EUROPEAN (EU) RISK MANAGEMENT PLAN (RMP) FOR ORSERDU (ELACESTRANT)

RMP version to be assessed as part of this application:

RMP version number: 1.0

Data lock point for this RMP: 08 July 2022

Rationale for submitting an updated RMP: Not applicable

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Details of the currently approved RMP: Not applicable

Qualified Person for Pharmacovigilance (QPPV) name: Jennifer Parise

Date of final sign-off: 19 July 2023

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

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PART I: PRODUCT(S) OVERVIEW

Table Part I.1: Product(s) overview

Active substance(s) (INN or common name)	Elacestrant
Pharmacotherapeutic group(s) (ATC Code)	Endocrine therapy, anti-estrogens (ATC code: L02BA04)
Marketing Authorization Applicant	Stemline Therapeutics B.V., a Menarini Group Company Basisweg 10 1043 AP Amsterdam The Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ORSERDU
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Elacestrant is a tetrahydronaphthalene compound that acts as a selective estrogen receptor (ER) degrader.
	Summary of mode of action: Elacestrant binds with high affinity and selectivity to the ERα. In the presence of 17β-estradiol (E2), elacestrant shows dose-dependent antagonism of E2-mediated stimulation of MCF7 breast cancer cell proliferation through down-regulation and degradation of the ER.
	Important information about its composition: The drug product is an immediate release film-coated tablet containing elacestrant.
Hyperlink to the Product Information	Please refer to Module 1.3.1 for the proposed Product Information.
Indication(s) in the EEA	Current: ORSERDU monotherapy is indicated for the treatment of postmenopausal women, and men, with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose is 345 mg (one 345 mg film-coated tablet), once daily, with food.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 86 mg film-coated tablet and 345 mg film-coated tablet.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ATC = Anatomical Therapeutic Chemical Classification System; CDK4/6 = Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; E2 = estradiol (17β-estradiol); EEA = European Economic Area; ER = estrogen receptor; ERα = estrogen receptor-alpha; EU = European Union; HER2 = human epidermal growth factor receptor 2; INN = International Nonproprietary Name; RMP = Risk Management Plan.

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Indication: ORSERDU monotherapy is indicated for the treatment of postmenopausal women, and men, with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation who have disease progression following at least one line of endocrine therapy including a CDK4/6 inhibitor.

Incidence/prevalence: Breast cancer is the leading cause of cancer and cancer deaths in women (*Bray et al., 2018*). Worldwide, there were 2.3 million new cases and over 685000 deaths from breast cancer in 2020 (*Bray et al., 2018*; *WHO 2021*). In comparison, breast cancer in men is very rare, occurring in < 1% of the total number of cancer cases. Nevertheless, the American Cancer Society estimates that there will be 2650 new cases of invasive breast cancer in men, and about 530 men will die from breast cancer in 2021 (*Breastcancer.org 2021a*).

In the United States (US) and Europe, improved treatments are prolonging survival and improving quality of life but, in the US, the death rate for women's breast cancer remains 2nd only to lung cancer. Furthermore, preventive methods are not abolishing new cases; breast cancers account for approximately 30% of all newly diagnosed cancers among US women (*Breastcancer.org 2021b*). Approximately 330840 (approximately 281550 invasive and approximately 49290 noninvasive or in situ) new cases were expected for 2021, while an estimated 43600 American women will die from the disease during this same period (*Breastcancer.org 2021b*). For European women, there were approximately 576300 new cases and, concurrently, approximately 157100 deaths from breast cancer in 2020 (*Europa Donna 2021*). Mortality rate predictions across Europe are expected to reach relatively uniform levels in 2025. The largest predicted decrease in breast cancer mortality was estimated for the United Kingdom (12.2 in 100000 women in 2025), leading to the estimated avoidance of 150000 breast cancer deaths over the period of 1994 to 2025 and 470000 in the rest of Europe (*Wojtyla et al., 2021*).

Demographics of the population in the proposed indication and risk factors for the disease: The number of risk factors (including demographics) for breast cancer is significant and includes both modifiable and nonmodifiable factors, as listed below (*Łukasiewicz et al., 2021*).

Table SI.1: Breast cancer risk factors

Nonmodifiable Factors	Modifiable Factors
Female sex	Hormonal replacement therapy
Older age	Diethylstilbestrol
Race/ethnicity	Physical activity
Family history (of breast or ovarian cancer)	Overweight/obesity
Genetic mutations	Alcohol intake
Pregnancy and breastfeeding	Smoking
Menstrual period and menopause	Insufficient vitamin supplementation
Density of breast tissue	Excessive exposure to artificial light
Previous history of breast cancer	Intake of processed food
Noncancerous breast diseases	Exposure to chemicals
Previous radiation therapy	Other drugs

Nonmodifiable risk factors are discussed below.

Age: Currently, about 75% to 80% of breast cancer cases occur in individuals aged > 50 years, with an incidence of < 5% in people aged up to 35 years (*Dafni et al., 2019*; *Łukasiewicz et al., 2021*). European demographic trends show an aging population, with a median age of 41.9 years compared to the world median age of 29.2 years. Thus, the aging population in Europe will result in a further increase in the burden of breast cancer and its impact on public health (*Dafni et al., 2019*).

Gender: Breast cancer is the leading cause of cancer and cancer deaths in women (*Bray et al., 2018*). Being a woman is a major risk factor due to the enhanced hormonal stimulation. A woman's breast cells are very vulnerable to hormones, as well as any disruptions in their balance.

Increases in circulating sex hormones of hormones in pre- and postmenopausal women results in a higher risk of breast cancer (*Łukasiewicz et al., 2021*; *Key et al., 2013*). In comparison, breast cancer in men is very rare, occurring in < 1% of the total number of cancer cases (*Breastcancer.org 2021a*).

Race and/or ethnicity: According to the Surveillance, Epidemiology, and End Results (SEER) cancer query system searched between 2012 to 2016, age-adjusted incidence of breast cancer is highest in white women (103 per 100000 population). Incidence of age-adjusted breast cancer in black and Asian/Pacific Islander women is 98.6 and 81.3 per 100000 population, respectively. Breast cancer risk is lower in Hispanic women, with an age-adjusted incidence rate of 77.7 per 100000 population (*SEER 2022*). However, the mortality rate due to breast cancer is significantly higher among black women; this group is also characterized by the lowest survival rates (*ACS 2016*).

Family history: Family history is another major risk factor for breast cancer, with approximately 13% to 19% of those diagnosed having a 1st-degree relative (eg, mother, sister, or daughter) who has or had breast cancer. Furthermore, the incidence rate of breast cancer is significantly higher in all patients with a family history, regardless of age (*Łukasiewicz et al., 2021*).

Genetic mutations: The 2 major genes associated with increased risk of breast cancer are *BRCA1* (Breast Cancer gene 1) (located on chromosome 17) and *BRCA2* (Breast Cancer gene 2) (located on chromosome 13) (*Shiovitz and Korde 2015*). The mutations within the above-mentioned genes are mainly inherited in an autosomal dominant manner; however, sporadic mutations are also frequently reported (*Łukasiewicz et al., 2021*).

Reproductive history: The occurrence of pregnancy, breastfeeding, 1st menstruation, and menopause, along with their duration and associated hormonal imbalance, are crucial in terms of potential carcinogenic events in the breast microenvironment. Women who have early menarche or late menopause have a higher risk of developing breast cancer. Nulliparous women and women who are older (e.g., > 30 years old) with their 1st birth may also have a greater chance of developing breast cancer (*Łukasiewicz et al., 2021*).

Density of breast tissue: Generally, a greater breast tissue density correlates with a greater risk of breast cancer; this trend is observed both in pre- and postmenopausal women (*Kim et al., 2020*).

History of breast cancer and benign breast diseases: A personal history of breast cancer is associated with a greater risk of renewed breast cancer (*Schacht et al., 2014*). In addition, benign breast diseases (eg, atypical hyperplasia) also significantly increase (4 to 5 times) the risk of breast cancer (*Hartmann et al., 2005*; *Wang et al., 2004*; *McPherson et al., 2000*).

Previous radiation therapy: Children or young adults (< 30 years old) exposed to radiation therapy to the chest area have significantly increased risk of developing breast cancer later in life (*Ronckers et al., 2005*; *Ng and Shuryak 2015*).

The main existing treatment options: Currently, recommended 1st-line standard of care (SOC) for locally advanced or metastatic estrogen receptor (ER)-positive/HER2-negative breast cancer is endocrine therapy, with either aromatase inhibitors (AIs) or fulvestrant, plus a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor (*NCCN 2021*; *Bentzon et al., 2008*; *Burstein et al., 2021*; *Gennari et al., 2021*). Once the disease progresses, there are limited therapeutics options. When the pivotal study (RAD1901-308) was initiated in 2018, treatment guidelines recommended the use of sequential endocrine therapy in the absence of visceral crisis or until all endocrine therapy options have been exhausted (*NCCN 2018*; *NCCN 2021*). Endocrine therapy includes endocrine monotherapy, such as fulvestrant, if the 1st-line therapy contained an AI-based therapy, or AIs if the 1st-line therapy applied a fulvestrant-based therapy (*NCCN 2021*; *Burstein et al., 2021*; *Gennari et al., 2021*).

Fulvestrant is currently the only approved selective estrogen receptor degrader for the treatment of subjects with ER-positive/HER2-negative metastatic breast cancer (*Niikura et al., 2014*). Fulvestrant effectively degrades ER and has demonstrated clinical benefit in ER-positive/HER2-negative metastatic breast cancer. A 500-mg monthly dose of fulvestrant, after a biweekly dose during the 1st month, in patients with ER-positive/HER2-negative metastatic breast cancer who failed previous endocrine therapy was associated with a median progression-free survival (PFS) of 6.5 months (*Di Leo et al., 2010*). However, these data were generated prior to the approval of CDK4/6 inhibitors. Recently, data on fulvestrant monotherapy post CDK4/6 inhibitor treatment are starting to emerge.

- In a recent Phase 2 trial of 2nd- or 3rd-line venetoclax + fulvestrant versus fulvestrant alone in ER-positive/HER2-negative metastatic breast cancer who experienced disease recurrence/progression during/after CDK4/6 inhibitor therapy (VERONICA study), treatment with fulvestrant as a single agent was associated with a median PFS of 1.94 months and with a clinical benefit rate of 13.7% (*Lindeman et al., 2021*).
- In the plasmaMATCH Phase 2a clinical trial, high-dose fulvestrant was associated with a median PFS of 2.2 months and a clinical benefit rate of 16% among patients with a detectable estrogen receptor 1 gene *(ESR1) mutation*, where few subjects received prior CDK4/6 inhibitors (*Turner et al., 2020*).

In addition to the need for effective treatment options for patients with ER-positive/HER2-negative metastatic breast cancer after progression on CDK4/6 inhibitors, the intramuscular route of administration of fulvestrant underscores the need for novel oral ER antagonists in this setting (*Bihani et al., 2017*). Although a long-acting intramuscular formulation of fulvestrant was approved, which can be administered monthly after 3 biweekly doses, the total volume of the injections per dose is 10 mL, a volume that is difficult to tolerate by some patients (*Wardell et al., 2015*).

Available 2nd-line combination therapy options are everolimus + exemestane and everolimus + fulvestrant. For subjects with PIK3CA (Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha)-mutant breast cancer, the combination of fulvestrant and alpelisib is another option. These combinations are associated with an approximate 25% treatment discontinuation rate because of adverse events in clinical studies (*Alpelisib USPI*; *Everolimus USPI*; *Kornblum et al., 2018*).

In this context, next-generation, orally bioavailable selective estrogen receptor degraders with improved pharmacokinetic properties have garnered significant interest as novel therapies for ER-positive metastatic breast cancer (*Bentzon et al., 2008*; *Gluck, 2014*; *McDonnell and Wardell, 2010*; *Osborne and Schiff, 2011*).

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Breast cancer stage is usually expressed as a number on a scale of 0 through IV, as tabulated below (*Cancer.net 2020*). Mortality resulting from breast cancer is discussed earlier in this section, under incidence/prevalence.

Table SI.2: Breast cancer stages

Stage	Description
Stage 0	Disease is only in the ducts of the breast tissue and has not spread to the surrounding tissue of the breast. This is also called noninvasive or in situ cancer (Tis, N0, M0).
Stage IA	The tumor is small, invasive, and has not spread to the lymph nodes (T1, N0, M0).
Stage IB	The tumor has spread to the lymph nodes, and the tumor in the lymph node is larger than 0.2 mm but < 2 mm in size. There is either no evidence of a tumor in the breast or the tumor in the breast is 20 mm or smaller (T0 or T1, N1mi, M0).
Stage IIA	Any 1 of these conditions: • There is no evidence of a tumor in the breast, but the cancer has spread to 1 to 3 axillary lymph nodes. It has not spread to distant parts of the body (T0, N1, M0). • The tumor is 20 mm or smaller and has spread to 1 to 3 axillary lymph nodes (T1, N1, M0). • The tumor is larger than 20 mm but not larger than 50 mm and has not spread to the axillary lymph nodes (T2, N0, M0).
Stage IIB	Either of these conditions: • The tumor is larger than 20 mm but not larger than 50 mm and has spread to 1 to 3 axillary lymph nodes (T2, N1, M0). • The tumor is larger than 50 mm but has not spread to the axillary lymph nodes (T3, N0, M0).
Stage IIIA	The tumor of any size has spread to 4 to 9 axillary lymph nodes or to internal mammary lymph nodes. It has not spread to other parts of the body (T0, T1, T2, or T3; N2; M0). Stage IIIA may also be a tumor larger than 50 mm that has spread to 1 to 3 axillary lymph nodes (T3, N1, M0).
Stage IIIB	The tumor has spread to the chest wall or caused swelling or ulceration of the breast, or it is diagnosed as inflammatory breast cancer. It may or may not have spread to up to 9 axillary or internal mammary lymph nodes. It has not spread to other parts of the body (T4; N0, N1, or N2; M0).
Stage IIIC	A tumor of any size that has spread to 10 or more axillary lymph nodes, the internal mammary lymph nodes, and/or the lymph nodes under the collarbone. It has not spread to other parts of the body (any T, N3, M0).
Stage IV (metastatic)	The tumor can be any size and has spread to other organs, such as the bones, lungs, brain, liver, distant lymph nodes, or chest wall (any T, any N, M1).

M = metastasis; mi = micrometastatic; N = node; T = Tumor; Tis = carcinoma in situ.

Events that frequently occur in untreated patients with metastatic breast cancer are described below. These include events associated with the disease or with therapies.

Bone metastases: Among breast cancer patients with distant metastases, bone is the most common site for metastasis (reported in 70.6% of patients) (*Savci-Heijink et al., 2015*). In a retrospective study of 35912 Danish patients with breast cancer, it was found that 4% of patients had bone metastases at the time of diagnosis or developed bone metastasis during follow-up (up to 5 years). Among these patients, 47.6% already had or went on to develop skeletal-related events, defined as pathological fractures, spinal cord compression, bone pain requiring palliative radiotherapy, and orthopedic surgery (*Jensen et al., 2011*).

Hepatotoxicity/Liver metastases: Among breast cancer patients with distant metastases, liver is also a common site for metastasis (reported in 54.5% of patients) (*Savci-Heijink et al 2015*). In 78.6% of cases, liver metastases are asymptomatic at the time of metastatic diagnosis. The remainder are symptomatic, presenting with epigastric pain or fullness (21.4%), palpable hepatomegaly (27.3%), and ascites (6.2%) (*Wyld et al., 2003*).

Pulmonary metastases: Among breast cancer patients with distant metastases, 31.4% suffer lung metastasis (Savci-Heijink et al 2015). Metastasis to lung is associated with poor prognosis and presents with clinical symptoms such as pain, cough, hemoptysis, pleural effusion, and pulmonary dysfunction (*Jin et al., 2018*).

Brain metastases: Brain metastases are found in 5.1% of patients with breast cancer (*Barnholtz-Sloan et al., 2004; Pestalozzi et al., 2006*). Headache (35%), vomiting (26%), nausea (23%), hemiparesis (22%), visual changes (13%), and seizures (12%) are the most common presentation with brain metastases (*Rostami et al., 2016*). In a retrospective study of clinical data of German patients with breast cancer who had brain metastasis, median overall survival time after brain metastasis development was reported as 7.4 months, with a 1-year survival rate of 37.7% (*Witzel et al., 2018*).

Important comorbidities: The presence of comorbidities in patients with cancer has a negative association with health outcomes for patients. Poorer survival from cancer has been found overall in cancer survivors with comorbidities compared to those without. Whilst all women have risks for developing chronic illnesses or comorbidities due to aging; women who survive cancer are at risk for chronic conditions (such as obesity, hypertension, diabetes, dyslipidemia, and decreased bone mass) not only because of aging, but sometimes due to the after effects of cancer treatment (*Fu et al., 2015*). In a prospective quality of life study in breast cancer survivors, Fu et al 2015 found that among 134 patients, 73.8% had at least 1 of comorbidity, 54.7% had 2 to 4 comorbidities, and 7.4% had 5 to 8 comorbidities. The 5 most common comorbidities were hypertension (32.8%), arthritis (32.8%), thyroid problem (22.4%), hypercholesterolemia (12.7%), and diabetes (12.0%). In an observational study in patients being treated for breast cancer between January and December 2012, *Sharma et al., 2016* found that the most common comorbidities were hypertension (21.8%), chronic obstructive pulmonary disease (19.9%), rheumatologic disease (18.6%), and diabetes mellitus (16.7%); all 4 conditions were reported in more than 75% of the patients.

Part II: Module SII - Nonclinical Part of the Safety Specification

Table SII.1: Key safety findings from nonclinical studies and relevance to human usage

Key safety findings from nonclinical studies	Relevance to human usage
Gastrointestinal toxicity	
Oral gavage of elacestrant treatment (30 and 100 mg/kg/day for 7 days) resulted in emetic events (retching and vomiting) in ferrets, occurring more frequently at higher doses. The number of emesis observations following the 30 mg/kg dose decreased over time, suggesting tolerance to elacestrant over time. The 100 mg/kg dose was not tolerated. Findings in the gastrointestinal tract have been also observed in repeat dose toxicity studies: emesis has been observed in female monkeys, vacuolation of the mucosa of non-glandular stomach in both male and female rats, infiltrates of activated macrophages in the small intestine in both rats and monkeys.	Gastrointestinal effects (such as nausea, vomiting, diarrhoea, constipation, and dyspepsia) have also been detected in patients.
General toxicity	
Elacestrant displayed a low acute toxicity. The highest doses devoid of lethal effects were 900 and 500 mg/kg after a single oral administration in Sprague Dawley rats and cynomolgus monkeys, respectively. The results of repeat-dose toxicity studies in rats (up to 26 weeks) and monkeys (up to 39 weeks) were relatively consistent across the studies and species. In both female rats and monkeys, atrophy of the uterus, cervix, and vagina and increased ovary weight due to the presence of prominent ovarian cystic follicles were observed at all doses in studies lasting 4 weeks or longer at lower exposure levels than in humans. In rats, the increase in ovary weight was also associated with a decrease in pituitary weight. In the 39-week monkey study, beyond the atrophy of the uterus/cervix/vagina, mammary gland, and the occurrence of ovarian follicular cysts, microscopic findings included, increased ovarian stroma at doses ≥ 10 mg/kg/day.	The atrophy of the uterus, cervix, and vagina represents a direct inhibitory effect of elacestrant on the trophic activity exerted by E2 on these organs, whereas ovarian cystic follicles are likely caused by the interruption of the negative feedback loop between E2 and pituitary hormones. These findings, observed in animals with reproductive potential, are not relevant for the target patient population of postmenopausal women which have already lost the reproductive function.
Reproductive and developmental toxicity	
Fertility studies were not conducted; however, adverse effects of elacestrant on both male and female fertility can be anticipated based on its mechanism of action. Decreased cellularity of Leydig cells was noted in male rats at the highest dose of elacestrant (50 mg/kg/day) in the 26-week repeat-dose study, in line with impaired male (and female) fertility in ERα knockout mice (*Korach, 1994*). In rat embryo-fetal developmental studies, elacestrant treatment during the period of organogenesis resulted in maternal and fetal toxicities and malformations.	Long term treatment with elacestrant could impair male and female fertility (the latter is not applicable to postmenopausal women). Observations of estrogen-disruptive pharmacological activity of elacestrant in pregnant female rats indicate a potential teratogenic risk for women (not applicable to postmenopausal women).

Key safety findings from nonclinical studies	Relevance to human usage
Carcinogenicity	
Carcinogenicity studies were not conducted with elacestrant, in accordance with ICH S9 Guidance for Nonclinical Evaluation for Anticancer Pharmaceuticals (*ICH S9 2010*). However, granulosa ovary cell benign tumors were present in female rats following 26-week treatment with elacestrant at doses of ≥ 25 mg/kg.	Such tumors have been associated with long-term perturbation of endocrine function induced by selective ER modulators/ degraders. Indeed, these tumors also spontaneously develop in mice lacking ERα. This endocrine perturbation should not occur in postmenopausal women, where the hypophyseal-ovarian loop is already impaired. Furthermore, carcinogenicity due to deoxyribonucleic acid damage can be excluded because elacestrant is devoid of genotoxic potential.

E2 = estradiol (17β-estradiol); ER = estrogen receptor; ERα = estrogen receptor- alpha; ICH = International Council for Harmonization.

Part II: Module SIII - Clinical Trial Exposure

SIII.1 Exposure in healthy volunteers and subjects with hepatic impairment

The elacestrant clinical development plan included 11 studies in healthy volunteers (RAD1901-101, RAD1901-104, RAD1901-109, RAD1901-110, RAD1901-111, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, RAD1901-116, and RAD1901-118) and 1 study in subjects with hepatic impairment (RAD1901-117 which included 20 subjects with hepatic impairment (10 subjects with mild hepatic impairment, 10 subjects with moderate hepatic impairment and 16 additional control subjects with normal hepatic function).

In the pooled healthy volunteer studies, the mean (standard deviation [SD]) duration on treatment was 3.8 (3.05) days. In subjects with hepatic impairment, the duration on-treatment was 1.0 (0.00) day.

Table SIII 1.1: Duration of Exposure

	Pooled Studies[1] (N = 358)	RAD1901-117 (N = 36)
Duration on treatment (days)		
n	358	36
Mean	3.8	1.0
Median	3.0	1.0
SD	3.05	0.00
Min	1	1
Max	14	1

N = number of subjects in a treatment group; n = number of subjects in a category; max = maximum; min = minimum; SD = standard deviation.

1 RAD1901-001, RAD1901-004, RAD1901-109, RAD1901-110, RAD1901-111, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, RAD1901-116, and RAD1091-118 have been pooled together.

Note 1: Only elacestrant intakes have been taken into account for this table (also for drug-drug interaction studies).

Note 2: For RAD1901-001 and RAD1901-004, subjects belonging to the Safety Population treated with placebo have been excluded. One subject belonging to Safety Population in RAD1901-118 has been excluded since the subject was withdrawn prior to receiving elacestrant.

Note 3: Duration on treatment has been computed in a different way according to the study: for RAD1901-001, the duration for subjects in the multiple ascending dose part is computed as (date of last elacestrant intake - date of first elacestrant intake) + 1, while for subjects in the single ascending dose part, it is equal to 2 days (except for 1 subject who received only 1 dose). For

RAD1901-004 and RAD1901-110, the duration has been computed as (date of last elacestrant intake – date of first elacestrant intake) + 1. For RAD1901-109, RAD1901-111, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, RAD1901-116, RAD1901-117, and RAD1901-118, the duration has been computed taking into account the exact number of days on which the subject had been treated with elacestrant.

Table SIII.1.2: Dose

	Pooled Studies[1] (N = 358)	RAD1901-117 (N = 36)
Total dose received (mg)		
n	358	36
Mean	1092.9	200.0
Median	800.0	200.0
SD	1124.9	0.00
Min	26	200
Max	7000	200
Absolute dose intensity (mg/day)		
n	358	36
Mean	311.8	200.0
Median	400.0	200.0
SD	190.11	0.00
Min	10	200
Max	1000	200
Relative dose intensity (%)		
n	358	36
Mean	41.8	100.0
Median	33.3	100.0
SD	26.11	0.00
Min	7	100
Max	100	100

N = number of subjects in a treatment group; n = number of subjects in a category; max = maximum; min = minimum; SD = standard deviation.

1 RAD1901-001, RAD1901-004, RAD1901-109, RAD1901-110, RAD1901-111, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, RAD1901-116, and RAD1091-118 have been pooled together.

Note 1: Only elacestrant intakes have been taken into account for this table (also for drug-drug interaction studies).
Note 2: For RAD1901-001 and RAD1901-004, subjects belonging to the Safety Population treated with placebo have been excluded. One subject belonging to Safety Population in RAD1901-118 has been excluded since the subject was withdrawn prior to receiving elacestrant.

Demographic characteristics in the pooled healthy volunteer studies were slightly different from the subjects in the RAD1901-117 hepatic impairment study, as follows:

- Age: the subjects in the pooled healthy volunteer studies were younger than in the RAD1901-117 hepatic impairment study (53.8 [11.72] years versus 60.1 [6.09] years, respectively).
- Gender: the proportion of males to females was similar in the pooled healthy volunteer studies, whilst there were more males in the RAD1901-117 hepatic impairment study (69.4% males versus 30.6% females).
- Ethnicity: the proportion of Hispanic or Latino subjects was lower in the pooled healthy volunteer studies than in the RAD1901-117 hepatic impairment study (26.0% versus 47.2%, respectively).

Table SIII 1.3: Age Group and Gender

	Pooled Studies[1] (N = 358)	RAD1901-117 (N = 36)
Age (years)		
n	358	36
Mean	53.8	60.1
Median	56.0	60.0
SD	11.72	6.09
Min	22	48
Max	75	75
Age group (years), n (%)		
n	358	36
< 50	110 (30.7)	2 (5.6)
≥ 50	248 (69.3)	34 (94.4)
< 65	293 (81.8)	28 (77.8)
≥ 65	65 (18.2)	8 (22.2)
< 75	354 (98.9)	35 (97.2)
≥ 75	4 (1.1)	1 (2.8)
Gender, n (%)		
n	358	36
Male	189 (52.8)	25 (69.4)
Female	169 (47.2)	11 (30.6)

N = number of subjects in a treatment group; n = number of subjects in a category; max = maximum; min = minimum; SD = standard deviation.

1 RAD1901-001, RAD1901-004, RAD1901-109, RAD1901-110, RAD1901-111, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, RAD1901-116, and RAD1091-118 have been pooled together.

Note 1: For RAD1901-001 and RAD1901-004, subjects belonging to the Safety Population treated with placebo have been excluded. One subject belonging to Safety Population in RAD1901-118 has been excluded since the subject was withdrawn prior to receiving elacestrant.

Table SIII 1.4: Ethnic Origin

	Pooled Studies[1] (N = 358)	RAD1901-117 (N = 36)
Race, n (%)[a]		
n	358	36
American Indian or Alaska Native	2 (0.6)	0 (0.0)
Asian	5 (1.4)	1 (2.8)
Black or African American	41 (11.5)	4 (11.1)
Multiple	12 (3.4)	0 (0.0)
White	298 (83.2)	31 (86.1)
Ethnicity, n (%)		
n	358	36
Hispanic or Latino	93 (26.0)	17 (47.2)
Not Hispanic or Latino	265 (74.0)	19 (52.8)
Region, n (%)		
n	358	36
United States	358 (100.0)	36 (100.0)

N=number of subjects in a treatment group; n=number of subjects in a category.

1 RAD1901-001, RAD1901-004, RAD1901-109, RAD1901-110, RAD1901-111, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, RAD1901-116, and RAD1091-118 have been pooled together.

Note 1: For RAD1901-001 and RAD1901-004, subjects belonging to the Safety Population treated with placebo have been excluded. One subject belonging to Safety Population in RAD1901-118 has been excluded since the subject was withdrawn prior to receiving elacestrant.

a Subjects may select more than 1 race.

SIII.2 Exposure in patients with metastatic breast cancer

The elacestrant clinical development plan included 3 studies in metastatic breast cancer.

- RAD1901-005 was a Phase 1, multicenter, open-label, multipart dose-escalation trial of elacestrant in postmenopausal women with ER-positive/HER2-negative metastatic breast cancer.
- RAD1901-106 was a pharmacodynamic trial to assess target engagement of the ER in metastatic breast cancer lesions of postmenopausal women with ER-positive/HER2-negative metastatic breast cancer as detected by 16α-^{18}F-fluoro-17β-estradiol positron emission tomography imaging following 14 days of treatment.
- RAD1901-308 was an international, multicenter, randomized, open-label, active controlled, event driven, Phase 3 trial comparing elacestrant dihydrochloride 400 mg (corresponding to elacestrant 345 mg) once daily with the SOC options of either fulvestrant or an AI in postmenopausal women and men with ER-positive/HER2-negative metastatic breast cancer.

In the RAD1901-308 study, the mean (SD) duration on treatment was highest for patients in the elacestrant group at 157.7 (180.53) days and lowest in patients receiving AIs in the SOC group at 98.9 (108.34) days. Almost all patients (230 [97%]) in the elacestrant group and patients receiving AIs (68 [100%]) had a relative dose intensity between 90% and 100%.

In the pooled Phase 1 studies, the overall mean (SD) duration on elacestrant treatment was 213.5 (239.07) days. Similar to the RAD1901-308 study, 68 (100%) patients had a relative dose intensity of > 90%.

Table SIII 1.5: Duration of Exposure

	RAD1901-005 and RAD1901-106			RAD1901-308		
	Elacestrant 400 mg Capsules (N = 40)	Elacestrant 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)	Elacestrant 400 mg Tablets (N = 237)	SOC-Fulvestrant (N = 162)	SOC-AIs (N = 68)
Duration on treatment (days)						
n	40	24	64	237	162	68
Mean	215.1	210.9	213.5	144.1	128.4	98.9
SD	264.04	195.77	239.07	180.53	122.40	108.34
Median	117.0	140.0	117.0	84.0	83.5	64.5
Min	5	14	5	13	2	1
Max	1288	760	1288	978	779	693

AI = aromatase inhibitor; N = number of patients in a treatment group; n = number of patients in a category; max = maximum; min = minimum; SD = standard deviation; SOC = standard of care.
Note: Duration on treatment for elacestrant and AIs was calculated as (last dose date–1st dose date)+1. Duration on treatment for fulvestrant was calculated as (end date of last cycle–1st dose date)+1.
Source: Updated Module 2.7.4 (Summary of Clinical Safety) data cut-off 08July2022.

Table SIII.1.6: Dose

	RAD1901-005 and RAD1901-106			RAD1901-308		
	Elacestrant 400 mg Capsules (N = 40)	**Elacestrant 400 mg Tablets (N = 24)**	**Elacestrant 400 mg Overall (N = 64)**	**Elacestrant 400 mg Tablets (N = 237)**	**SOC-Fulvestrant (N = 162)**	**SOC-AIs (N = 68)**
Total dose received (mg)[a]						
n	40	24	64	237	NA	68
Mean	82647.5	83533.3	82979.7	61739.2	NA	1918.2
SD	102532.64	77674.88	93332.01	55315.16	NA	2148.10
Median	45000.0	56000.0	45400.0	33600.0	NA	1412.5
Min	2000	5600	2000	2800	NA	1
Max	515200	304000	515200	390800	NA	12500
Absolute dose intensity (mg/day)[b]						
n	40	24	64	237	NA	68
Mean	393.07	400.00	395.67	397.55	NA	19.24
SD	32.020	0.000	25.419	11.906	NA	10.053
Median	400.00	400.00	400.00	400.00	NA	25.00
Min	217.4	400.0	217.4	318.5	NA	1.0
Max	400.0	400.0	400.0	400.0	NA	25.0
Relative dose intensity (%)[c]						
n	40	24	64	237	NA	68
Mean	98.3	100.0	98.9	99.4	NA	100.0
SD	8.00	0.00	6.35	2.98	NA	0.00
Median	100.0	100.0	100.0	100.0	NA	100.0
Min	54	100	54	80	NA	100
Max	100	100	100	100	NA	100

AI = aromatase inhibitor; max = maximum; min = minimum; N = number of patients in a treatment group; n = number of patients in a category; NA = not applicable; SD = standard deviation; SOC = standard of care.

[a] Total dose received was calculated by summing the doses in all the periods that each patient participated in.

[b] Absolute dose intensity was calculated as the total amount of doses taken during treatment divided by total number of days on treatment.

[c] Relative dose intensity was calculated as total dose received divided by the total intended dose×100, where the total intended dose is the sum of (assigned dose×duration of treatment for the assigned dose).

Source: Updated Module 2.7.4 (Summary of Clinical Safety) data cut-off 08July2022.

In the RAD1901-308 study, groups were balanced with respect to all baseline demographic characteristics. The median age in all groups was between 63.5 and 64 years (range: 24 to 89 years). There were 6 (3%) males in the elacestrant group and 1 (<1%) male in the SOC group. Postmenopausal women accounted for 471 (100%) of the patients.

Demographic characteristics in the pooled Phase 1 studies were similar to those in the RAD1901-308 study, with the following exceptions:

- Race: there were no Asian patients in the pooled Phase 1 studies (0% versus 9% elacestrant, 8% SOC).
- Region: there was a lower percentage of patients from Europe in the pooled Phase 1 studies (22% versus 57% elacestrant, 51% SOC).
- Region: there was a higher percentage of patients from North America in the pooled Phase 1 studies (78% versus 27% elacestrant, 31% SOC).
- Region: there were no patients from Asia in the pooled Phase 1 studies (0% versus 10% elacestrant, 11% SOC).

Table SIII. 1.7: Age Group and Gender

	RAD1901-005 and RAD1901-106			RAD1901-308	
	Elacestrant 400 mg Capsules (N = 40)	**Elacestrant 400 mg Tablets (N = 24)**	**Elacestrant 400 mg Overall (N = 64)**	**Elacestrant 400 mg Tablets (N = 237)**	**SOC (N = 230)**
Age (years)					
n (missing)	40 (0)	24 (0)	64 (0)	237 (0)	230 (0)
Mean	59.3	64.8	61.4	62.6	63.5
SD	9.87	8.62	9.72	12.05	10.89
Median	61.0	63.5	62.5	63.0	64.0
Min	43	51	43	24	32
Max	84	81	84	89	83
Age group (years), n (%)					
n (missing)	40 (0)	24 (0)	64 (0)	237 (0)	230 (0)
< 50	9 (22.5)	0 (0.0)	9 (14.1)	33 (13.9)	27 (11.7)
≥ 50	31 (77.5)	24 (100.0)	55 (85.9)	204 (86.1)	203 (88.3)
< 65	27 (67.5)	13 (54.2)	40 (62.5)	134 (56.5)	120 (52.2)
≥ 65	13 (32.5)	11 (45.8)	24 (37.5)	103 (43.5)	110 (47.8)
< 75	39 (97.5)	20 (83.3)	59 (92.2)	197 (83.1)	184 (80.0)
≥ 75	1 (2.5)	4 (16.7)	5 (7.8)	40 (16.9)	46 (20.0)
Gender, n (%)					
n (missing)	40 (0)	24 (0)	64 (0)	237 (0)	230 (0)
Male	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.5)	1 (0.4)
Female	40 (100.0)	24 (100.0)	64 (100.0)	231 (97.5)	229 (99.6)

N = number of patients in a treatment group; n = number of patients in a category; max = maximum; min = minimum; SD = standard deviation; SOC = standard of care. Source: Updated Module 2.7.4 (Summary of Clinical Safety) data cut-off 08July2022.

Table SIII. 1.8: Ethnic Origin

	RAD1901-005 and RAD1901-106			RAD1901-308	
	Elacestrant 400 mg Capsules (N = 40)	Elacestran 400 mg Tablets (N = 24)	Elacestrant 400 mg Overall (N = 64)	Elacestrant 400 mg Tablets (N = 237)	SOC (N = 230)
Race, n (%)[a]					
n (missing)	39 (1)	24 (0)	63 (1)	189 (48)	186 (44)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	16 (8.5)	15 (8.1)
Black or African American	1 (2.6)	3 (12.5)	4 (6.3)	5 (2.6)	8 (4.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White/Caucasian	37 (94.9)	21 (87.5)	58 (92.1)	167 (88.4)	162 (87.1)
Other	1 (2.6)	0 (0.0)	1 (1.6)	1 (0.5)	1 (0.5)
Ethnicity, n (%)					
n (missing)	36 (4)	24 (0)	60 (4)	237 (0)	230 (0)
Hispanic or Latino	1 (2.8)	1 (4.2)	2 (3.3)	19 (8.0)	17 (7.4)
Not Hispanic or Latino	35 (97.2)	23 (95.8)	58 (96.7)	193 (81.4)	184 (80.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	25 (10.5)	29 (12.6)
Region, n (%)					
n (missing)	40 (0)	24 (0)	64 (0)	237 (0)	230 (0)
Europe	14 (35.0)	0 (0.0)	14 (21.9)	135 (57.0)	117 (50.9)
North America	26 (65.0)	24 (100.0)	50 (78.1)	65 (27.4)	72 (31.3)
Asia	0 (0.0)	0 (0.0)	0 (0.0)	23 (9.7)	26 (11.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	14 (5.9)	15 (6.5)

N = number of patients in a treatment group; n = number of patients in a category.
a Patients may select more than 1 race.
Source: Updated Module 2.7.4 (Clinical Summary of Safety) data cut-off 08July2022.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table: SIV.1.1: Important exclusion criteria in the pivotal RAD1901-308 trial

Criterion 1: Presence of symptomatic metastatic visceral disease, including but not limited to, extensive hepatic involvement, untreated or progressive central nervous system (CNS) metastases, or symptomatic pulmonary lymphangitic spread	
Reason for exclusion	Patients excluded as per this criterion most likely require other treatments (chemotherapy, radiation treatments, etc) with potential effects on the target symptoms. Interactions between chemotherapeutic drugs and elacestrant are unknown.
Included as missing information	No
Rationale (if not included as missing information)	Elacestrant is not expected to be a treatment for this group of patients.
Criterion 2: Intact uterus with a history of endometrial intraepithelial neoplasia (atypical endometrial hyperplasia or higher-grade lesion)	
Reason for exclusion	Patients with prior malignant disease would most likely require other treatments (chemotherapy, radiation treatments, etc) with potential effects on the assessment of study drugs in breast cancer. Interactions between chemotherapeutic drugs and elacestrant are unknown. Furthermore, patients with prior malignancies are at risk for cancer recurrence in general, which may increase the risk for early withdrawal from the study, thereby reducing the ability to detect safety and efficacy signals.
Included as missing information	No
Rationale (if not included as missing information)	Elacestrant is not expected to be a treatment for these types of cancers.
Criterion 3: Diagnosis of any other malignancy within 5 years before enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or 2nd primary breast cancer	
Reason for exclusion	Patients with prior malignant disease most likely require other treatments (chemotherapy, radiation treatments, etc.) with potential effects on the assessment of study drugs in breast cancer. Interactions between chemotherapeutic drugs and elacestrant are unknown. Furthermore, patients with malignancies within the last 5 years are at risk for cancer recurrence in general, which may increase the risk for early withdrawal from the study, thereby reducing the ability to detect safety and efficacy signals.
Included as missing information	No
Rationale (if not included as missing information)	Elacestrant is not expected to be a treatment for these types of cancers.
Criterion 4: Any of the following within 6 months before enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE v5.0 Grade ≥ 2, prolonged QTcF Grade ≥ 2 (ie, > 480 msec), uncontrolled atrial fibrillation of any grade, coronary/peripheral artery bypass graft, heart failure Class ≥ II as defined by the New York Heart Association guidelines, or cerebrovascular accident including transient ischemic attack	
Reason for exclusion	Patients at increased risk for developing complications from cardiac/vascular disease may require additional evaluation/assessments outside the scope of a clinical study. As a standard precautionary measure, patients with significant cardiac/vascular history were excluded.
Included as missing information	No
Rationale (if not included as missing	There is no evidence to suggest that the safety profile of elacestrant

information)	in these patients would be different from that of the populations intended for treatment.
Criterion 5: Child-Pugh Score greater than Class A (ie, score > 6)	
Reason for exclusion	Patients at increased risk for developing complications from hepatic impairment may require additional evaluation/assessments outside the scope of a clinical study. As a standard precautionary measure, patients with significant hepatic impairment were excluded.
Included as missing information	No
Rationale (if not included as missing information)	Based on pharmacokinetic modeling, reduced dose of elacestrant is recommended in patients with hepatic impairment.
Criterion 6: Coagulopathy or any history of coagulopathy within the past 6 months, including history of deep vein thrombosis or pulmonary embolism	
Reason for exclusion	Venous thromboembolism is a common adverse reaction in patients treated with fulvestrant. As a standard precautionary measure, patients with coagulopathy or any history of coagulopathy were excluded.
Included as missing information	No
Rationale (if not included as missing information)	There is no evidence to suggest that the safety profile of elacestrant in these patients would be different from that of the populations intended for treatment.
Criterion 7: Known bleeding disorder which, in the opinion of the investigator, would prohibit administration of fulvestrant if that would be the standard of care choice for the subject	
Reason for exclusion	Fulvestrant has been shown to induce vaginal bleeding (common) and bleeding at the injection site (uncommon). As a standard precautionary measure, patients with known bleeding disorders were excluded.
Included as missing information	No
Rationale (if not included as missing information)	There is no evidence to suggest that the safety profile of elacestrant in these patients would be different from that of the populations intended for treatment.
Criterion 8: Known difficulty in tolerating oral medications or conditions, which would impair absorption of oral medications, such as: uncontrolled nausea or vomiting (ie, CTCAE Grade ≥ 3 despite antiemetic therapy), ongoing gastrointestinal obstruction/motility disorder, malabsorption syndrome, or prior gastric bypass	
Reason for exclusion	Patients with known difficulty in tolerating oral medications could present as a compliance risk, thereby increasing the risk of protocol deviations. Patients with conditions that impair absorption could adversely affect the efficacy of elacestrant.
Included as missing information	No
Rationale (if not included as missing information)	Elacestrant is not expected to be used in patients who cannot tolerate oral medications or who have conditions that could impair the effectiveness of the medication.
Criterion 9: Known hypersensitivity reaction to drugs chemically related to elacestrant or their excipients	
Reason for exclusion	As a standard precautionary measure, clinical studies generally exclude patients with known hypersensitivities to the product under study.
Included as missing information	No
Rationale (if not included as missing information)	Elacestrant is not expected to be used in patients who have a hypersensitivity reaction to the drug or any of its excipients.
Criterion 10: Known hypersensitivity to fulvestrant, anastrozole, letrozole, or exemestane (or to any of their excipients), unless treatment with 1 of the other 3 of these 4 treatment options would be appropriate therapy	
Reason for exclusion	As a standard precautionary measure, clinical studies generally exclude patients with known hypersensitivities to the products under study.
Included as missing information	No
Rationale (if not included as missing information)	Patients treated with elacestrant would not be treated concomitantly with fulvestrant, anastrozole, letrozole, or exemestane.

CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; CVA = cerebrovascular accident; NCI = National Cancer Institute; QTcF = QT corrected by Fridericia's formula.

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

Long-term safety information on elacestrant is limited; however, this is not of major concern due to the long-standing experience with fulvestrant which is a similar drug-in-class.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table SIV.3.1: Exposure of special populations included or not in clinical trial development programs

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Pregnant or breastfeeding women</td><td>Pregnant or breastfeeding women have not been included in the clinical development program. The treatment is intended for postmenopausal women and men</td></tr>
<tr><td colspan="2">Patients with relevant comorbidities:</td></tr>
<tr><td>Patients with hepatic impairment</td><td>20 subjects with hepatic impairment (10 subjects with mild hepatic impairment, 10 subjects with moderate hepatic impairment) and an additional 16 control subjects with normal hepatic function were enrolled into the RAD1901-117 study.

Patients from the ITT population in the elacestrant arm of Study RAD1901-308 and patients treated with elacestrant 400 mg in Study RAD1901-005 and Study RAD1901-106 with baseline hepatic impairment are presented by level of impairment according to either Child Pugh* or National Cancer Institute (NCI) ** classification:
<table>
<tr><th colspan="3">Study RAD1901-308</th></tr>
<tr><td>Child Pugh Classification</td><td>Total</td><td>239</td></tr>
<tr><td></td><td>Missing</td><td>2 (0.8%)</td></tr>
<tr><td></td><td>Normal</td><td>203 (84.9%)</td></tr>
<tr><td></td><td>Mild</td><td>33 (13.8%)</td></tr>
<tr><td></td><td>Moderate</td><td>1 (0.4%)</td></tr>
<tr><td></td><td>Severe</td><td>0 (0%)</td></tr>
<tr><td>NCI Classification</td><td>Total</td><td>239</td></tr>
<tr><td></td><td>Missing</td><td>1 (0.4%)</td></tr>
<tr><td></td><td>Normal</td><td>160 (66.9%)</td></tr>
<tr><td></td><td>Mild dysfunction- Group 1</td><td>77 (32.2%)</td></tr>
<tr><td></td><td>Mild dysfunction- Group 2</td><td>0 (0%)</td></tr>
<tr><td></td><td>Moderate dysfunction</td><td>1 (0.4%)</td></tr>
<tr><th colspan="3">Study RAD1901-005</th></tr>
<tr><td>Child Pugh Classification</td><td>Total</td><td>50</td></tr>
<tr><td></td><td>Missing</td><td>0 (0%)</td></tr>
<tr><td></td><td>Normal</td><td>38 (76%)</td></tr>
<tr><td></td><td>Mild</td><td>10 (20%)</td></tr>
<tr><td></td><td>Moderate</td><td>2 (4%)</td></tr>
<tr><td></td><td>Severe</td><td>0 (0%)</td></tr>
<tr><td>NCI Classification</td><td>Total</td><td>50</td></tr>
<tr><td></td><td>Missing</td><td>0 (0%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>Normal</td><td>36 (72%)</td></tr>
<tr><td></td><td>Mild dysfunction- Group 1</td><td>13 (26%)</td></tr>
<tr><td></td><td>Mild dysfunction- Group 2</td><td>1 (2%)</td></tr>
<tr><td></td><td>Moderate dysfunction</td><td>0 (0%)</td></tr>
<tr><td colspan="3">Study RAD1901-106</td></tr>
<tr><td>Child Pugh Classification</td><td>Total</td><td>16</td></tr>
<tr><td></td><td>Missing</td><td>2 (12.5%)</td></tr>
<tr><td></td><td>Normal</td><td>9 (56.3%)</td></tr>
<tr><td></td><td>Mild</td><td>4 (25%)</td></tr>
<tr><td></td><td>Moderate</td><td>1 (6.3%)</td></tr>
<tr><td></td><td>Severe</td><td>0 (0%)</td></tr>
<tr><td>NCI Classification</td><td>Total</td><td>16</td></tr>
<tr><td></td><td>Missing</td><td>2 (12.5%)</td></tr>
<tr><td></td><td>Normal</td><td>9 (56.3%)</td></tr>
<tr><td></td><td>Mild dysfunction- Group 1</td><td>5 (31.3%)</td></tr>
<tr><td></td><td>Mild dysfunction- Group 2</td><td>0 (0%)</td></tr>
<tr><td></td><td>Moderate dysfunction</td><td>0 (0%)</td></tr>
<tr><td colspan="3">Overall</td></tr>
<tr><td>Child Pugh Classification</td><td>Total</td><td>305</td></tr>
<tr><td></td><td>Missing</td><td>4 (1.3%)</td></tr>
<tr><td></td><td>Normal</td><td>250 (82%)</td></tr>
<tr><td></td><td>Mild</td><td>47 (15.4%)</td></tr>
<tr><td></td><td>Moderate</td><td>4 (1.3%)</td></tr>
<tr><td></td><td>Severe</td><td>0 (0%)</td></tr>
<tr><td>NCI Classification</td><td>Total</td><td>305</td></tr>
<tr><td></td><td>Missing</td><td>3 (1%)</td></tr>
<tr><td></td><td>Normal</td><td>205 (67.2%)</td></tr>
<tr><td></td><td>Mild dysfunction- Group 1</td><td>95 (31.1%)</td></tr>
<tr><td></td><td>Mild dysfunction- Group 2</td><td>1 (0.3%)</td></tr>
<tr><td></td><td>Moderate dysfunction</td><td>1 (0.3%)</td></tr>
</table>
*Child Pugh classification is based on EMA, 2005 Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function (CPMP/EWP/2339/02,2005)
**NCI classification (NCI) for hepatic dysfunction is based on the NCI organ dysfunction working group (NCI-ODWG) criteria.
</td></tr>
<tr><td>Patients with renal impairment</td><td>
Patients with renal impairment have not been included in the clinical development program. Elacestrant undergoes only minor renal excretion, and dosage adjustment is not needed based on impaired renal function.
Patients from the ITT population in the elacestrant arm of Study RAD1901-308 and patients treated with elacestrant 400 mg in Study RAD1901-005 and Study RAD1901-106 with baseline renal impairment are presented by level of impairment:
<table>
<tr><th colspan="2">Study RAD1901-308</th></tr>
<tr><td>Total</td><td>239</td></tr>
<tr><td>Missing</td><td>0 (0%)</td></tr>
<tr><td>< 15 (End stage renal disease ESRD - Requiring Dialysis Treatment)</td><td>0 (0%)</td></tr>
<tr><td>≥15 - <30 (severely decreased renal function - Not Requiring Dialysis)</td><td>1 (0.4%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td></td><td>
<table>
<tr><td>≥30 - ≤60 (moderately decreased renal function)</td><td>46 (19.2%)</td></tr>
<tr><td>≥60 - ≤90 (mildly decreased renal function)</td><td>86 (36%)</td></tr>
<tr><td>>90 (normal renal function)</td><td>106 (44.4%)</td></tr>
<tr><td colspan="2">Study RAD1901-005</td></tr>
<tr><td>Total</td><td>50</td></tr>
<tr><td>Missing</td><td>0 (0%)</td></tr>
<tr><td>< 15 (End stage renal disease ESRD - Requiring Dialysis Treatment)</td><td>0 (0%)</td></tr>
<tr><td>≥15 - <30 (severely decreased renal function - Not Requiring Dialysis)</td><td>0 (0%)</td></tr>
<tr><td>≥30 - ≤60 (moderately decreased renal function)</td><td>9 (18%)</td></tr>
<tr><td>≥60 - ≤90 (mildly decreased renal function)</td><td>20 (40%)</td></tr>
<tr><td>>90 (normal renal function)</td><td>21 (42%)</td></tr>
<tr><td colspan="2">Study RAD1901-106</td></tr>
<tr><td>Total</td><td>16</td></tr>
<tr><td>Missing</td><td>2 (12.5%)</td></tr>
<tr><td>< 15 (End stage renal disease ESRD - Requiring Dialysis Treatment)</td><td>0 (0%)</td></tr>
<tr><td>≥15 - <30 (severely decreased renal function - Not Requiring Dialysis)</td><td>0 (0%)</td></tr>
<tr><td>≥30 - ≤60 (moderately decreased renal function)</td><td>1 (6.3%)</td></tr>
<tr><td>≥60 - ≤90 (mildly decreased renal function)</td><td>6 (37.5%)</td></tr>
<tr><td>>90 (normal renal function)</td><td>7 (43.8%)</td></tr>
<tr><td colspan="2">Overall</td></tr>
<tr><td>Total</td><td>305</td></tr>
<tr><td>Missing</td><td>2 (0.7%)</td></tr>
<tr><td>< 15 (End stage renal disease ESRD - Requiring Dialysis Treatment)</td><td>0 (0%)</td></tr>
<tr><td>≥15 - <30 (severely decreased renal function - Not Requiring Dialysis)</td><td>1 (0.3%)</td></tr>
<tr><td>≥30 - ≤60 (moderately decreased renal function)</td><td>56 (18.4%)</td></tr>
<tr><td>≥60 - ≤90 (mildly decreased renal function)</td><td>112 (36.7%)</td></tr>
<tr><td>>90 (normal renal function)</td><td>134 (43.9%)</td></tr>
</table>

Absolute GFR is based on the EMA Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/CHMP/83874/2014, 2015).
</td></tr>
<tr><td>Patients with cardiovascular impairment</td><td>Patients with significant cardiovascular impairment have not been included in the clinical development program. Sinus bradycardia and QT prolongation have not been observed in patients receiving elacestrant.</td></tr>
<tr><td>Immunocompromised patients</td><td>Immunocompromised patients have not been included in the clinical development program.</td></tr>
<tr><td>Patients with a disease severity different from inclusion criteria in clinical trials</td><td>Patients with disease severity different from inclusion criteria have not been included in the clinical development program.</td></tr>
</table>

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Population with relevant different ethnic origin</td><td>
<table>
<tr><th></th><th>RAD1901-005 and RAD1901-106 (N = 64) n (%)</th><th>RAD1901-308 (N = 237) n (%)</th></tr>
<tr><td colspan="3">Ethnicity</td></tr>
<tr><td>Missing</td><td>4</td><td>0</td></tr>
<tr><td>Not Hispanic or Latino</td><td>58 (96.7)</td><td>193 (81.4)</td></tr>
<tr><td>Hispanic or Latino</td><td>2 (3.3)</td><td>19 (8.0)</td></tr>
<tr><td>Unknown</td><td>0 (0.0)</td><td>25 (10.5)</td></tr>
<tr><td colspan="3">Race</td></tr>
<tr><td>Missing</td><td>1</td><td>48</td></tr>
<tr><td>White/Caucasian</td><td>58 (92.1)</td><td>167 (88.4)</td></tr>
<tr><td>Asian</td><td>0 (0.0)</td><td>16 (8.5)</td></tr>
<tr><td>Black or African American</td><td>4 (6.3)</td><td>5 (2.6)</td></tr>
<tr><td>Other</td><td>1 (1.6)</td><td>1 (0.5)</td></tr>
</table>
</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Patients carrying genetic polymorphisms have not been included in the clinical development program.</td></tr>
<tr><td colspan="2">Other special populations</td></tr>
<tr><td>Men with ER- positive/HER2-negative metastatic breast cancer</td><td>Six (6) men with ER-positive/HER2-negative metastatic breast cancer (in the RAD1901-308 study) have been treated with elacestrant.</td></tr>
<tr><td>Premenopausal women</td><td>Premenopausal women with ER-positive/HER2-negative metastatic breast cancer have not been included in the clinical development program. The study was designed to evaluate the safety and efficacy of elacestrant in postmenopausal women and men</td></tr>
<tr><td>Patients with ESR1-mutations (including those who were associated with resistance to endocrine therapy)</td><td>Overall, 149 patients with ESR1-mutations were exposed in the clinical development program.
<table>
<tr><th>Study number</th><th>Patients exposed</th></tr>
<tr><td>RAD1901-005</td><td>25</td></tr>
<tr><td>RAD1901-106</td><td>9</td></tr>
<tr><td>RAD1901-308</td><td>115</td></tr>
</table>
</td></tr>
</table>

ER = estrogen receptor; ESR1 = estrogen receptor 1 gene; HER = human epidermal growth factor receptor.

Part II: Module SV - Post-authorization Experience

Not applicable as this is an initial RMP.

Part II: Module SVI - Additional EU Requirements for the Safety Specification Potential for misuse for illegal purposes

Elacestrant is not expected to have the potential to be used for illegal purposes; hence, the potential for misuse is considered negligible. There has been no known incidence of abuse with the use of elacestrant. The product will be made available by prescription only.

Part II: 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 (in relation to the severity of the indication treated):

- Apart from embryo-fetal toxicity, hepatic failure, and thromboembolic events (venous) which are included in the section, "Other reasons for considering the risks not important," adverse drug reactions included in the Summary of Product Characteristics (SmPC) are considered to have minimal impact in relation to the indication treated.

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 (e.g., 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:

- Embryo-fetal toxicity is not applicable in relation to postmenopausal women for which elacestrant is indicated.
- Thromboembolic events (venous; VTEEs): The risk of VTEEs in patients treated with estrogen receptor antagonists are well known to the healthcare professionals. These risks are well characterised and they do not require additional PV measures or risk minimisation measures. The Applicant's position is that there is not enough evidence that elacestrant causes VTEEs vs. underlying disease; however, considering the clinical significance, VTEEs have been included as ADRs in the SmPC section 4.8 consistent with the fulvestrant product information. For these risks, Healthcare Professionals have adequate measures in place to treat patients. Hence, the risk of VTEEs will be reviewed as a part of routine pharmacovigilance activities and current labelling information is considered sufficient.
- Hepatic failure: One patient across the clinical development program experienced acute hepatic failure and disease progression that resulted in death. However, this patient's underlying stage IV breast cancer with liver and bone metastases at baseline were major confounders to determine the causality with elacestrant. Overall, the abnormal liver function tests observed with elacestrant are reflected by asymptomatic, non-serious

elevation of the transaminases with no impact on treatment or benefit-risk balance. One serious case of blood bilirubin increased occurred; however, it was determined to be related to progressive disease. The Applicant's position is that there is not enough evidence that elacestrant causes acute hepatic failure; however, considering the clinical significance, increased liver enzymes and acute hepatic failure are included as ADRs in the SmPC section 4.8 consistent with the fulvestrant product information. The adverse events suggestive of hepatic failure including abnormal liver function tests are being monitored through routine pharmacovigilance.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP:
A review of the data does not currently indicate any important identified risks or important potential risks of elacestrant. Details concerning areas of missing information are discussed below.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

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

A review of the data does not currently indicate any important identified or important potential risks of elacestrant or any areas of missing information.

SVII.3.2. Presentation of the missing information

A review of the data does not currently indicate any missing information.

Part II: Module SVIII - Summary of the Safety Concerns

Table SVIII.1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

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

III.1 Routine pharmacovigilance activities

Based on clinical safety data, there are no routine pharmacovigilance activities warranted beyond adverse reactions reporting and signal detection.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary table of additional pharmacovigilance activities

There are no proposed additional pharmacovigilance activities.

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due Dates
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization.				
None				
Category 2: Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing application or a marketed authorization under exceptional circumstances.				
None				
Category 3: Required additional pharmacovigilance activities.				
None				

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no plans for post-authorization efficacy studies.

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

Risk minimisation plan

V.1. Routine risk minimisation measures

Table Part V.1.1: Description of routine risk minimisation measures by safety concern

Safety concerns	Routine risk minimisation activites
Not applicable	Not applicable

V.2. Additional risk minimisation measures

There are no proposed additional risk minimisation activities. Routine risk minimisation activities as described in Part V.1 are considered sufficient for the adequate management of the safety profile of elacestrant.

V.3 Summary of risk minimisation measures

Table Part V.3.1: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Not applicable	Not applicable	Not applicable

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan (RMP) for ORSERDU (Elacestrant dihydrochloride)

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

ORSERDU's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ORSERDU should be used.

This summary of the RMP for ORSERDU 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 are part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for:

ORSERDU is intended as monotherapy for the treatment of postmenopausal women and men, with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy that could have been in combination with a CDK4/6 inhibitor.

It contains elacestrant dihydrochloride as the active substance and it is given orally with food.

Further information about the evaluation of ORSERDU's benefits can be found in ORSERDU's EPAR, including in its plain-language summary, available on the European Medicines Agency website.

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

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report 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 ORSERDU is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of ORSERDU 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 to the use of ORSERDU. 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 (eg, on the long-term use of the medicine).

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

II.B Summary of important risks

There are currently no important identified risks, important potential risks, or any areas of missing information of ORSERDU.

II.C Post-authorization Development Plan

II.C.1 Studies that are conditions of the marketing authorization

Not applicable.

II.C.2 Other studies in post-authorisation development plan

Not applicable.

PART VII: ANNEXES

Table of Contents of Annexes

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.