5
3 to <6 months (183 days)	45	211.9
6 to <12 months (365 days)	48	431.0
≥12 months	33	597.3
Total	**190**	**1357.6**
Imlunestrant + abemaciclib[f]		
<1 month (30 days)	2	0.5
1 to <3 months (91 days)	11	21.7
3 to <6 months (183 days)	13	57.7
6 to <12 months (365 days)	25	234.4
≥12 months	18	298.3
Total	**69**	**612.6**
Imlunestrant + Other Combinations[d]		
<1 month (30 days)	1	0.5
1 to <3 months (91 days)	5	10.7
3 to <6 months (183 days)	10	45.9
6 to <12 months (365 days)	13	117.8
≥12 months	13	221.7
Total	**42**	**396.7**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_mbc_esr1_d.rtf		

Abbreviations: ABC = advanced breast cancer; Abema = abemaciclib; AI = aromatase inhibitor; BC = breast cancer; EEC = endometrioid endometrial carcinoma; ESR1 = oestrogen receptor 1; Imlun =imlunestrant.

a Tumour types: ABC and EEC.

[b] Monotherapy includes Studies JZLC Arm A, JZLB all patients, JZLF all patients, JZLA Phase 1a (BC and EEC), and Phase 1b E3 and E8.
[c] Imlun + Abema includes Studies JZLC Arm C and JZLA Phase 1b E1 and E9.
[d] Imlun + Other Combinations: Includes Study JZLA E2 (Imlun + Abema + AI), E4 (Imlun + everolimus), E5 (Imlun + alpelisib), E6 (Imlun + trastuzumab), E7 (Imlun + Abema + trastuzumab), E10 (Imlun + trastuzumab + pertuzumab).
[e] Monotherapy includes Studies JZLC Arm A, JZLF all patients, and JZLA Phase 1a (BC only) and Phase 1b E3.
[f] Imlun + Abema includes Studies JZLC Arm C and JZLA Phase 1b E1.
[g] Monotherapy includes Studies JZLC Arm A and JZLA Phase 1a (BC and EEC), Phase 1b E3 and E8.
[h] Monotherapy includes Studies JZLC Arm A and JZLA Phase 1a (BC only) and Phase 1b E3.

Note: All completed clinical trials with patients exposed to imlunestrant are included.

Table SIII.2. Age Group and Gender

Cumulative for all tumour types (person time)[a]: Safety Population				
All imlunestrant treated patients (monotherapy and combination therapy)				
Age group	**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**
18 to 64 years	5	627	58.1	4510.9
65-74 years	3	270	49.1	2293.7
75-84 years	0	97	0	725.7
85 + years	0	14	0	56.0
Total	**8**	**1008**	**107.2**	**7586.4**
Imlunestrant monotherapy[b]				
18 to 64 years	4	357	45.2	2036.5
65-74 years	1	154	18.6	1188.8
75-84 years	0	58	0	415.2
85 + years	0	8	0	25.1
Total	**5**	**577**	**63.8**	**3665.6**
Imlunestrant + abemaciclib[c]				
18 to 64 years	0	162	0	1431.3
65-74 years	2	83	30.5	792.6
75-84 years	0	30	0	254.5
85 + years	0	6	0	30.9
Total	**2**	**281**	**30.5**	**2509.3**
Imlunestrant + Other Combinations[d]				
18 to 64 years	1	108	12.9	1043.1
65-74 years	0	33	0	312.4
75-84 years	0	9	0	56.0
85 + years	0	0	0	0
Total	**1**	**150**	**12.9**	**1411.5**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_age_female_all.rtf /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_age_male_all.rtf				

Age Group and Gender Exposure in Advanced breast cancer: Safety Population				
All imlunestrant treated patients (monotherapy and combination therapy)				
Age group	**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**
18 to 64 years	5	541	58.1	4243.1
65-74 years	3	215	49.1	2120.1
75-84 years	0	82	0	686.1
85 + years	0	13	0	50.5
Total	**8**	**851**	**107.2**	**7099.9**
Imlunestrant monotherapy[e]				
18 to 64 years	4	286	45.2	1863.1
65-74 years	1	111	18.6	1067.2
75-84 years	0	48	0	408.8
85 + years	0	8	0	25.1
Total	**5**	**453**	**63.8**	**3364.3**
Imlunestrant + abemaciclib[f]				
18 to 64 years	0	147	0	1336.9
65-74 years	2	71	30.5	740.5
75-84 years	0	25	0	221.3
85 + years	0	5	0	25.4
Total	**2**	**248**	**30.5**	**2324.1**
Imlunestrant +Other Combinations[d]				
18 to 64 years	1	108	12.9	1043.1
65-74 years	0	33	0	312.4
75-84 years	0	9	0	56
85 + years	0	0	0	0
Total	**1**	**150**	12.9	**1411.5**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_age_male_mbc.rtf /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_age_female_mbc.rtf				
Cumulative for all tumour types: ESR1-Mutation-Detected Safety Population				
Age group	**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**
18 to 64 years	0	188	0	1395.2
65-74 years	0	75	0	706.2
75-84 years	0	35	0	258.1
85 + years	0	4	0	9.3
Total	**0**	**302**	**0**	**2368.7**
Imlunestrant monotherapy[g]				
18 to 64 years	0	120	0	764
65-74 years	0	45	0	432.5
75-84 years	0	22	0	153.7
85 + years	0	4	0	9.3
Total	**0**	**191**	**0**	**1359.4**
Imlunestrant + abemaciclib[c]				
18 to 64 years	0	39	0	345.2
65-74 years	0	22	0	193.3
75-84 years	0	8	0	74.1
85 + years	**0**	0	0	0

Total	**0**	**69**	**0**	**612.6**
Imlunestrant +Other Combinations[d]				
18 to 64 years	0	29	0	286.0
65-74 years	0	8	0	80.4
75-84 years	0	5	0	30.3
85 + years	0	0	0	0
Total	**0**	**42**	**0**	**396.7**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_age_male_all_esr1_d.rtf /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_age_female_all_esr1_d.rtf				
Age Group and Gender Exposure in Advanced breast cancer: ESR1-Mutation-Detected Safety Population				
Age group	**Patients**		**Person time (months)**	
	M	**F**	**M**	**F**
18 to 64 years	0	188	0	1395.2
65-74 years	0	74	0	704.3
75-84 years	0	35	0	258.1
85 + years	0	4	0	9.3
Total	**0**	**301**	**0**	**2366.9**
Imlunestrant monotherapy[h]				
18 to 64 years	0	120	0	764.0
65-74 years	0	44	0	430.6
75-84 years	0	22	0	153.7
85 + years	0	4	0	9.3
Total	**0**	**190**	**0**	**1357.6**
Imlunestrant + abemaciclib[f]				
18 to 64 years	0	39	0	345.2
65-74 years	0	22	0	193.3
75-84 years	0	8	0	74.1
85 + years	0	0	0	0
Total	**0**	**69**	**0**	**612.6**
Imlunestrant +Other Combinations[d]				
18 to 64 years	0	29	0	286.0
65-74 years	0	8	0	80.4
75-84 years	0	5	0	30.3
85 + years	0	**0**	0	**0**
Total	**0**	**42**	**0**	**396.7**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_age_male_mbc_esr1_d.rtf /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_age_female_mbc_esr1_d.rtf				

Abbreviations: ABC = advanced breast cancer; Abema = abemaciclib; AI = aromatase inhibitor; BC = breast cancer; EEC = endometrioid endometrial carcinoma; ESR1 = oestrogen receptor 1; F = female; Imlun = Imlunestrant; M = male.

a Tumour types: ABC and EEC.

b Monotherapy includes Studies JZLC Arm A, JZLB all patients, JZLF all patients, and JZLA Phase 1a (BC and EEC), Phase 1b E3 and E8.

c Imlun + Abema includes Studies JZLC Arm C and JZLA Phase 1b E1 and E9.

d Imlun + Other Combinations includes Study JZLA E2 (Imlun + Abema + AI), E4 (Imlun + everolimus), E5 (Imlun + alpelisib), E6 (Imlun + trastuzumab), E7 (Imlun + Abema + trastuzumab), E10 (Imlun + trastuzumab +

pertuzumab).

e Monotherapy includes Studies JZLC Arm A, JZLF all patients, and JZLA Phase 1a (BC only) and Phase 1b E3.

f Imlun + Abema: includes Studies JZLC Arm C and JZLA Phase 1b E1.

g Monotherapy includes Studies JZLC Arm A and JZLA Phase 1a (BC and EEC), Phase 1b E3 and E8.

h Monotherapy includes Studies JZLC Arm A and JZLA Phase 1a (BC only) and Phase 1b E3.

Note: All completed clinical trials with patients exposed to imlunestrant are included.

Table SIII.3. Dose

Cumulative for all tumour types[a]: Safety population		
Dose of exposure	**Patients**	**Person time (months)**
Imlunestrant single agent[b]		
200 mg orally QD	57	153.2
400 mg orally QD	449	3202.5
600 mg orally QD	20	133.3
800 mg orally QD	53	211.4
1200 mg orally QD	3	29.1
Total	**582**	**3729.4**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_dose_all.rtf		
Imlunestrant Combination		
Imlunestrant 200 mg + abemaciclib[c]	0	0
Imlunestrant 400 mg + abemaciclib[c]	275	2447.2
Imlunestrant 800 mg + abemaciclib[c]	8	92.6
Total	**283**	**2539.8**
Imlunestrant 400 mg + abemaciclib + AI (Anastrozole, Exemestane, or Letrozole)	42	536.2
Imlunestrant 800 mg + abemaciclib + AI (Anastrozole, Exemestane, or Letrozole)	1	17.7
Total	**43**	**554.0**
Imlunestrant 400 mg + everolimus	36	386.3
Imlunestrant 800 mg + everolimus	6	67.5
Total	**42**	**453.8**
Imlunestrant 400 mg + alpelisib	19	134.5
Imlunestrant 800 mg + alpelisib	2	7.0
Total	**21**	**141.5**
Imlunestrant 400 mg+ trastuzumab	18	104.1
Total	**18**	**104.1**
Imlunestrant 400 mg + abemaciclib + trastuzumab	20	122.3
Imlunestrant 800 mg + abemaciclib + trastuzumab	1	2.3
Total	**21**	**124.6**
Imlunestrant 400 mg + trastuzumab + pertuzumab	6	46.4
Total	**6**	**46.4**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_dose_combo_all.rtf		
Dose of Exposure in Advanced breast cancer: Safety population		
Imlunestrant single agent[d]		
Dose of exposure	**Patients**	**Person time (months)**
200 mg orally QD	29	137.5
400 mg orally QD	387	2988.5
600 mg orally QD	20	133.3

800 mg orally QD	19	139.7
1200 mg orally QD	3	29.1
Total	**458**	**3428.1**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_dose_mbc.rtf		
Imlunestrant Combination		
Imlunestrant 400 mg + abemaciclib[e]	246	2296.4
Imlunestrant 800 mg + abemaciclib[e]	4	58.3
Total	**250**	**2354.7**
Imlunestrant 400 mg + abemaciclib + AI (Anastrozole, Exemestane, or Letrozole)	42	536.2
Imlunestrant 800 mg + abemaciclib + AI (Anastrozole, Exemestane, or Letrozole)	1	17.7
Total	**43**	**554.0**
Imlunestrant 400 mg + everolimus	36	386.3
Imlunestrant 800 mg + everolimus	6	67.5
Total	**42**	**453.8**
Imlunestrant 400 mg + alpelisib	19	134.5
Imlunestrant 800 mg + alpelisib	2	7.0
Total	**21**	**141.5**
Imlunestrant 400 mg+ trastuzumab	18	104.1
Total	**18**	**104.1**
Imlunestrant 400 mg + abemaciclib + trastuzumab	20	122.3
Imlunestrant 800 mg + abemaciclib + trastuzumab	1	2.3
Total	**21**	**124.6**
Imlunestrant 400 mg + trastuzumab + pertuzumab	6	46.4
Total	**6**	**46.4**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_dose_combo_mbc.rtf		
Cumulative for all tumour types[a]: ESR1-Mutation-Detected Safety Population		
Imlunestrant single agent[f]		
Dose of exposure	**Patients**	**Person time (months)**
200 mg orally QD	12	44.5
400 mg orally QD	166	1198.3
600 mg orally QD	8	72.5
800 mg orally QD	5	44.1
1200 mg orally QD	0	0
Total	**191**	**1359.4**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_dose_all_esr1_d.rtf		
Imlunestrant Combination		
Dose of exposure	**Patients**	**Person time (months)**
Imlunestrant 400 mg + abemaciclib[c]	68	587.7
Imlunestrant 800 mg + abemaciclib[c]	1	24.9
Total	**69**	**612.6**

Imlunestrant 400 mg + abemaciclib + AI (Anastrozole, Exemestane, or Letrozole)	4	51.3
Total	**4**	**51.3**
Imlunestrant 400 mg + everolimus	17	172.6
Imlunestrant 800 mg + everolimus	3	43.2
Total	**20**	**215.9**
Imlunestrant 400 mg + alpelisib	8	66.3
Imlunestrant 800 mg + alpelisib	1	4.6
Total	**9**	**70.9**
Imlunestrant 400 mg+ trastuzumab	4	30.5
Total	**4**	**30.5**
Imlunestrant 400 mg + abemaciclib + trastuzumab	5	28.2
Total	**5**	**28.2**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_dose_combo_all_esr1_d.rtf		
Dose of Exposure in Advanced breast cancer: ESR1-Mutation-Detected Safety Population		
Imlunestrant single agent[g]		
Dose of exposure	**Patients**	**Person time (months)**
200 mg orally QD	12	44.5
400 mg orally QD	165	1196.5
600 mg orally QD	8	72.5
800 mg orally QD	5	44.1
1200 mg orally QD	0	0
Total	**190**	**1357.6**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_dose_mbc_esr1_d.rtf		
Imlunestrant Combination		
Imlunestrant 400 mg + abemaciclib[e]	68	587.7
Imlunestrant 800 mg + abemaciclib[e]	1	24.9
Total	**69**	**612.6**
Imlunestrant 400 mg + abemaciclib + AI (Anastrozole, Exemestane, or Letrozole)	4	51.3
Total	**4**	**51.3**
Imlunestrant 400 mg + everolimus	17	172.6
Imlunestrant 800 mg + everolimus	3	43.2
Total	**20**	**215.9**
Imlunestrant 400 mg + alpelisib	8	66.3
Imlunestrant 800 mg + alpelisib	1	4.6
Total	**9**	**70.9**

Imlunestrant 400 mg+ trastuzumab	4	30.5
Total	**4**	**30.5**
Imlunestrant 400 mg + abemaciclib + trastuzumab	5	28.2
Total	**5**	**28.2**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_dose_combo_mbc_esr1_d.rtf		

Abbreviations: ABC = advanced breast cancer; Abema = abemaciclib; AI = aromatase inhibitor; BC = breast cancer; EEC = endometrioid endometrial carcinoma; ESR1 = oestrogen receptor 1; Imlun = imlunestrant; QD = once daily.

a Tumour types includes ABC and EEC.

b Monotherapy includes Studies JZLC Arm A, JZLB all patients, JZLF all patients, and JZLA Phase 1a (BC and EEC), Phase 1b E3 and E8

c Imlun + Abema: includes Studies JZLC Arm C and JZLA Phase 1b E1 and E9.

d Monotherapy includes Studies JZLC Arm A, JZLF all patients and JZLA Phase 1a (BC only) and Phase 1b E3

e Imlun + Abema: includes Studies JZLC Arm C and JZLA Phase 1b E1.

f Monotherapy includes Studies JZLC Arm A and JZLA Phase 1a (BC and EEC), Phase 1b E3 and E8.

g Monotherapy includes Studies JZLC Arm A and JZLA Phase 1a (BC only) and Phase 1b E3.

Table SIII.4. Ethnic Origin

Cumulative for all tumour types[a]: Safety population		
Ethnic/racial origin	**Patients**	**Person time (months)**
Imlunestrant single agent[b]		
American Indian or Alaska Native	26	289.2
Asian	132	911.2
Black or African American	17	96.5
Native Hawaiian or Other Pacific Islander	0	0
White	375	2279.0
Multiple	2	8.7
Unknown	30	144.8
Total	**582**	**3729.4**
Imlunestrant + abemaciclib[c]		
American Indian or Alaska Native	3	30.6
Asian	88	850.3
Black or African American	11	106.6
Native Hawaiian or Other Pacific Islander	2	35.1
White	156	1290.2
Multiple	3	42.2
Unknown	20	184.9
Total	**283**	**2539.8**
Imlunestrant + Other Combinations[d]		
American Indian or Alaska Native	0	0
Asian	37	341.5
Black or African American	6	48.4
Native Hawaiian or Other Pacific Islander	0	0
White	101	976.8
Multiple	1	4.0

Unknown	6	53.7
Total	**151**	**1424.4**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_race_all.rtf		
Ethnic/racial origin in advanced breast cancer: Safety Population		
Imlunestrant single agent[e]		
Ethnic/racial origin	**Patients**	**Person time (months)**
American Indian or Alaska Native	24	262.6
Asian	122	853.8
Black or African American	15	90.9
Native Hawaiian or Other Pacific Islander	0	0
White	274	2073.0
Multiple	2	8.7
Unknown	21	139.1
Total	**458**	**3428.1**
Imlunestrant + abemaciclib[f]		
American Indian or Alaska Native	3	30.6
Asian	79	775.3
Black or African American	10	101.2
Native Hawaiian or Other Pacific Islander	1	24.9
White	135	1195.9
Multiple	3	42.2
Unknown	19	184.6
Total	**250**	**2354.7**
Imlunestrant + Other Combinations[d]		
American Indian or Alaska Native	0	0
Asian	37	341.5
Black or African American	6	48.4
Native Hawaiian or Other Pacific Islander	0	0
White	101	976.8
Multiple	1	4
Unknown	6	53.7
Total	**151**	**1424.4**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_race_mbc.rtf		
Cumulative for all tumour types[a]: ESR1-Mutation-Detected Safety Population		
Ethnic/racial origin	**Patients**	**Person time (months)**
Imlunestrant single agent[g]		
American Indian or Alaska Native	8	93.3
Asian	43	326.6
Black or African American	11	64.5
Native Hawaiian or Other Pacific Islander	0	0
White	119	812.3
Multiple	1	5.9
Unknown	9	56.8

Total	**191**	**1359.4**
Imlunestrant + abemaciclib[c]		
American Indian or Alaska Native	1	5.5
Asian	18	185.7
Black or African American	1	7.3
Native Hawaiian or Other Pacific Islander	1	24.9
White	42	307.2
Multiple	0	0
Unknown	6	82.1
Total	**69**	**612.6**
Imlunestrant + Other Combinations[d]		
American Indian or Alaska Native	0	0
Asian	5	55.8
Black or African American	3	15.9
Native Hawaiian or Other Pacific Islander	0	0
White	32	314.8
Multiple	1	4
Unknown	1	6.1
Total	**42**	**396.7**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_race_all_esr1_d.rtf		
Ethnic/racial origin in advanced breast cancer: ESR1-Mutation-Detected Safety Population		
Imlunestrant single agent[h]		
Ethnic/racial origin	**Patients**	**Person time (months)**
American Indian or Alaska Native	8	93.3
Asian	43	326.6
Black or African American	11	64.5
Native Hawaiian or Other Pacific Islander	0	0
White	118	810.5
Multiple	1	5.9
Unknown	9	56.8
Total	**190**	**1357.6**
Imlunestrant + abemaciclib[f]		
American Indian or Alaska Native	1	5.5
Asian	18	185.7
Black or African American	1	7.3
Native Hawaiian or Other Pacific Islander	1	24.9
White	42	307.2
Multiple	0	0
Unknown	6	82.1
Total	**69**	**612.6**

Imlunestrant + Other Combinations[d]		
American Indian or Alaska Native	0	0
Asian	5	55.8
Black or African American	3	15.9
Native Hawaiian or Other Pacific Islander	0	0
White	32	314.8
Multiple	1	4
Unknown	1	6.1
Total	**42**	**396.7**
Source: /lillyce/prd/ly3484356/rmp2024/output/t_rmp_ex_race_mbc_esr1_d.rtf		

Abbreviations: ABC = advanced breast cancer; Abema = abemaciclib; AI = aromatase inhibitor; BC = breast cancer; EEC = endometrioid endometrial carcinoma; ESR1 = oestrogen receptor 1; Imlun = imlunestrant.

[a] Tumour types includes ABC and EEC

b Monotherapy includes Studies JZLC Arm A, JZLB all patients, JZLF all patients, and JZLA Phase 1a (BC and EEC), Phase 1b E3 and E8.

[c] Imlun + Abema includes Studies JZLC Arm C and JZLA Phase 1b E1 and E9.

[d] Imlun + Other Combinations includes Study JZLA E2 (Imlun + Abema + AI), E4 (Imlun + everolimus), E5 (lmlun + alpelisib), E6 (Imlun + trastuzumab), E7 (lmlun + Abema + trastuzumab), E10 (Imlun + trastuzumab + pertuzumab).

[e] Monotherapy includes Studies JZLC Arm A, JZLF all patients, and JZLA Phase 1a (BC only) and Phase 1b E3.

[f] Imlun + Abema includes Studies JZLC Arm C and JZLA Phase 1b E1.

[g] Monotherapy includes Studies JZLC Arm A and JZLA Phase 1a (BC and EEC), Phase 1b E3 and E8.

h Monotherapy includes Studies JZLC arm A and JZLA Phase 1a (BC only) and Phase 1b E3

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criterion: Patients previously treated with an investigational ER-directed therapy and fulvestrant, any PI3K-, mTOR-, or AKT-inhibitor or prior systemic cytotoxic chemotherapy in advanced breast cancer setting.

Reasons for exclusion: To maintain homogenous patient population in the pivotal randomised Phase 3 study, EMBER-3, and to minimise confounding factors in safety and efficacy data interpretation. This enables adequate evaluation of safety and efficacy of imlunestrant monotherapy and imlunestrant plus abemaciclib in the enrolled population.

Is it considered to be included as missing information?: No

Rationale: Although data are limited, patients previously treated with fulvestrant or prior systemic cytotoxic chemotherapy were enrolled in Study EMBER, the Phase 1a/1b study. Based on data from EMBER, there is no evidence to suggest that the imlunestrant safety profile in patients previously treated with an approved ER-directed therapy, such as fulvestrant, or systemic cytotoxic chemotherapy would differ from those not previously treated.

Criterion: Patients with inflammatory breast cancer, visceral crisis, lymphangitic spread within the lung, evidence of leptomeningeal disease, or symptomatic or untreated brain metastasis

Reason for exclusion: Patients with these clinical characteristics have a worse prognosis and are therefore excluded to maintain a homogenous patient population, which minimises confounding factors in efficacy interpretation. In addition, these patients may be symptomatic from high disease burden, which may confound safety data interpretation and are, therefore, excluded.

Is it considered to be included as missing information? No

Rationale: Based on the imlunestrant mechanism of action, pre-clinical safety data, the review of the imlunestrant safety profile characterised to date, and the known safety profile of other ET used in BC, the imlunestrant safety profile in these patients is not anticipated to differ from the established safety profile.

Criterion: Patients with a serious cardiac condition, such as congestive heart failure, New York Heart Association Class III/IV heart disease, unstable angina pectoris, clinically significant valvulopathy, arrhythmias that are symptomatic or require treatment, recent myocardial infarction or cerebrovascular accident, a mean QT interval corrected for heart rate of ≥470 msec on screening ECG, as calculated using the Fridericia's formula at several consecutive days of assessment baseline bradycardia with resting heart rate <60 beats per minute.

Reason for exclusion: Prior conditions could confound expected adverse drug reaction profile. Exclusion of these patients was precautionary and standard.

Is it considered to be included as missing information? No

Rationale: There is no evidence to suggest that the imlunestrant safety profile in patients with these cardiac conditions would differ from the established safety profile. Concentration-QTcF analyses showed no effect of imlunestrant concentrations across the 200- to 1200-mg daily dose range on QTc interval.

Criterion: Have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (such as severe, pre-existing medical condition of ILD/pneumonitis, severe dyspnoea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in clinically significant diarrhoea).

Reason for exclusion: Significant comorbidities increase the risks of complications, which could confound the interpretation of efficacy and safety data. For example, imlunestrant is an oral SERD, so medical conditions such as Crohn's disease, ulcerative colitis, extensive stomach, or small bowel resection could potentially interfere with intestinal absorption, potentially leading to inadequate exposure and confound efficacy. In addition, if such medical conditions are poorly controlled, worsening diarrhoea could impact safety data interpretation.

Is it considered to be included as missing information? No

Rationale: It should be left to the clinical judgement of the treating physician if the expected treatment benefit with imlunestrant outweighs the potential risk for patients with pre-existing conditions.

Criterion: Patient is pregnant or a lactating woman.

Reason for exclusion: Animal studies showed reproductive and developmental toxicity.

Is it considered to be included as missing information? No

Rationale: Labelling information will specify that imlunestrant should not be used in women who are pregnant or breastfeeding and that women of childbearing potential should use highly effective contraception.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

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

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
• Pregnant women • Breastfeeding women	Not included in the clinical development programme.
Patients with hepatic impairment	Patients were required to have adequate organ function in Studies EMBER and EMBER-3. In clinical pharmacology Study JZLG, 18 women, without breast cancer and with hepatic impairment • 6 mild • 6 moderate • 6 severe hepatic impairment were compared with 9 participants with normal hepatic function, based on Child-Pugh classification. No clinically meaningful difference in exposure for patients with mild hepatic impairment was observed. Significant increases in AUC exposure of 2-fold and 3-fold were noted in patients with moderate and severe hepatic impairment. No significant increase in C_{max} was noted.
Patients with renal impairment (serum creatinine <1.5 × ULN or measured creatinine clearance ≥50 mL/min)	Imlunestrant is not cleared renally, and therefore renal impairment has no effect on the PK of imlunestrant. Urinary elimination of imlunestrant was negligible (0.278% of the total radioactivity excreted). eGFR is not expected to change clearance.
Patients with severe renal impairment	Not included in the clinical development programme
Patients with relevant comorbidities: • Patients with a serious cardiac condition • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Population with relevant different ethnic origin	No restrictions concerning ethnic origin were outlined in the protocol. The distribution of patients according to race can be found in Table SIII.4.
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; eGFR = estimated glomerular filtration rate; PK = pharmacokinetics; ULN = upper-limit of normal.

Module SV - Post-Authorisation Experience

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Not applicable

SV.1.2 Exposure

Not applicable

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

The SERD class is not known to produce psychoactive effects, such as sedation, euphoria, perceptual and other cognitive distortions, hallucinations, or mood changes, which could lead to the potential for misuse, abuse, or addiction. Adverse events of medication misuse or abuse are monitored as a part of routine pharmacovigilance activities.

Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

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

- musculoskeletal pain
- diarrhoea, and
- vomiting.

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:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (for example, actions being part of standard clinical practice in each EU Member state where the product is authorised)

- None

Known risks that do not impact the risk-benefit profile

- None

Other reasons for considering the risks not important

- Aspartate aminotransferase and alanine aminotransferase increases have been noted in animal studies for imlunestrant without morphological correlates. These events are adverse drug reactions for other drugs in this class, that is, fulvestrant and elacestrant, and are considered adverse drug reactions for patients receiving imlunestrant. The majority of clinical events are non-serious, low grade (1 or 2), and are reversible on interruption of imlunestrant and manageable with supportive care. The events are not observed with concurrent increases in bilirubin, and there is no evidence that imlunestrant is associated with more severe forms of liver injury. These events are not considered important as they have low impact on public health and benefit/risk.
- Adverse effects on embryofoetal development were observed in rats, are expected due to the mechanism of actions of SERDs, and are attributed to exaggerated pharmacology. Pregnant women should not receive imlunestrant. Men and pre-/peri-menopausal women treated with monotherapy imlunestrant or combination therapy of imlunestrant plus abemaciclib must be treated with a luteinising hormone-releasing hormone agonist according to current clinical practice standards.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: None

Important Potential Risk: Gastrointestinal bleeding

Risk-benefit impact

GI bleeding has the potential to impact the risk-benefit balance of imlunestrant, as it can be life-threatening if severe. In the EMBER-3 study, 2 participants who received imlunestrant monotherapy died due to upper GI bleeding events. An association with imlunestrant is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing Information: None

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable, as this is the initial RMP.

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

Important Identified Risk: None

Important Potential Risk: Gastrointestinal bleeding

Potential mechanisms

There is no mechanism linking GI bleeding to imlunestrant, SERDs, or oestrogen-targeting therapies in general. Patients who have breast cancer may be more likely to have risk factors for GI bleeding, such as

- thrombocytopenia caused by bone marrow infiltration
- concomitant use of anticoagulants
- concomitant use of SSRIs which can impair platelet function
- concomitant use of corticosteroids or non-steroidal anti-inflammatory drugs, which are known to increase GI bleeding risk through impaired platelet function and effects on the GI mucosa, and
- metastasis to the GI tract, although this is rare. For instance, in a retrospective study of 12 001 patients, GI metastasis was pathologically confirmed in just 73 patients (0.6%) (McLemore et al. 2005).

Evidence source(s) and strength of evidence

While GI bleeding occurs infrequently in this population, recent observations warrant the consideration as a potential risk. Overall, the strength of the available relevant evidence is limited to a few case reports.

GI bleeding has not been associated with oestrogen-targeted therapies for breast cancer. Only a few cases of GI bleeding have been reported in case series and clinical trials, including fulvestrant in the CONFIRM (NCT00099437) and MONALEESA-3 trials (NCT02422615) and anastrozole in the FALCON trial (NCT01602380).

A longitudinal study that planned to assess haemorrhagic complications of liver metastases in patients with advanced cancer demonstrated an increased risk of GI bleeding. However, there are substantial differences between the population of this study, which included patients referred for palliative care and did not study any patients with breast cancer, and the population enrolled in EMBER-3 (Mercadante et al. 2000).

For imlunestrant, a causal association with GI bleeding has not been established; a low number of GI bleeding events have been reported in the clinical development programme, including 2 events with fatal outcomes.

Characterisation of the risk

In the EMBER-3 study, 2 patients who received imlunestrant monotherapy died due to upper GI bleeding events (1 upper GI haemorrhage and 1 hypovolaemic shock 20 days after the last dose of imlunestrant). Both cases had confounding factors such as the progression of liver metastases.

A broad review of upper GI bleeding events revealed only 1 additional case of low-grade haematemesis in a patient receiving imlunestrant monotherapy. This event resolved without treatment modification and may have been confounded by baseline dyspepsia. In addition, there were no reported treatment emergent adverse events related to an upper GI bleed in the combination arm (imlunestrant + abemaciclib).

Risk factors and risk groups

Due to the low number of cases, it is not possible to identify specific risk factors or patient subgroups from the imlunestrant clinical data. In general, upper GI bleeding has been more frequently reported in patients with liver metastases, peptic ulcer disease, or those receiving medications such as SSRIs, non-steroidal anti-inflammatory drugs, and corticosteroids. Additional risk factors include older age, low body weight, and chronic kidney disease (Mercadante et al. 2000; Dalton et al. 2003; EMEA 2005; Wong et al. 2013; Narum et al. 2014; Bosch et al. 2025).

Preventability

In general, the risk of GI bleeding can be reduced with gastroprotective medications. A large metanalysis showed a reduction in the odds of upper GI bleeding (odds ratio, 0.40) if a gastroprotective medication was co-administered with drugs associated with GI bleeding

(Scally et al. 2018). It is a routine clinical practice to prescribe gastroprotective medications, such as proton pump inhibitors, for patients who are at an increased risk of developing GI bleeding or who develop symptoms of peptic ulcer disease. Therefore, no additional risk minimisation measures are required.

Impact on the risk-benefit balance of the product

GI bleeding has the potential to impact the risk-benefit balance of imlunestrant, as it can be life-threatening if severe. In the EMBER-3 trial, 2 cases with fatal outcome were reported; however, only 1 case of non-fatal upper GI bleeding was reported; it resolved without the interruption of imlunestrant therapy. Given the very low incidence of GI bleeding in the imlunestrant clinical development programme and the routine use of gastroprotective medications for prevention and treatment, GI bleeding is not considered to have a significant impact on risk-benefit balance of imlunestrant.

Public health impact

GI bleeding has been observed in a very low number of cases within the EMBER-3 study. The indication for imlunestrant is limited to patients with advanced metastatic breast cancer. Therefore, the public health impact is estimated to be low.

SVII.3.2 Presentation of the Missing Information

None

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of safety concerns	
Important identified risk	None
Important potential risk	Gastrointestinal bleeding
Missing information	None

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

None.

Other forms of routine pharmacovigilance activities for safety concerns:

None

III.2 Additional Pharmacovigilance Activities

None

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important potential risk	
Gastrointestinal bleeding	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** **Pack size:** Not applicable **Legal status**: Not applicable

V.2 Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risk		
Gastrointestinal bleeding	**Routine risk minimisation measures:** Not applicable. **Additional risk minimisation measures:** Not applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Inluriyo (Imlunestrant)

This is a summary of the RMP for Inluriyo.

Inluriyo's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Inluriyo should be used.

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

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

I - The Medicine and What It is Used for

Inluriyo is authorised for adults with ER-positive, HER2-negative, and ESR1-mutated locally advanced or metastatic BC in patients previously treated with endocrine therapy (see SmPC for the full indication). It contains imlunestrant as the active substance and it is given orally.

Further information about the evaluation of Inluriyo's benefits can be found in Inluriyo's European Public Assessment Report, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Inluriyo, together with measures to minimise such risks and the proposed studies for learning more about Inluriyo's risks, are outlined below.

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

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

Together, these measures constitute *routine risk minimisation* measures.

II.A List of Important Risks and Missing Information

Important risks of Inluriyo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

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 Inluriyo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Gastrointestinal bleeding
Missing information	None

II.B Summary of Important Risks

Important potential risk 1: gastrointestinal bleeding	
Evidence for linking the risk to the medicine	While GI bleeding occurs infrequently in this population, recent observations warrant the consideration as a potential risk. Overall, the strength of the available relevant evidence is limited to a few case reports. GI bleeding has not been associated with oestrogen-targeted therapies for breast cancer. Only a few cases of GI bleeding have been reported in case series and clinical trials, including fulvestrant in the CONFIRM (NCT00099437) and MONALEESA-3 trials (NCT02422615) and anastrozole in the FALCON trial (NCT01602380). A longitudinal study that planned to assess haemorrhagic complications of liver metastases in patients with advanced cancer demonstrated an increased risk of GI bleeding. However, there are substantial differences between the population of this study, which included patients referred for palliative care and did not study any patients with breast cancer, and the population enrolled in EMBER-3 (Mercadante et al. 2000). For imlunestrant, a causal association with GI bleeding has not been established; a low number of GI bleeding events have been reported in the clinical development programme, including 2 events with fatal outcomes.
Risk factors and risk groups	Due to the low number of cases, it is not possible to identify specific risk factors or patient subgroups from the imlunestrant clinical data. In general, upper GI bleeding has been more frequently reported in patients with liver metastases, peptic ulcer disease, or those receiving medications such as SSRIs, non-steroidal anti-inflammatory drugs, and corticosteroids. Additional risk factors include older age, low body weight, and chronic kidney disease (Mercadante et al. 2000; Dalton et al. 2003; EMEA 2005; Wong et al. 2013; Narum et al. 2014; Bosch et al. 2025).

Important potential risk 1: gastrointestinal bleeding	
Risk minimisation measures	**Routine risk minimisation measures:** Not applicable. **Additional risk minimisation measures:** Not applicable.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None. See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation Development Plan

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

There are no studies that are conditions of the marketing authorisation or specific obligation of Inluriyo.

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

There are no studies required for Inluriyo.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

None

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.