EU RISK MANAGEMENT PLAN (RMP)

LYNKUET®

BAY No. 3427080
(Elinzanetant)

No. 1.3

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18 AUG 2025

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EU Risk Management Plan for Lynkuet (Elinzanetant)

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LYNKUET®
(Elinzanetant)
EU Risk Management Plan

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List of abbreviations

%	Percent
<	Less Than
>	Greater Than
≥	Greater Than or Equal To
ADR	Adverse Drug Reaction
AE	Adverse Event
AET	Adjuvant Endocrine Therapy
AAGLT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BID	*Bis in Die* (twice daily)
BMI	Body Mass Index
C_{max}	Maximum concentration
CSR	Clinical Study Report
CVD	Cardiovascular Disease
CYP2D6	Cytochrome P450 2D6
EAIR	Exposure-Adjusted Incidence Rate
EEA	European Economic Area
ECG	Electrocardiogram
EFD	Embryofetal Development
eGFR	estimated Glomerular Filtration Rate

EU	European Union
EPAR	European Public Assessment Report
FMP	Final Menstrual Period
GnRH	Gonadotropin-Releasing Hormone
hERG	human Ether-a-go-go Related Gene
HF	Hot Flash (also referred to as Hot Flush)
HR+	Hormone-Receptor positive
HRQoL	Health-Related Quality of Life
HRT	Hormone Replacement Therapy
HT	Hormone Therapy
INN	International Nonproprietary Name
INR	International Normalised Ratio
K^+	Potassium Ion
KNDy	Kisspeptin, Neurokinin B, And Dynorphin Neurons
LOAEL	Lowest Observed Adverse Effect Level
LPLV	Last Patient Last Visit
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA Labelling Grouping
N/A	Not Applicable
NK	Neurokinin
NK3R	Neurokinin- 3 Receptor
NOAEL	No-Observed-Adverse-Effect Level
OD	Once Daily

PASS	Post Authorization Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PPND	Pre- and Post- natal Development
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
QT/QTc	Interval on an electrocardiogram/QT corrected
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SNRI	Serotonin Norepinephrine-Reuptake Inhibitor
SSRI	Selective Serotonin-Reuptake Inhibitor
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
trt	Treatment
UK	United Kingdom
US/USA	United States/United States of America
VMS	Vasomotor Symptoms (also known as hot flushes)

LYNKUET®
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Part I: Product(s) Overview

Part I: Product(s) overview

Table Part I-1 – Product(s) overview

Active substance(s) (INN or common name)	Elinzanetant
Pharmacotherapeutic group(s) (ATC Code)	G02CX07
Marketing Authorisation Applicant	Bayer AG, Germany
Medicinal products to which this RMP refers	Elinzanetant 60 mg soft capsule
Invented name(s) in the European Economic Area (EEA)	Lynkuet
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical name (IUPAC): 2-[3,5-bis(trifluoromethyl)phenyl]-*N*-{4-(4-fluoro-2-methylphenyl)-6-[(7*S*,9*aS*)-7-(hydroxymethyl) hexahydropyrazino [2,1-c] [1,4] oxazin-8(1*H*)-yl]-3-pyridinyl}-*N*,2-dimethylpropanamide
	Summary of mode of action: Elinzanetant (BAY 3427080) is a neurokinin targeted therapy, a non-hormonal, neurokinin -1, and -3 (NK-1,3) receptor antagonist which exerts its pharmacological effects through blockade of these receptors on kisspeptin, neurokinin B, and dynorphin (KNDy) neurons in the hypothalamus, normalizing the activity of the KNDy neurons. This results in improvement of menopausal symptoms including vasomotor symptoms (VMS), also called hot flashes [HFs], sleep disturbances and menopause-related quality of life.
	Important information about its composition: None
Hyperlink to the Product Information	Provided by the EMA after centralised procedure. SmPC
Indication(s) in the EEA	Treatment of moderate to severe vasomotor symptoms (VMS) • associated with menopause • caused by adjuvant endocrine therapy related to breast cancer
Dosage in the EEA	The recommended dose is 120 mg administered as two soft capsules of 60 mg taken orally once daily at bedtime.
Pharmaceutical form(s) and strengths	The dosage form is a 60 mg soft capsule.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

SI.1 Indication

The proposed indication for elinzanetant is:

Treatment of moderate to severe vasomotor symptoms (VMS)

- associated with menopause
- caused by adjuvant endocrine therapy (AET) related to breast cancer.

SI.1.1 Incidence and prevalence

Vasomotor symptoms (VMS) during menopause are reported by up to 80% of women at some point during the menopausal transition (1, 2). The daily incidence of symptoms varies, but on average, women report 4-5 VMS [also known as hot flashes (HFs) at day or night] per day, although some women have reported to have as many as 20 per day (3). About 25% of women report daily VMS, with daytime VMS being reported more often than VMS at night (also referred to as night sweats) (1, 2).

Globally, the prevalence of diagnosed VMS varies with differences by age group, region, and reported severity. In the European population, the prevalence of VMS (at daytime or nighttime) reported in the past week was 67% and 68%, respectively. Similar estimates were reported among women in the United States (US), while women in Japan reported lower prevalence of VMS. Around 54%-69% of women globally report experiencing both VMS in the past 12 months (4).

Symptoms can also occur in patients with breast cancer who are receiving AET for prevention of breast cancer or cancer recurrence. Globally, there were 2.3 million new cases of breast cancer in 2020 (5, 6). In recent years, the incidence of female breast cancer was 119.2 per 100,000 population in the US and 147.6 per 100,000 population in Europe (7, 8). Most cases are early stage diagnoses and treatment with adjuvant tamoxifen or aromatase inhibitors is recommended for patients with hormone-receptor positive (HR+) early breast cancer (5, 9).

In trial data, VMS are reported in 35%-40% of participants, while observational studies report that VMS occur in 90%-95% of women receiving endocrine therapy (9-11).

SI.1.2 Demographics of the population in the proposed indication – stratified by age, gender, racial/ethnic origin

According to the US Census Bureau in 2020, there were an estimated 44 million women between the ages of 35-55 in the transition period to menopause; in the European Union (EU), an estimated 65 million women belonged to this age group in 2022 (12, 13). During this period, women begin to experience variations in the menstrual cycle and commonly experience VMS (14).

Prevalence rates of VMS have been reported to vary by severity across different countries. Most women reported experiencing moderate to severe symptoms with up to 87% of women in France reporting moderate VMS; rates were similar in Germany, Spain, and the United Kingdom (UK). By contrast, severe VMS was reported by 74% of women in Italy whereas 17%-30% of women in other European countries experienced severe symptoms (4).

Racial/ethnic differences in VMS prevalence and severity were assessed in studies conducted in other countries. In a pooled analysis spanning across the US, Europe, and Australia, 55% of Caucasian European women reported any VMS, with 45% reporting moderate to severe symptoms (15). Across several studies, women of Asian descent reported the lowest VMS prevalence (15-20). By contrast, the prevalence among Hispanic and White women was higher, but below that of Black women (15-19). Among postmenopausal women in the US, VMS were most common overall in African American women, followed by Hispanic and non-Hispanic White women (18).

In the breast cancer population, incidence is higher among older age groups. In the US, the incidence is highest among women aged 45-79 while in Europe, 50% of cases occurred among women aged 45-69 (7, 8). Population estimates of age distributions and racial/ethnic distribution have not been assessed for VMS resulting from AET. In some observational studies, most women experiencing menopausal symptoms from AET were aged 40 and older (10, 21).

SI.1.3 Risk factors associated with VMS

In the general population, certain lifestyle and socio-demographic factors may be associated with the frequency and severity of VMS. Important risk factors in the general population include Body Mass Index (BMI), smoking, other lifestyle factors, psychosocial factors, gynaecological factors, and ethnicity.

Higher BMI was found in several studies to be associated with increased risk of VMS in pre-and perimenopausal women, but with reduced risk in post menopause (2). Early age at menarche was identified as a risk factor for VMS, with the risk increased among those with higher BMI at midlife (15).

Current smoking was found to be associated with a higher frequency or severity of VMS. However, former smokers who quit at < 40 years of age were only at a slightly increased risk of having a higher frequency or severity of VMS (22). Smoking was also found to be associated with more frequent VMSs among younger women compared to older women (23).

Anxiety and depression are associated with VMS, although the direction of a causal relationship between VMS and psychological distress is unclear. In some studies, anxiety and depressive symptoms preceded VMS (24, 25). Other studies did not find a significant association between the occurrence of VMSs and perceived high stress when adjusted for other factors (23).

Women with medically induced premature menopause (patients who have undergone oophorectomy, chemotherapy, or radiotherapy) are at higher risk of experiencing more severe VMS (26, 27). Additionally, VMS are more likely in women with a hysterectomy, even with ovarian conservation, than in women with a natural menopause (28).

With respect to racial and ethnic differences, African American women have been shown to experience more severe VMS compared to White women in multiple studies (16, 17, 24). Various studies also found that Hispanic women tend to report more VMS when compared to White women which may be due to factors such as socioeconomic status, education, anxiety, and depression (16, 29). Women of Asian ethnicity consistently report both fewer and shorter durations of VMS than other groups, according to several studies (15, 16, 18, 19, 28).

In the breast cancer population, nearly all women receiving AET will experience VMS (9) Higher risk of VMS due to AET was associated with prior chemotherapy, adjuvant hormone therapy (HT), oophorectomy, and depression (27, 30, 31).

SI.1.4 The main existing treatment options

Hormone replacement therapy (HRT)

The most effective treatment for VMS associated with menopause currently available is Hormone replacement therapy (HRT), also known as hormone therapy (HT) with systemic estrogen (32). Hormone replacement therapy includes warnings for increased risk of hormone-dependent cancers, thrombotic risk, and cardiovascular adverse effects (33, 34). However, benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause (35). Estrogen alone is given to hysterectomised women. Progestogens are added in regimens for non-hysterectomised women to reduce the increased risk of endometrial hyperplasia and carcinoma, which occurs with unopposed estrogen. The two main routes of administration are oral and transdermal (patches and gels).

While most progestogens are given orally, norethisterone and levonorgestrel are available in transdermal patches combined with estradiol; and levonorgestrel can be delivered directly to the uterus with an intrauterine device. Tibolone is a synthetic steroid compound that is in itself inert, but whose metabolites have estrogenic, progestogenic, and androgenic actions. It is classified as HRT and is used in postmenopausal women (35).

Hormone replacement therapy is contraindicated among women with breast cancer (or history of) who may receive AET for prevention of breast cancer recurrence (5, 11).

Non-Hormonal treatments

Non-hormonal treatments include non-hormonal medications, lifestyle modifications, diet, food supplements, behavioural and alternative complementary therapies (36, 37).

Selective serotonin-reuptake inhibitors (SSRIs) and serotonin norepinephrine-reuptake inhibitors (SNRIs) have been proposed as an alternative to HRT for VMS. The SSRIs, such as paroxetine, have been studied and are effective in decreasing both the frequency and severity of hot flushes (38). Of the SSRIs, paroxetine is approved in the US for the treatment of VMS associated with menopause, but has limited efficacy and a range of safety and tolerability concerns that prevent its widespread usage (36, 37, 39). Paroxetine is a potent cytochrome P450 2D6 (CYP2D6) inhibitor and decrease the metabolism of tamoxifen and may reduce its anticancer effect and thus should be avoided in tamoxifen users (32). The SNRIs venlafaxine and desvenlafaxine have been used off-label to treat menopausal symptoms (32).

Up until recently, the only non-hormonal treatment option approved for the treatment of VMS in some EU countries, and the UK was clonidine, a centrally acting a2-adrenergig agonist (40). Since 2023, fezolinetant, a neurokinin 3 receptor (NK3R) antagonist is approved for the treatment of moderate to severe VMS associated with menopause (36, 41). Fezolinetant selectively and reversibly blocks neurokinin B signalling, slowing gonadotropin-releasing hormone (GnRH) pulse frequency consistent with a decrease in kisspeptin, neurokinin B, and dynorphin (KNDy) neurons activity (42, 43).

Soy isoflavones, coumestans, and lignans are all phytoestrogen supplements that have been proposed as alternatives to HRT for VMS. Phytoestrogens are found in soybeans (isoflavones), hops (*Humulus lupulus*), flaxseed (lignans), fruits, vegetables, whole grains, and legumes. Extracted or synthesised soybean isoflavones have been suggested to reduce VMS frequency and severity; however, there is no conclusive evidence that phytoestrogen supplements effectively reduce the frequency or severity of VMS (44).

Cognitive-behavioural therapy has been used to deal with menopausal symptoms and is recommended for the treatment of VMS (36). Cognitive-behavioural therapy has also been recommended for the treatment of anxiety and depression for women during the menopause transition and post menopause (45).

SI.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Vasomotor symptoms are reported by up to 80% of women at some point during the menopausal transition (1). Vasomotor symptoms are transient but recurrent episodes of flushing, perspiration, and intense heat sensation. When VMS occur at night, they are also called night sweats and can cause insomnia and fatigue (46, 47). Vasomotor symptoms are one of the most common, bothersome, and distressing symptoms felt by women during this phase (48). Vasomotor symptoms can vary in frequency, with some women experiencing multiple episodes daily, and can last 10 years or more after the last menstrual period (49, 50). Night sweats were reported in 27%-65% of women across studies in the US, the UK, and Australia (15).

The occurrence and frequency of VMS were observed to have peaked in the late perimenopause and early postmenopausal years, lasting for a median duration of 7.4 years (49). However, many women reported VMS before the onset of the menstrual cycle changes, which continued for many years post menopause (47). Severe VMS, defined in terms of higher frequency, severity, and bother, have a peak prevalence of 50% near the final menstrual period (FMP) (28).

In the breast cancer population, most women receiving AET (tamoxifen or aromatase inhibitors) will experience VMS (9-11). While new breast cancer cases typically occur in women aged 45 or older, 95% of premenopausal and over 30% of postmenopausal women with a history of breast cancer will experience treatment-related VMS; VMSs have been reported in 70% of women with breast cancer undergoing endocrine therapy (40).

Vasomotor symptoms have been associated with all aspects of perceived sleep disturbance that contribute to poor sleep continuity and quality, including falling asleep, staying asleep, and early morning awakening. Vasomotor symptoms stand out as a consistent factor that contributes to reporting of poor sleep, controlling for other important predictive factors (47). The impact of VMS on sleep is related to disruption of the sleep cycle by VMS, coexistent psychological disorders such as anxiety and depression that contribute to impaired sleep, and the altered central neural control of sleep-wake states and thermal threshold associated with hormonal alterations (14).

Vasomotor symptoms have been strongly associated with reduced health-related quality of life (HRQoL), although menopause stage itself was not associated with HRQoL. The negative association between VMS and HRQoL is strongest in those with more frequent VMS (47).

SI.1.6 Important comorbidities and mortality

Some studies have investigated VMS as markers for conditions such as cardiovascular disease (CVD) and osteoporosis (see studies' details below). Vasomotor symptoms are commonly experienced by menopausal women and have been associated with an unfavourable risk of diseases that can threaten the morbidity and mortality of women worldwide. The two most commonly associated conditions are CVD and osteoporosis in the general population.

Cardiovascular disease is the leading cause of death worldwide (51). Frequency and persistency of VMS were found to be associated with a higher risk of future cardiovascular events including myocardial infarction, stroke, and heart failure (52). In addition, the lifetime risk of a woman developing CVD by age 50 is estimated to be 39% (53).
Expected co-medications for CVD include beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and statins (51).

Osteoporosis is a systemic skeletal disorder characterised by reduced bone mineral density and a propensity to fractures, which are usually associated with significant morbidity.

Osteoporosis and osteoporosis-related fractures are most common among postmenopausal women. Expected comedications for osteoporosis include oral bisphosphonates, raloxifene, teriparatide, biologic medications such as denosumab, and HRT (54).

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

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

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non- clinical studies)	Relevance to human usage
Repeat-dose toxicity studies were conducted in rats and Cynomolgus monkeys	
Reproductive tract: In female rats, daily administration of elinzanetant for four weeks at doses of 100 mg/kg showed mucification of the vaginal epithelium, uterine atrophy, and persistent corpora lutea. In monkeys, daily administration of elinzanetant for 39 weeks with BID dosing at doses equal to or greater than 60 mg/kg/day showed reduced cyclical ovarian activity.	These effects indicating an estrous cycle arrest in the reproductive tract of female rats and monkeys are not considered relevant for postmenopausal women treated for VMS associated with menopause. In premenopausal women a prolongation, but no arrest of the estrous cycle was observed in a 21-day study. NOAEL rat: 25 mg/kg Safety margin in rat: 10 NOAEL monkey: 30 mg/kg Safety margin in monkey: 0.3
Involuntary muscle contractions and convulsions: In a single 13-week study in rats with BID dosing, daily administration of elinzanetant from doses of 50 and 20 mg/kg/day onwards in males or females (7- and 4-fold the human AUC at the human therapeutic dose) led to involuntary muscle contractions from Day 24 in 10/88 animals, which later had also convulsions from Day 34. An increased incidence of convulsions was also observed in a two-year rat study from doses of 60 mg/kg/day onwards (20-fold the AUC at the human therapeutic dose).	Involuntary muscle contractions and convulsions were neither observed in monkeys nor in rabbits or mice. No effects in humans are expected. LOAEL: 50 mg/kg in male rats/20 mg/kg in female rats Safety margin in male/female rats: < 4.2/< 7.0
Skeletal muscle toxicity: In the 13-week study in rats with BID dosing, daily administration of elinzanetant at doses equal to or greater than 100 mg/kg/day (16-fold the AUC at the human therapeutic dose) showed skeletal muscle degeneration and necrosis.	Skeletal muscle toxicity was only observed at high multiples of exposure and is therefore not expected to occur in humans. NOAEL: 120 mg/kg in male rats/50 mg/kg in female rats Safety margin in male/female rats: 9.1/18
Diarrhoea: In monkeys, administration of elinzanetant at doses from 40 mg/kg per dose occasion showed diarrhoea. This was also observed after twice daily dosing with 40 mg/kg, corresponding to 80 mg/kg/day.	Since women during treatment with 120 mg elinzanetant per day receive a lower oral dose of approximately 2 mg/kg than the monkeys in the toxicological studies, severe diarrhoea is not expected in human patients.

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

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non- clinical studies)	Relevance to human usage
	NOAEL: 30 mg/kg/dose occasion BID in monkeys (60 mg/kg/day) Safety margin: 0.3
Increase in liver enzymes: Minor increases of transaminases and increased total bilirubin without histopathological correlates were seen sporadically in monkeys and rats; hepatocellular toxicity was only observed in a few animals (rats, monkeys at doses ≥100 mg/kg/day) *in extremis*.	Preclinical data give no indication for drug-induced liver injury in the range of human therapeutic exposure. NOAEL for hepatotoxicity in female rats/monkeys after chronic dosing (26 weeks in rat/39 weeks in monkeys): 80 mg/kg Safety margin in female rats/female monkeys: 36/2.0 (value of 2.0: based on total AUC at 60 mg/kg in female monkeys, which was 1.8-fold higher than at 80 mg/kg)
Reproductive/developmental toxicity	
In the **embryo-foetal development studies** with elinzanetant, no evidence of embryo-foetal lethality or teratogenicity occurred at high doses up to 100 mg/kg/day in rats and up to 140 mg/kg/day in rabbits (23-fold and 1-fold the AUC at the human therapeutic dose respectively). In the **female fertility and early embryonic development study**, increased percentage of pre-implantation and post-implantation embryo loss, resulting in reduced litter size, and lower foetal body weights were seen at 100 mg/kg/day (16-fold the AUC at the human therapeutic dose). These effects were not observed following dosing at 25 mg/kg/day (4-fold the human AUC at the human therapeutic dose). In the **pre- and post-natal development studies** in rats, F0 females showed post-implantation loss, increase in gestation length, delayed parturition and dystocia, as well as lower pup weights at doses of 100 mg/kg/day (23-fold the AUC at the human therapeutic dose). Increase in total litter loss and a corresponding decrease of pup viability on post-natal day five was observed in the range of human therapeutic exposure.	Preclinical data indicate that treatment with elinzanetant is not recommended during pregnancy. If pregnancy occurs during medication with elinzanetant, treatment should be withdrawn immediately. Women of childbearing potential should use adequate contraception during elinzanetant treatment. FEED female rat: NOAEL 25 mg/kg Safety margin: 3.8 EFD rat: NOAEL 100 mg/kg Safety margin: 16 EFD rabbit: NOAEL 140 mg/kg Safety margin: 1.2 PPND rat: NOAEL for prolonged gestation length, delayed parturition and dystocia: 25 mg/kg Safety margin: 6.7 NOAEL for total litter loss/decreased pup viability (lack of nursing): 1.5 mg/kg Safety margin: 0.2
Genotoxicity	
There is no evidence for a genotoxic potential of elinzanetant.	No risk for genotoxic effects identified

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

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non- clinical studies)	Relevance to human usage
Carcinogenicity	
In a Two-year carcinogenicity study on elinzanetant in rats, an increase in uterine neoplasms (especially uterine adenocarcinoma) and lymphomas was reported from doses representing at least 29-fold the total AUC at the human's therapeutic dose. Exposure at the dose free of these findings corresponds to a safety margin of seven based on total AUC. The increased incidence of uterine neoplasms in aged rats undergoing reproductive senescence with pronounced body weight reduction resembles effects in dietary restriction studies in rats and chronic, drug-induced hypoprolactinaemia, a rat-specific mode of action, which is not relevant for humans. No drug-related neoplasms were observed in the 26-week carcinogenicity study on elinzanetant in transgenic mice up to the highest dose tested of 85 mg/kg in males and 70 mg/kg/day in females, which represents 3- and 2-fold the human AUC at the therapeutic dose.	Increased incidences of uterine neoplasms and lymphomas were only observed at exposure multiples of 29 and higher and are thus not considered clinically relevant. Moreover, the increased incidence of uterine tumours in aged rats undergoing reproductive senescence with pronounced body weight reduction resembles effects in dietary restriction studies in rats and chronic, drug-induced hypoprolactinaemia, a rat-specific mode of action, which is not relevant for humans. NOAEL 20 mg/kg Safety margin: 7
Safety pharmacology as applicable	
In safety pharmacology studies in rat and cynomolgus monkey *in vivo*, elinzanetant did not produce physiologically significant acute effects on vital organ functions i.e. neurobehavioural, respiratory, and cardiovascular. Elinzanetant did not interfere with cardiac ventricular repolarisation *in vitro* (hERG K^+ channel) and *in vivo* (QT/QTc interval).	Acute negative interferences of elinzanetant with vital organ functions is not expected in patients.
Other toxicity-related information or data	
Phototoxicity	
Elinzanetant absorbs light in the visible part of the spectrum. An *in vitro* phototoxicity assay indicated a potential for phototoxicity at a concentration of 67-fold the unbound C_{max} at the maximum recommended human dose. These effects were not observed at a concentration of 21-fold the unbound C_{max} at the maximum recommended human dose.	The *in vitro* phototoxicity assay was only positive at concentrations exceeding the maximum clinical exposure; however, clinical relevance of the non-clinical phototoxicity findings for humans is unknown but cannot be excluded.

AUC: Area Under the Curve; BID: Twice Daily; C_{max}: Maximum Plasma Concentration; EFD: Embryofetal Development; FEED: Fertility And Early Embryonic Development; hERG: Human Ether-A-Go-Go Related Gene; K^+: Potassium Ion; LOAEL: Lowest Observed Adverse Effect Level; NOAEL: No-Observed-Adverse-Effect Level; PPND: Pre- and Post-natal Development; VMS: Vasomotor Symptoms; QT: Interval on An Electrocardiogram; QTc: QT Corrected
Safety margin based on total AUC: total AUC at the NOAEL in the animal study divided by the total AUC at a once daily dose of 120 mg in humans (MHRD)

No safety concerns from the non-clinical data have been identified.

Part II: Module SIII - Clinical trial exposure

SIII.1. Clinical Trial exposure

Key information of the Phase 2 and 3 clinical studies relevant for the assessment of the safety of elinzanetant is presented in the Table Part II SIII-1 below.

Table Part II SIII-1: Overview of Phase 2/3 studies of elinzanetant for the treatment of moderate to severe VMS associated with menopause or caused by AET

Study identifier **Study no.** ***(Report no.)*** *location*	**Study title**	**Dose arms (treatment duration)**	**Number of women treated/ completed trt**
SWITCH-1 **21686/** **814-PM-02** ***(R-13559)*** *Canada, UK, USA*	A double-blind, randomised, placebo-controlled, adaptive design study of the efficacy, safety, and pharmacokinetics of NT-814 in female subjects with moderate to severe vasomotor symptoms associated with the menopause	Elinzanetant 40 mg, OD Elinzanetant 80 mg, OD Elinzanetant 120 mg, OD Elinzanetant 160 mg, OD (12 weeks) Placebo, OD (12 weeks)	31/29 17/14 52/51 52/43 47/43
	Treatment of moderate to severe VMS associated with menopause		
Phase 3 – Pivotal studies			
OASIS 1 **21651** ***(PH-42782)*** *Europe, Israel, USA*	A double-blind, randomized, placebo-controlled multicentre study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women	Elinzanetant 120 mg, OD (26 weeks) Placebo, OD (12 weeks), followed by elinzanetant 120 mg (14 weeks)	198[a]/156 195[a]/159
OASIS 2 **21652** ***(PH-42780)*** *Canada, Europe, USA*	A double-blind, randomized, placebo-controlled multicentre study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women	Elinzanetant 120 mg, OD (26 weeks) Placebo, OD (12 weeks), followed by elinzanetant 120 mg (14 weeks)	200[b]/160 200[b]/170
Phase 3 – 52-week efficacy and safety study			
OASIS 3 **21810** ***(PH-42784)*** *Canada, Europe, USA*	A double-blind, randomized, placebo-controlled multicentre study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 52 weeks in postmenopausal women	Elinzanetant 120 mg, OD (52 weeks) Placebo, OD (52 weeks)	313/226 315/232

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Table Part II SIII-1: Overview of Phase 2/3 studies of elinzanetant for the treatment of moderate to severe VMS associated with menopause or caused by AET

Study identifier Study no. *(Report no.)* *location*	Study title	Dose arms (treatment duration)	Number of women treated/ completed trt
Treatment of moderate to severe VMS caused by AET			
Phase 3 – Pivotal study			
OASIS 4 **21656** **B003017** *Canada, Europe, Israel, Kazakhstan*	A double-blind, randomized, placebo-controlled multicentre study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms caused by AET, over 52 weeks and optionally for an additional two years in women with, or at high risk for developing hormone-receptor positive breast cancer	Elinzanetant 120 mg, OD (52 weeks); optionally additional 2 years	315/271[c]
		Placebo, OD (12 weeks), followed by elinzanetant 120 mg (40 weeks); optionally additional two years	158/139[c]/139[d]

AET: Adjuvant Endocrine Therapy, OD: Once Daily, trt: Treatment, VMS: Vasomotor Symptoms, UK: United Kingdome; USA: United States of America
a In the safety analyses, elinzanetant 120 mg Week 1-12 arm comprises 199 women and placebo Week 1-12 arm comprises 194 women, because one woman who was randomized to placebo started treatment with elinzanetant 120 mg.
b In the safety analyses, elinzanetant 120 mg Week 1-12 arm comprises 201 women and placebo Week 1-12 arm comprises 199 women, because one woman who was randomized to placebo started treatment with elinzanetant 120 mg
c Completed 26 weeks of treatment (Part A of the study)
d Completed 52 weeks of treatment (Parts A+B of the study)

SIII.1.1 Moderate to severe vasomotor symptoms (VMS) associated with menopause [Pool 1-52 weeks (OASIS 1, OASIS 2, OASIS 3, and SWITCH-1 120mg arm)]

Table Part II SIII-2: Duration of exposure (week 1-52; safety analysis set)

Cumulative for all indications (person time)			
Duration of exposure	**Number of patients**	**Person time [months]**	**Person time [years]**
<1 month	51	26.07	2.00
1 to <2 months	44	66.36	5.09
2 to <3 months	78	215.82	16.54
3 to <4 months	339	1,128.50	86.51
4 to <5 months	22	95.18	7.30
5 to <6 months	8	45.54	3.49
6 to <7 months	325	2,073.32	158.94
7 to <8 months	3	21.45s	1.65
8 to <9 months	5	43.18	3.31
9 to <10 months	2	18.86	1.45

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Table Part II SIII-2: Duration of exposure (week 1-52; safety analysis set)

Cumulative for all indications (person time)			
Duration of exposure	**Number of patients**	**Person time [months]**	**Person time [years]**
10 to <11 months	3	31.96	2.45
11 to <12 months	3	34.86	2.67
12 to <13 months	212	2,695.07	206.60
13 to <14 months	18	238.00	18.25
Total person time	**1,113**	**6,734.25**	**516.25**

<: Less Than

Table Part II SIII-3: Age group (week 1-52; safety analysis set)

Age group	**Number of patients**	**Person time [months]**	**Person time [years]**
40 – 49 years	156	981.39	75.23
50 – 59 years	761	4,545.32	348.44
60 – 65 years	196	1,207.54	92.57
Total	**1,113**	**6,734.25**	**516.25**

<: Less Than

Table Part II SIII-4: Race (week 1-52; safety analysis set)

Race	**Number of patients**	**Person time [months]**	**Person time [years]**
White	883	5,307.25	406.85
Black or African American	187	1,075.11	82.42
Asian	6	44.57	3.42
American Indian or Alaska Native	4	19.07	1.46
Native Hawaiian or Other Pacific Islander	1	12.96	0.99
Multiple	5	22.96	1.76
Not reported	27	252.32	19.34
Total	**1,113**	**6,734.25**	**516.25**

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Table Part II SIII-5: Ethnic origin (week 1-52; safety analysis)

Ethnic origin	Number of patients	Person time [months]	Person time [years]
Not Hispanic or Latino	991	5,947.75	455.95
Hispanic or Latino	102	631.75	48.43
Not reported	20	154.75	11.86
Total	**1,113**	**6,734.25**	**516.25**

SIII.1.2 Moderate to severe vasomotor symptoms (VMS) caused by AET related to breast cancer (OASIS 4)

Table Part II SIII-6: Duration of exposure (52; safety analysis set)

Duration of exposure	Number of patients	Person time [months]	Person time [years]
<1 month	14	8.6	0.7
1 to <2 months	13	16.9	1.3
2 to <3 months	3	7.3	0.6
3 to <4 months	8	27.8	2.1
4 to <5 months	4	17.7	1.4
5 to <6 months	9	49.1	3.8
6 to <7 months	9	57.4	4.4
7 to <8 months	4	30	2.3
8 to <9 months	4	34.4	2.6
9 to <10 months	123	1,182.3	90.6
10 to <11 months	10	101	7.7
11 to <12 months	1	11.1	0.9
12 to <13 months	245	3,108.7	238.3
Total person time	**465**	**4,888.3**	**374.7**

<: Less Than

Table Part II SIII-7:Age group (safety analysis set)

Duration of exposure	Number of patients	Person time [months]	Person time [years]
< 40 years	30	314	24.1
40 - 49 years	153	1,648.9	126.4
50 - 59 years	230	2,361.6	181

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Table Part II SIII-7:Age group (safety analysis set)

Duration of exposure	Number of patients	Person time [months]	Person time [years]
60 - 65 years	39	405	31
> 65 years	13	158.7	12.2
Total	**465**	**4,888.3**	**374.7**
Total person time	**465**	**4,888.3**	**374.7**

<: Less Than; >: Greater Than

Table Part II SIII-8:Race (safety analysis set)

Race	Number of patients	Person time [months]	Person time [years]
White	411	4,305.6	330.1
Black or African American	7	85.7	6.6
Asian	2	22.4	1.7
American Indian or Alaska Native	3	35.2	2.7
Not reported	42	439.3	33.7
Total	**465**	**4,888.3**	**374.7**

Table Part II SIII-9:Ethnic origin (safety analysis)

Ethnic origin	Number of patients	Person time [months]	Person time [years]
Not Hispanic or Latino	425	4,469.6	342.6
Hispanic or Latino	12	109.8	8.4
Not reported	28	308.9	23.7
Total	**465**	**4,888.3**	**374.7**

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

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

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
History of arrhythmias, heart block and QT prolongation, either determined through clinical history or on ECG evaluation	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Evaluation of the Phase 1 and 3 data did not reveal a safety concern.
Current or history (except complete remission for five years or more) of any malignancy (except basal and squamous cell skin tumours). Women receiving AET (e.g., tamoxifen, aromatase inhibitors, GnRH analogues) could not be enrolled in this study **Note:** this criterion only applied to OASIS 1, 2, 3	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Women receiving AET (e.g., tamoxifen, aromatase inhibitors, GnRH analogues) are studied in the ongoing OASIS 4 study.
Clinically relevant abnormal findings on mammogram	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Evaluation of the Phase 3 data did not reveal a safety concern.
Any unexplained postmenopausal uterine bleeding	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Transvaginal ultrasound and endometrial biopsy performed at baseline and at end of study timepoints. No safety concern aroused based on the assessment of the data.

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

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Disordered proliferative endometrium, endometrial hyperplasia, polyp, or endometrial cancer diagnosed based on endometrial biopsy during screening.	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Transvaginal ultrasound and endometrial biopsy performed at baseline and at end of study timepoints. No safety concern aroused based on the assessment of the data.
Abnormal liver parameters (AST, ALT, AP, TBL, INR), diagnosis of hepatitis B or C infection	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial.	No	Liver function testing performed regularly in clinical studies. No safety concern aroused from this evaluation.
Patients with eGFR <30 mL/min/1.73 m^2 or on dialysis	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial	No	Adequately reflected in the SmPC (section 4.2).
Specific to OASIS 4			
Initial diagnosis of metastatic hormone-receptor positive breast cancer (stage IV) or recurrence under AET of hormone-receptor positive breast cancer.	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial	No	Not the intended population to be treated for VMS caused by AET. Evaluation of the available Phase 3 data did not reveal a safety concern.
Surgery or non-surgical (e.g., chemotherapy, radiotherapy, immunotherapy) treatment for breast cancer within the last 3 months prior to signing informed consent (except use of tamoxifen, aromatase inhibitors, GnRH analogues).	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial	No	Not the intended population to be treated for VMS caused by AET.

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

Table Part II SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing Information Yes/No	Rationale
Planned surgery, chemotherapy, radiotherapy, or immunotherapy within the duration of the study (reconstructive breast surgery allowed after Week 12).	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial	No	Not the intended population to be treated for VMS caused by AET.
Current pregnancy or less than 3 months since delivery, abortion or stop of lactation prior to signing informed consent.	This exclusion criterion was applied to avoid factors that may confound the evaluation of safety and efficacy in the trial	No	Adequately reflected in the SmPC (section 4.6).

AET: Adjuvant Endocrine Therapy; ALT: Alanine Aminotransferase; AP: Alkaline Phosphatase; AST: Aspartate Aminotransferase; ECG: Electrocardiogram; eGFR: estimated Glomerular Filtration Rate; GnRH: Gonadotropin-Releasing Hormone; INR: International Normalised Ratio; SmPC: Summary of Product Characteristics; TBL: Total Bilirubin; VMS: Vasomotor Symptoms

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 Part II SIV-2: Exposure of special populations in the Pool of OASIS 1, 2, 3 and SWITCH-1 (1-52 weeks) included or not in clinical trial development programmes for the indication "Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause"

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities:	
• Patients with hepatic impairment	21 women (7.73 person years)
• Patients with renal impairment	
• Missing	67 women (17.72 person years)

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

Table Part II SIV-2: Exposure of special populations in the Pool of OASIS 1, 2, 3 and SWITCH-1 (1-52 weeks) included or not in clinical trial development programmes for the indication "Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause"

Type of special population	Exposure
• eGFR 25- <45 mL/min/1.73 m^2	2 women (1.00 person years)
• eGFR 45- <60 mL/min/1.73 m^2	22 women (7.00 person years)
• eGFR ≥ 60 mL/min/1.73 m^2	1,022 women (376.97 person years)
• Total	**1,113 women (402.69 person years)**
Population with relevant different ethnic origin:	
• Not Hispanic or Latino	991 women (455.95 person years)
• Hispanic or Latino	102 women (48.43 person years)
• Not reported	20 women (11.86 person years)

<: Less Than, ≥: Greater Than or Equal To, GFR: estimated Glomerular Filtration Rate, VMS: vasomotor symptoms

Table Part II SIV-3: Exposure of special populations in OASIS 4 included or not in clinical trial development programmes for the indication "Treatment of moderate to severe vasomotor symptoms (VMS) caused by adjuvant endocrine therapy related to breast cancer"

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities:	
• Patients with hepatic impairment	15 women (12.59 person years)
• Patients with renal impairment	
• Missing	2 women (1.72 person years)
• eGFR 25- <45 mL/min/1.73 m2	2 women (1.95 person years)
• eGFR 45- <60 mL/min/1.73 m2	10 women (8.69 person years)
• eGFR ≥60 mL/min/1.73 m^2	451 women (362.38 person years)
• Total	**465 women (374.74 person years)**
Population with relevant different ethnic origin:	
• Not Hispanic or Latino	425 women (342.6 person years)
• Hispanic or Latino	12 women (8.4 person years)
• Not reported	28 women (23.7 person years)

<: Less Than, ≥: Greater Than or Equal To, eGFR: estimated Glomerular Filtration Rate, VMS: Vasomotor Symptoms

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Lynkuet is not marketed in any country.

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

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

SVI.1 Potential for misuse for illegal purposes

Elinzanetant is a central nervous system-active and brain-penetrant dual neurokinin (NK)-1 and 3 antagonist. Neurokinin (NK)-1 and NK-3 receptors are expressed in the central as well as in the peripheral nervous system.

Preclinical in vitro and *in vivo* data do not indicate an on-/off-target related abuse potential.

Based on the sum of elinzanetant clinical data in both healthy participants and in postmenopausal women with VMS/women on AET with VMS, there is currently no indication that the use of elinzanetant is associated with a potential for drug abuse.

In conclusion, there is no potential for misuse for illegal purposes with elinzanetant.

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

All adverse reactions outlined in Table Part II SVII-1 are reflected as adverse drug reactions (ADRs) in the Lynkuet Summary of Product Characteristics (SmPC).

The safety profile of elinzanetant is based on data from women who received at least one dose of elinzanetant 120 mg:

- 1,113 treated women with VMS associated with menopause in 3 phase III (OASIS 1, OASIS 2, OASIS 3) and one phase II (SWITCH-1) clinical study and
- 465 treated women with VMS caused by AET in a separate phase III study (OASIS 4).

Table Part II SVII-1: Adverse reactions

System organ class	Frequency	VMS associated with menopause	VMS caused by AET
Psychiatric disorders	Common		Depression Depressive mood
Nervous system disorders	Common	Dizziness Headache Somnolence	Dizziness Somnolence Vertigo
Gastrointestinal disorders	Common	Abdominal pain Diarrhoea	Diarrhoea
Skin and subcutaneous tissue disorders	Common	Rash	Alopecia
Musculoskeletal and connective tissue disorders	Common	Muscle spasms	Muscle spasms
General disorders and administration site conditions	Very Common		Fatigue
	Common	Fatigue	

AET: Adjuvant Endocrine Therapy, VMS: Vasomotor Symptoms

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SVII.1.1.1 Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Table Part II SVII-2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
Nervous System Disorders	
Headache	Headache-related adverse events (AEs) were retrieved using the MedDRA Labelling Grouping (MLG) Headache. This MLG includes the Preferred Terms (PTs): Drug withdrawal headache, Exertional headache, Head discomfort, Headache, Hypnic headache, Medication overuse headache, New daily persistent headache, Primary headache associated with sexual activity, Primary stabbing headache, Sinus headache, Tension headache, and Vascular headache. The PTs Sinus headache and Tension headache were identified in the pooled data (week 1-52), and the PTs Headache, Tension headache and Head discomfort were identified in OASIS 4 (week 1-52). <u>Frequency/seriousness:</u> In the pooled data (week 1-52), headache treatment-emergent adverse events (TEAEs) were reported in 87 women (7.8%) on elinzanetant, compared to 38 women (5.0%) on placebo. Headache TEAEs were considered as study drug-related in 38 women (3.4%) on elinzanetant *vs.* 12 women (1.6%) on placebo. The majority of headache TEAEs in both treatment arms were of mild to moderate intensity and had resolved. In the elinzanetant arm, one TEAE in one woman (<0.1%) was of severe intensity and led to drug withdrawal. Overall, few TEAEs of headache led to discontinuation: 12 women (1.1%) on elinzanetant *vs.* 5 (0.7%) on placebo. In OASIS 4, (week 1-52), headache was reported in 59 women (12.7.0%, EAIR 16.58) on elinzanetant, compared to 22 women (13.9%, EAIR 65.43) on placebo. Overall, there were no treatment-emergent serious adverse events (TESAEs) of headache in women on elinzanetant or on placebo. <u>Clinical and benefit/risk impact:</u> Elinzanetant is a centrally acting drug. Considering its pharmacological mode of action, the use of elinzanetant may lead to headache. However, taking into account that all headache TEAEs in the elinzanetant arm were non-serious, most mild to moderate in intensity with few discontinuations, the risk of headache associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. Headache is adequately reflected as common ADR in the indication treatment of moderate to severe VMS associated with menopause in the SmPC.

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Table Part II SVII-2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
Dizziness	Dizziness-related AEs were retrieved using the MLG Dizziness. This MLG includes the PTs: Dizziness, Dizziness exertional, Dizziness postural, and Persistent postural-perceptual dizziness. The PT Dizziness was identified in both the pooled data (week 1-52) and in OASIS 4 (week 1-52). <u>Frequency/seriousness:</u> In the pooled data (week 1-52), dizziness TEAEs were reported in 32 women (2.9%) on elinzanetant compared to nine women (1.2%) on placebo. Dizziness TEAEs were considered as study drug-related in 19 women (1.7%) on elinzanetant *vs.* seven women (0.9%) on placebo. The majority of dizziness TEAEs in both treatment arms were of mild to moderate intensity and had resolved. In the elinzanetant arm, one TEAE in one woman (<0.1%) was of severe intensity and led to drug interruption. The same woman had a second TEAE of dizziness after nine days from the first, of moderate intensity and assessed as related to elinzanetant, which led do drug withdrawal. Overall, few TEAEs of dizziness led to discontinuation: five women (0.4%) on elinzanetant *vs*. three (0.4%) on placebo. In OASIS 4, (week 1-52), dizziness was reported in 20 women (4.3%) on einzanetant compared to two women (1.3%) in the placebo arm. Overall, there were no TESAEs of dizziness in women on elinzanetant or on placebo. <u>Driving ability study:</u> Bayer conducted a driving ability study to evaluate the effect of elinzanetant use on the ability of women to drive. No clinically relevant next-day residual effect on simulated driving performance after evening bedtime dosing of therapeutic and supratherapeutic doses of elinzanetant were identified. <u>Clinical and benefit/risk impact:</u> Elinzanetant is a centrally acting drug. Considering its pharmacological mode of action, the use of elinzanetant may lead to dizziness. However, taking into account that all dizziness TEAEs in the elinzanetant arm were non-serious, most mild to moderate in intensity with few discontinuations, the risk of dizziness associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. In addition, no clinically relevant impact on the ability to drive was identified in a dedicated driving study. Dizziness is adequately reflected as common ADR in the SmPC.

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Table Part II SVII-2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
Vertigo	Vertigo-related AEs were retrieved using the MLG Vertigo. This MLG includes the PTs: Vertigo, Vertigo CNS origin, Vertigo labyrinthine, and Vertigo positional. The PT Vertigo was identified in the OASIS 4 (week 1-52). Frequency/seriousness: In OASIS 4, (week 1-52), vertigo was reported in 10 women (2.2%, EAIR 2.59) on einzanetant compared to zero women in the placebo arm. Overall, there were no TESAEs of vertigo in women on elinzanetant. Driving ability study: Bayer conducted a driving ability study to evaluate the effect of elinzanetant use on the ability of women to drive. No clinically relevant next-day residual effect on simulated driving performance after evening bedtime dosing of therapeutic and supratherapeutic doses of elinzanetant were identified. Clinical and benefit/risk impact: Elinzanetant is a centrally acting drug. Considering its pharmacological mode of action, the use of elinzanetant may lead to vertigo. However, taking into account that all vertigo TEAEs in the elinzanetant arm were non-serious, most mild to moderate in intensity, with no discontinuations, the risk of vertigo associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. In addition, no clinically relevant impact on the ability to drive was identified in a dedicated driving study. Vertigo is adequately reflected as common ADR in the indication treatment of VMS caused by AET in the SmPC.
Somnolence	Somnolence related AEs were retrieved using the MLG Somnolence. This MLG includes the PTs Somnolence and Hypersomnia, both of which were identified in the pooled data (week 1-52), and in OASIS 4 (week 1-52). Frequency/seriousness: In the pooled data (week 1-52), somnolence TEAEs were reported in 28 (2.5%) women on elinzanetant and seven (0.9%) on placebo. It was considered study drug-related by the investigator in 25 women (2.2%). The majority of the events occurred during the first two weeks of treatment, were mild (20 women, 1.8%) or moderate (eight women, 0.7%) and resolved. The participants recovered in all but one case. In total, two (0.2%) TEAEs of somnolence led to discontinuation of elinzanetant. In OASIS 4, during the (week 1-52), somnolence was reported in 44 women (9.5%, EAIR 12.25) on einzanetant compared to six women (3.8%, EAIR 16.95) in the placebo arm. Overall, no serious TEAEs of somnolence were reported on elinzanetant or on placebo.

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Table Part II SVII-2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
	Sleepiness scale: A decrease in the sleepiness total score indicates an improvement in the degree of sleepiness. For the mean daily sleepiness total score, there was a similar numerical decrease from baseline over time in both treatment arms. Of the single item scores (morning score, afternoon score, and evening score), a more pronounced numerical decrease from baseline over time in the morning score was observed in the elinzanetant 120 mg arm compared to the placebo arm in OASIS 3. In the OASIS 4, a decrease in the sleepiness total score indicates an improvement in the degree of sleepiness. For mean daily sleepiness total score, there was a time-dependent decrease from baseline to Week 12 in both treatment arms. At Week 12, the numerical decrease was slightly larger in the elinzanetant 120 mg arm compared to the placebo-elinzanetant 120 mg arm. After Week 12, when the participants initially randomised to placebo had switched to elinzanetant 120 mg, numerical decrease in the daily sleepiness total score was observed until Week 26. The numerical decrease was comparable to that observed in the elinzanetant 120 mg arm at Week 26 and was maintained in both treatment arms until Week 50. Driving ability study: Bayer conducted a driving ability study to evaluate the effect of elinzanetant use on the ability of women to drive. No clinically relevant next-day residual effect on simulated driving performance after evening bedtime dosing of therapeutic and supratherapeutic doses of elinzanetant were identified. Clinical and benefit/risk impact: Elinzanetant is a centrally acting drug. Considering its pharmacological mode of action, the use of elinzanetant may lead to somnolence. Taking into account that all somnolence TEAEs in the elinzanetant arm were non-serious, mild to moderate in intensity with few discontinuations, and the population-based sleepiness score data, the risk of somnolence associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. In addition, no clinically relevant impact on the ability to drive was identified in a dedicated driving study. Somnolence is adequately reflected as a common ADR for both indications in the SmPC.
General disorders and administration site conditions	
Fatigue	Fatigue related AEs were retrieved using MLG Decreased general strength and energy. This MLG includes the PTs Asthenia, Decreased activity, Fatigue, Fatigue management, Mental fatigue, Physical deconditioning, and Sluggishness. Fatigue and Asthenia were identified in the pooled data (week 1-52), and the PTs Fatigue, Asthenia and Mental fatigue in OASIS 4 (week 1-52).

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ADVERSE REACTIONS	Justification for non-inclusion
	Frequency/seriousness: In the pooled data (week 1-52), fatigue was reported in 56 (5.0%) women on elinzanetant and 16 (2.1%) on placebo. 39 of the 56 TEAEs (3.9%) were considered study drug-related by the investigator. Events were either mild 36 (3.2%) or moderate 20 (1.8%) and recovered in the majority of the participants. Thirteen (13) (1.2%) women discontinued elinzanetant due to fatigue. In OASIS 4, (week 1-52), fatigue was reported in 66 women (14.2%, EAIR 19.01) on einzanetant compared to 10 women (6.3%, EAIR 28.47) in the placebo arm. Overall, no serious TEAEs of fatigue were reported on elinzanetant or on placebo. Driving ability study: Bayer conducted a driving ability study to evaluate the effect of elinzanetant use on the ability of women to drive. No clinically relevant next-day residual effect on simulated driving performance after evening bedtime dosing of therapeutic and supratherapeutic doses of elinzanetant were identified. Clinical and benefit/risk impact: Elinzanetant is a centrally acting drug. Considering its pharmacological mode of action, the use of elinzanetant may lead to fatigue. Taking into account that all fatigue TEAEs in the elinzanetant arm were non-serious, mild to moderate in intensity with few discontinuations, the risk of fatigue associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. In addition, no clinically relevant impact on the ability to drive was identified in a dedicated driving study. Fatigue is adequately reflected as common or very common (in OASIS 4) ADR in the SmPC for both indications.
Gastrointestinal Disorders	
Abdominal pain	Abdominal pain-related AEs were retrieved using the MLG Gastrointestinal and abdominal pains. This MLG includes the PTs: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, and Gastrointestinal pain. The PTs Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, and Gastrointestinal pain were identified in the pooled data (week 1-52). The PTs Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, and Gastrointestinal pain were identified in OASIS 4 (week 1-52). Frequency/seriousness: In the pooled data (week 1-52), abdominal pain TEAEs were reported in 37 women (3.3%) on elinzanetant compared to 11 women (1.5%) on placebo. Abdominal pain TEAEs were considered as study drug-related in

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ADVERSE REACTIONS	Justification for non-inclusion
	17 women (1.5%) on elinzanetant *vs*. three women (0.4%) on placebo. All abdominal pain TEAEs in the elinzanetant arm were of mild to moderate intensity and most of them had resolved. Two (2) TEAEs of abdominal pain assessed as of severe intensity were observed in the placebo arm. Overall, few TEAEs of abdominal pain led to discontinuation: Seven (7) women (0.6%) on elinzanetant *vs*. two (0.3%) on placebo. TESAEs were reported in one woman (<0.1%) on elinzanetant *vs*. zero on placebo. In this woman, the TESAE abdominal pain led to hospitalisation and resolved after two days. The event was of moderate intensity and assessed as unrelated to elinzanetant due to the presence of an alternative explanation. In OASIS 4, (week 1-52), abdominal pain was reported by 29 women (6.2%, EAIR 7.70) on einzanetant compared to 10 women (6.3%, EAIR 28.55) in the placebo arm. All events were non serious. <u>Clinical and benefit/risk impact:</u> Elinzanetant use may lead to abdominal pain. However, taking into account that all abdominal pain TEAEs in the elinzanetant arm were mild to moderate in intensity, most non-serious with few discontinuations, the risk of abdominal pain associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. Abdominal pain is adequately reflected as common ADR in the indication treatment of moderate to severe VMS associated with menopause in the SmPC.
Diarrhoea	Diarrhoea-related AEs were retrieved using the MLG Diarrhoea. This MLG includes the PTs: Antidiarrheal supportive care, Diarrhoea, Frequent bowel movements, Gastrointestinal stoma output increased, and Intestinal transit time decreased. The PTs Diarrhoea and Frequent bowel movements were identified in the pooled data (week 1-52), and the PTs Diarrhoea and Intestinal transit time decreased in OASIS 4 (week 1-52). <u>Frequency/seriousness:</u> In the pooled data (week 1-52), diarrhea TEAEs were reported in 35 women (3.1%) on elinzanetant and 15 (2.0%) on placebo. Diarrhea TEAEs were considered as study drug-related in 16 women (1.4%) on elinzanetant *vs*. five women (0.7%) on placebo. All diarrhoea TEAEs in the elinzanetant arm were of mild to moderate intensity and most of them had resolved. Overall, few TEAEs of diarrhoea led to discontinuation: four women (0.4%) on elinzanetant vs. two (0.3%) on placebo. In OASIS 4, (week 1-52), diarrhoea was reported by 33 women (7.1%, EAIR 8.90) on einzanetant compared to 3 women (1.9%, EAIR 8.32) in the placebo arm. Overall, no serious TEAEs of diarrhoea were reported on elinzanetant or on placebo.

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ADVERSE REACTIONS	Justification for non-inclusion
	Clinical and benefit/risk impact: Elinzanetant use may lead to diarrhoea. However, taking into account that all diarrhoea TEAEs in the elinzanetant arm were mild to moderate in intensity, all non-serious with few discontinuations, the risk of diarrhoea associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. Diarrhoea is adequately reflected as a common ADR in the SmPC for both indications.
Musculoskeletal and connective tissue disorders	
Muscle spasms	Muscle spasms-related AEs were retrieved using the MLG Increased muscle tone and cramping. This MLG includes the PTs: Cramp-fasciculation syndrome, Hypertonia, Muscle rigidity, Muscle spasms, Muscle tightness, Muscle twitching, Musculoskeletal stiffness, Myoclonus, and Paratonia. The PTs Muscle spasms, Muscle tightness and Musculoskeletal stiffness were identified in both the pooled data (week 1-52) and in OASIS 4 (week 1-52). Frequency/seriousness: In the pooled data (week 1-52), muscle spasms TEAEs were reported in 22 women (2.0%) on elinzanetant compared to five women (0.7%) on placebo. Muscle spasms TEAEs were considered as study drug-related in 11 women (1.0%) on elinzanetant *vs.* five woman (0.1%) on placebo. The majority of muscle spasms TEAEs in both treatment arms were of mild to moderate intensity and had resolved. In the elinzanetant arm, two TEAEs in two women (0.2%) were of severe intensity, one of them led to drug withdrawal. Overall, few TEAEs of muscle spasms led to discontinuation: theree women (0.3%) on elinzanetant *vs.* zero on placebo. In OASIS 4, (week 1-52), muscle spasm was reported by 24 women (5.2%, EAIR 6.37) on einzanetant compared to three women (1.9%, EAIR 8.25) in the placebo arm. Overall, there were no TESAEs of muscle spasms in women on elinzanetant or on placebo. Clinical and benefit/risk impact: Considering the findings of involuntary muscle contractions originated from animal studies and the afore-mentioned findings from clinical studies, the use of elinzanetant may lead to muscle spasms. However, taking into account that all muscle spasms TEAEs in the elinzanetant arm were non-serious, mild to moderate in intensity with few discontinuations, the risk of muscle spasms associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. Muscle spasms are adequately reflected as common ADR for both indications in the SmPC.

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Table Part II SVII-2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
Psychiatric disorders	
Depression	Depression-related AEs were retrieved using the MLG Depression. This MLG includes the PTs: Agitated depression, Childhood depression, Depression, Major depression, Menopausal depression, Perinatal depression, and Persistent depressive disorder. The PTs Agitated depression, Depression, Major depression were identified in the OASIS 4 (week 1-52). <u>Frequency/seriousness:</u> In the OASIS 4, (week 1-52), depression was reported by 29 women (6.2%, EAIR 7.77) on einzanetant compared to one woman (0.6%, EAIR 2.74) in the placebo arm. Overall, there were no TESAEs of depression in women on elinzanetant or on placebo. <u>Clinical and benefit/risk impact:</u> Considering the findings from clinical studies, the use of elinzanetant may lead to depression. However, taking into account that all depression TEAEs in the elinzanetant arm were non-serious, mostly mild to moderate in intensity (one event severe) with few discontinuations, the risk of depression associated with the use of elinzanetant is assessed as of limited clinical impact on women in relation to the severity of the indication treated. Depression is adequately reflected as common ADR in the indication treatment of VMS caused by AET use in the SmPC.
Depressive mood	Depressive mood-related AEs were retrieved using the MLG Depressive mood. Adjustment disorder with mixed anxiety and depressed mood, Anhedonia, Cabin fever, Crying, Depressed mood, Depressive symptom, Discouragement, Feeling guilty, Feeling of despair, This MLG includes the PTs: Adjustment disorder with depressed mood, Feeling of worthlessness, Mixed anxiety and depressive disorder, Morose, Negative thoughts, Seasonal affective disorder, Sense of foreshortened future, and Tearfulness. The PTs Depressed mood, Depressive symptom, and Mixed anxiety and depressive disorder were identified in the OASIS 4 (week 1-52). <u>Frequency/seriousness:</u> In the OASIS 4, (week 1-52), depressive mood was reported by 22 women (4.7%, EAIR 5.81) on einzanetant compared to two women (1.3%, EAIR 5.51) in the placebo arm. Overall, there were no TESAEs of depressive mood in women on elinzanetant or on placebo. <u>Clinical and benefit/risk impact:</u> Considering the findings from clinical studies, the use of elinzanetant may lead to depressive mood. However, taking into account that all depressive

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ADVERSE REACTIONS	Justification for non-inclusion
	mood TEAEs in the elinzanetant arm were non-serious, mostly mild to moderate in intensity (one event severe) with few discontinuations, the risk of depressive mood associated with the use of elinzanetant is assessed as of limited clinical impact on women in relation to the severity of the indication treated. Depressive mood is adequately reflected as common ADR in the indication treatment of VMS caused by AET use in the SmPC.
Skin and subcutaneous tissue disorders	
Alopecia	Alopecia related AEs were retrieved using the MLG Localized and generalized alopecia. This MLG includes the following PTs: Alopecia, Alopecia areata, Alopecia totalis. Alopecia universalis, Diffuse alopecia, Non-scarring alopecia, and Seborrhoeic alopecia. The PT Alopecia were identified in OASIS 4 (week 1-52). <u>Frequency/seriousness:</u> In the OASIS 4, (week 1-52), alopecia was reported by 15 women (3.2%, EAIR 3.90) on elinzanetant compared to 1 woman (0.6%, EAIR 2.74) the placebo arm. Overall, no serious TEAEs of alopecia were reported on elinzanetant or on placebo. <u>Clinical and benefit/risk impact:</u> The use of elinzanetant may lead to alopecia. Taking into account that all alopecia TEAEs in the elinzanetant arm were non-serious and mild to moderate in intensity with few discontinuations, the risk of alopecia associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. Alopecia is adequately reflected as common ADR in the indication treatment of VMS caused by AET in the SmPC.
Rash	Rash related AEs were retrieved using the MLG Rash. This MLG includes the following PTs: Butterfly rash, Drug eruption, Fixed eruption, Heliotrope rash, Mucocutaneous rash, Nodular rash, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash papular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash rubelliform, Rash scarlatiniform, Rash vesicular, and Symmetrical drug-related intertriginous and flexural exanthema. The PTs Rash, Rash maculo-papular, Rash papular, and Rash pruritic were identified in the pooled data (week 1-52), and the PTs Rash and Rash maculo-papular were identified in OASIS 4 (week 1-52). <u>Frequency/seriousness:</u> In the pooled data (week 1-52), rash was reported in 20 (1.8%) women on elinzanetant and 8 (1.1%) on placebo. 8 (0.7%) TEAEs were considered study drug-related by the investigator. Most of the TEAEs were mild

Table Part II SVII-2: List of adverse reactions and the justification for non-inclusion in the list of safety concerns in the RMP

ADVERSE REACTIONS	Justification for non-inclusion
	(17; 1.5%) or moderate (3; 0.3%) and recovered. Two (2) (0.2%) women discontinued elinzanetant due to rash. In OASIS 4, (week 1-52), rash was reported by nine women (1.9%) on elinzanetant compared to 2 women (1.3%) the placebo arm. Overall, no serious TEAEs of rash were reported on elinzanetant or on placebo. <u>Clinical and benefit/risk impact:</u> The use of elinzanetant may lead to rash. Taking into account that all rash TEAEs in the elinzanetant arm were non-serious and mild to moderate in intensity with few discontinuations, the risk of rash associated with the use of elinzanetant is assessed as of minimal clinical impact on women in relation to the severity of the indication treated. Rash is adequately reflected as common ADR in the indication treatment of moderate to severe VMS associated with menopause in the SmPC.

ADR: Adverse Drug Reaction; AE: Adverse Event; AET: Adjuvant Endocrine Therapy, CNS: Central Nervous System, EAIR: Exposure-Adjusted Incidence Rate; MedDRA: Medical Dictionary for Regulatory Activities; MLG: MedDRA Labelling Grouping; PT: Preferred Term; RMP: Risk Management Plan; SmPC: Summary of Product Characteristic; TEAE: Treatment-Emergent Adverse Event; TESAE: Treatment-Emergent Serious Adverse Event; VMS: Vasomotor Symptoms
Source: Report B002524 (Tables 1.4.4/1 to Table 1.4.4/5 and Table 1.4.4/7 to Table 1.4.4/11) and EU SmPC

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

There are no risks considered as important related to elinzanetant.

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

Not applicable

SVII.3.1 Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2 Presentation of the missing information

Long-term safety in the population of women using adjuvant endocrine therapy (AET) related to breast cancer

The use of elinzanetant for the treatment of VMS caused by AET, in women with, or at high risk for developing hormone-receptor positive breast cancer has been studied in the OASIS 4 study (21656). The length of use in this population, based on the currently available data, is limited to 52 weeks. Considering the characteristics of this population of women and the fact that the compound is new, inclusion of the “long-term safety” as missing information in the safety specification of Lynkuet is justified.

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No safety concerns are identified for elinzanetant.

Table Part II SVIII-1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety in the population of women using adjuvant endocrine therapy (AET) related to breast cancer

AET: Adjuvant Endocrine Therapy

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities will be conducted for elinzanetant as detailed in corresponding pharmacovigilance procedures that are in place at Bayer. These routine pharmacovigilance activities include:

- the collection, monitoring, evaluation, and expeditious reporting of individual cases,
- ongoing monitoring and evaluation of signals,
- preparation and submission of Periodic Benefit-Risk Evaluation Reports (PBRERs) /Periodic Safety Update Reports (PSURs).

There are no routine pharmacovigilance activities beyond the above-listed in place.

III.1.1 Specific adverse reaction follow-up questionnaires for safety concerns

Not applicable

III.1.2 Other forms of routine pharmacovigilance activities for safety concerns

Not applicable

III.2 Additional pharmacovigilance activities

Missing information: Long-term safety in the population of women using adjuvant endocrine therapy (AET) related to breast cancer

OASIS 4 (21656) is a double-blind, randomized, placebo-controlled multicentre study to investigate the efficacy and safety of elinzanetant for the treatment of vasomotor symptoms caused by AET, over 52 weeks and optionally for an additional two years in women with, or at high risk for developing, hormone-receptor positive breast cancer. The study has three parts:

- Part A covered the first 26 weeks. During Part A of the study, the women were treated with elinzanetant 120 mg for 26 weeks, or with placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks
- Part B covered the next 26 weeks. During Part B of the study, all women were treated with elinzanetant 120 mg for 26 weeks. Data of Part B provides additional efficacy assessments over time and further safety data

Part A + B of the OASIS 4 study (up to 52 weeks of treatment) have been completed.
The final clinical study report (CSR) of OASIS 4 Part A + B is provided in **Module 5.3.5.1, B003761 (OASIS 4)**.

- Part C: According to the 2nd Clinical study protocol amendment for the OASIS 4 study (dated 10 MAY 2023), an optional study participation extension of up to two years (Part C of the OASIS 4 study) is envisaged for the participants who finalized 52 weeks

study period (Part B of the OASIS 4 study). During this period, all women have the option to continue the treatment with Lynkuet until the product may be approved and be available for regular prescription.

A total of 395 participants have completed parts A and B of the OASIS 4 study, of which 262 have completed 52 weeks of treatment with elinzanetant, and approximately 90% have proceeded to part C of the study.

The collection of the AE data derived from OASIS 4 Part C is currently ongoing. Data from Part C will be reported separately, and any AE data will be included in the upcoming PSURs.

The collection of OASIS 4 Part C data is regarded as the corresponding additional pharmacovigilance activity (Category 3 Post Authorization Safety Study [PASS]) to sufficiently further characterize the missing information on ‘long-term safety’ regarding the indication ‘treatment of moderate to severe VMS caused by AET’.

III.3 Summary table of additional pharmacovigilance activities

Missing information: Long-term safety in the population of women using adjuvant endocrine therapy (AET) related to breast cancer

The collection of OASIS 4 Part C data is regarded as the corresponding additional pharmacovigilance activity (Category 3 PASS) to sufficiently further characterize the missing information on `long-term safety´ regarding the indication `treatment of moderate to severe VMS caused by AET´.

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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
OASIS 4 *Ongoing*	*To assess long-term safety, beyond 52 weeks of elinzanetant use, in women with moderate to severe VMS caused by adjuvant endocrine therapy (AET)´.*	*Long-term safety, beyond 52 weeks of elinzanetant use, in women with, moderate to severe VMS caused by adjuvant endocrine therapy (AET)´.*	*LPLV*	*Q4 2026*

AET: Adjuvant Endocrine Therapy; LPLV: Last Patient Last Visit, VMS: Vasomotor Symptoms

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies with elinzanetant are currently ongoing or planned.

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

Risk minimisation plan

No safety concerns have been identified for elinzanetant. Therefore, no specific risk minimisation plan is in place.

V.1 Routine risk minimisation measures

No important identified or potential risks are currently known for Lynkuet. All identified and potential risks are classified as non-important and are managed by the following routine risk minimisation measures:

- 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 so to ensure that the medicine is used correctly.
- The medicine's legal status-the medicine will be supplied to the patients via prescription only.

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

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

Table Part V-1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing information: Long term safety in the population of women using adjuvant endocrine therapy related to breast cancer	Routine risk communication in Product Information: *None* Other routine risk minimisation measures beyond the Product Information: Pack size: *The amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.* Legal status: *Prescription only.*

V.2 Additional risk minimisation measures

Not applicable, as no safety concerns have been identified for elinzanetant.

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

V.3 Summary of risk minimisation measures

Table Part V-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: Long-term safety in the population of women using adjuvant endocrine therapy related to breast cancer	Routine risk minimisation measures: *Routine risk communication in Product Information* *Pack size* *Legal status* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *PASS (Category 3)- Part C of the OASIS 4 study*

PASS: Post Authorization Safety Study

Part VI: Summary of the risk management plan

Summary of risk management plan for Lynkuet (elinzanetant)

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

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

This summary of the RMP for Lynkuet should be read in the context of the assessment report of the evaluation and its plain-language summary, which are part of the European Public Assessment Report (EPAR).

Important new concerns will be included in updates of Lynkuet's RMP.

I. The medicine and what it is used for

Lynkuet is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause or caused by AET related to breast cancer) (see EU-SmPC/PIL for the full prescribing information). It contains elinzanetant as the active substance and it is given orally once daily at bedtime as soft capsule.

Further information about the evaluation of Lynkuet's benefits can be found in Lynkuet's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

No important identified or potential risks are known for Lynkuet at this point in time.
All identified and potential risks are classified as non-important and are managed by the following *routine risk minimisation measures*:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- 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 medicine will be supplied to the patients via prescription only.

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

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

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EU Risk Management Plan
Part VI: Summary of the risk management plan

There is one missing information for Lynkuet: Long-term safety in the population of women using adjuvant endocrine therapy (AET). The collection of data from Part C of the Phase 3 study OASIS 4 is regarded as the corresponding additional pharmacovigilance activity (Category 3 PASS) to sufficiently further characterize the missing information on `long-term safety´ regarding the indication `treatment of moderate to severe VMS caused by AET, related to treatment of breast cancer.

II.A List of important risks and missing information

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

Table Part VI-1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety in the population of women using adjuvant endocrine therapy (AET) related to breast cancer

AET: Adjuvant Endocrine Therapy

II.B Summary of important risks

Table Part VI-2: Summary of important risks

Missing information: Long-term safety in the population of women using adjuvant endocrine therapy (AET) related to breast cancer	
Risk minimization measures	Routine risk minimisation measures: • Pack size • Legal status: Prescription only Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS (Category 3)- Part C of the OASIS 4 study

AET: Adjuvant Endocrine Therapy; PASS: Post Authorization Safety Study

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations of Lynkuet.

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

Missing information: Long-term safety in the population of women using adjuvant endocrine therapy (AET) related to breast cancer

OASIS 4 Part C will collect data up to 3 years of treatment in order to characterise the long-term safety in women treated with Lynkuet for moderate to severe VMS caused by AET related to breast cancer (Category 3 PASS).

Part VII: Annexes

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Annex 1 - EudraVigilance Interface

Available in electronic format only

LYNKUET®
(Elinzanetant)
EU Risk Management Plan
Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table Annex 2-1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
OASIS 4 Ongoing	To assess long-term safety, beyond 52 weeks of elinzanetant use, in women with moderate to severe VMS caused by AET related to breast cancer.	Long-term safety, beyond 52 weeks of elinzanetant use, in women with moderate to severe VMS caused by AET related to breast cancer.	LPLV	[redacted]

AET: Adjuvant Endocrine Therapy; LPLV: Last Patient Last Visit, VMS: Vasomotor Symptoms

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

Module 5.3.5.1 B003761 Appendix 10.1.1

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable

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

Not applicable

Annex 7 - Other supporting data (including referenced material)

Annex 7.1 - Literature references

Annex 7.1 - Literature references

1. El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). Menopause. 2019;26(10):1213-27.
2. Gold EB, Crawford SL, Shelton JF, Tepper PG, Crandall CJ, Greendale GA, et al. Longitudinal analysis of changes in weight and waist circumference in relation to incident vasomotor symptoms: the Study of Women's Health Across the Nation (SWAN). Menopause. 2017;24(1):9-26.
3. Thurston R, Bromberger J, Joffe H, Avis N, Hess R, Crandall C. Beyond frequency: who is most bothered by vasomotor symptoms? Menopause N Y N. 2008;15(5):841-7.
4. Nappi RE, Kroll R, Siddiqui E, Stoykova B, Rea C, Gemmen E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. Menopause. 2021;28(8):875-82.
5. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio I, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology. 2019;30(8):1194-220.
6. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers (Basel). 2021;13(17).
7. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in November 2023.
8. ECIS - European Cancer Information System. From https://ecis.jrc.ec.europa.eu, accessed on 20 March 2024 © European Union, 2024.
9. Cucciniello L, Garufi G, Di Rienzo R, Martinelli C, Pavone G, Giuliano M, et al. Estrogen deprivation effects of endocrine therapy in breast cancer patients: Incidence, management and outcome. Cancer Treat Rev. 2023;120:102624.
10. Cole KM, Clemons M, Alzahrani M, Liu M, Larocque G, MacDonald F, et al. Vasomotor symptoms in early breast cancer-a "real world" exploration of the patient experience. Support Care Cancer. 2022;30(5):4437-46.
11. Condorelli R, Vaz-Luis I. Managing side effects in adjuvant endocrine therapy for breast cancer. Expert Rev Anticancer Ther. 2018;18(11):1101-12.
12. U.S. Census Bureau 2020. 2020 Demographic Analysis Estimates. Accessed 20 March 2024.
13. Eurostat. Population and demography. Demography, population stock and balance database.

14. Ciano C, King TS, Wright RR, Perlis M, Sawyer AM. Longitudinal Study of Insomnia Symptoms Among Women During Perimenopause. J Obstet Gynecol Neonatal Nurs. 2017;46(6):804-13.

15. Chung HF, Zhu D, Dobson AJ, Kuh D, Gold EB, Crawford SL, et al. Age at menarche and risk of vasomotor menopausal symptoms: a pooled analysis of six studies. Bjog. 2021;128(3):603-13.

16. Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health. 2006;96(7):1226-35.

17. Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40-55 years of age. Am J Epidemiol. 2000;152(5):463-73.

18. Harrington LB, Blondon M, Cushman M, Kaunitz AM, Allison MA, Wang L, et al. Vasomotor symptoms and the risk of incident venous thrombosis in postmenopausal women. J Thromb Haemost. 2018;16(5):886-92.

19. Reed SD, Lampe JW, Qu C, Copeland WK, Gundersen G, Fuller S, et al. Premenopausal vasomotor symptoms in an ethnically diverse population. Menopause. 2014;21(2):153-8.

20. Tomida M, Otsuka R, Tange C, Nishita Y, Kimura T, Stoelzel M, et al. Vasomotor symptoms, sleep problems, and depressive symptoms in community-dwelling Japanese women. J Obstet Gynaecol Res. 2021;47(10):3677-90.

21. Peate M, Saunders C, Cohen P, Hickey M. Who is managing menopausal symptoms, sexual problems, mood and sleep disturbance after breast cancer and is it working? Findings from a large community-based survey of breast cancer survivors. Breast Cancer Research and Treatment. 2021;187:427-35.

22. Anderson DJ, Chung HF, Seib CA, Dobson AJ, Kuh D, Brunner EJ, et al. Obesity, smoking, and risk of vasomotor menopausal symptoms: a pooled analysis of eight cohort studies. Am J Obstet Gynecol. 2020;222(5):478.e1-.e17.

23. Rödström K, Weman L, Sundh V, Björkelund C. Perception of higher frequency of daily hot flashes in 50-year-old women today: a study of trends over time during 48 years in the Population Study of Women in Gothenburg, Sweden. Menopause. 2022;29(10):1124-9.

24. Freeman EW, Sammel MD, Grisso JA, Battistini M, Garcia-Espagna B, Hollander L. Hot flashes in the late reproductive years: risk factors for Africa American and Caucasian women. J Womens Health Gend Based Med. 2001;10(1):67-76.

25. Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S, Ferdousi T. The role of anxiety and hormonal changes in menopausal hot flashes. Menopause. 2005;12(3):258-66.

26. Gibson-Helm M, Teede H, Vincent A. Symptoms, health behavior and understanding of menopause therapy in women with premature menopause. Climacteric. 2014;17(6):666-73.

27. Khan F, Rojas K, Schlumbrecht M, Jeudin P. Oophorectomy in Premenopausal Patients with Estrogen Receptor-Positive Breast Cancer: New Insights into Long-Term Effects. Curr Oncol. 2023;30(2):1794-804.

28. Avis NE, Crawford SL, Green R. Vasomotor Symptoms Across the Menopause Transition: Differences Among Women. Obstet Gynecol Clin North Am. 2018;45(4):629-40.

29. Simpkins JW, Brown K, Bae S, Ratka A. Role of ethnicity in the expression of features of hot flashes. Maturitas. 2009;63(4):341-6.

30. Accortt EE, Bower JE, Stanton AL, Ganz PA. Depression and vasomotor symptoms in young breast cancer survivors: the mediating role of sleep disturbance. Arch Womens Ment Health. 2015;18(3):565-8.

31. Reeves KW, Pennell M, Foraker RE, Crandall CJ, Stefanick M, Paskett ED. Predictors of vasomotor symptoms among breast cancer survivors. J Cancer Surviv. 2018;12(3):379-87.

32. Neves ECM, Birkhauser M, Samsioe G, Lambrinoudaki I, Palacios S, Borrego RS, et al. EMAS position statement: The ten point guide to the integral management of menopausal health. Maturitas. 2015;81(1):88-92.

33. Company Core Data Sheet Cyclo-Progynova 2/250. (Estradiol valerate 2.0 mg, Estradiol valerate/Levonorgestrel 2.0 mg/0.25 mg) Coated tablets, Version 01, dated: 03 JUL 2020.

34. Saleh S, Ahmad G, Majumdar A. Group A streptococcus necrotising fasciitis from a levonorgestrel-containing intrauterine system ('Mirena' coil). J Obstet Gynaecol. 2011;31(2):192-4.

35. De Villiers T, Gass M, Haines C, Hall J, Lobo R, Pierroz D, et al. Global consensus statement on menopausal hormone therapy. Climacteric. 2013;16(2):203-4.

36. The 2023 nonhormone therapy position statement of The North American Menopause Society. Menopause. 2023;30(6):573-90.

37. Mintziori G, Lambrinoudaki I, Goulis DG, Ceausu I, Depypere H, Erel CT, et al. EMAS position statement: non-hormonal management of menopausal vasomotor symptoms. Maturitas. 2015;81(3):410-3.

38. Shams T, Firwana B, Habib F, Alshahrani A, Alnouh B, Murad MH, et al. SSRIs for hot flashes: a systematic review and meta-analysis of randomized trials. J Gen Intern Med. 2014;29(1):204-13.

39. Sobel JD, Funaro D, Kaplan EL. Recurrent group A streptococcal vulvovaginitis in adult women: family epidemiology. Clin Infect Dis. 2007;44(5):e43-5.

40. Lello S, Paris I, Cagnacci A, Sartori D, Caruso S, Iop A. Vasomotor symptoms and management of women undergoing treatment for breast cancer: literature review with focus on the therapeutic potential of cytoplasmic pollen extract. Gynecological Endocrinology. 2023;39(1):2162035.

41. Hoveyda HR, Fraser GL, Dutheuil G, El Bousmaqui M, Korac J, Lenoir F, et al. Optimization of Novel Antagonists to the Neurokinin-3 Receptor for the Treatment of Sex-Hormone Disorders (Part II). ACS Med Chem Lett. 2015;6(7):736-40.

42. Fraser GL, Hoveyda HR, Clarke IJ, Ramaswamy S, Plant TM, Rose C, et al. The NK3 Receptor Antagonist ESN364 Interrupts Pulsatile LH Secretion and Moderates Levels of Ovarian Hormones Throughout the Menstrual Cycle. Endocrinology. 2015;156(11):4214-25.

43. Fraser GL, Ramael S, Hoveyda HR, Gheyle L, Combalbert J. The NK3 Receptor Antagonist ESN364 Suppresses Sex Hormones in Men and Women. J Clin Endocrinol Metab. 2016;101(2):417-26.

44. Lethaby AE, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J. Phytoestrogens for vasomotor menopausal symptoms. Cochrane Database Syst Rev. 2007(4):CD001395.

45. NICE Menopause Guideline [Internet]. 2015. Available from: https://www.nice.org.uk/guidance/ng23/resources/menopause-diagnosis-andmanagement- pdf-1837330217413.

46. Ratner S, Ofri D. Menopause and hormone replacement: Part 1. Evaluation and treatment. West J Med. 2001;174(6):400-4.

47. Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. Obstetrics and Gynecology Clinics. 2011;38(3):489-501.

48. Pachman DR, Jones JM, Loprinzi CL. Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. Int J Womens Health. 2010;2:123-35.

49. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015;175(4):531-9.

50. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. Menopause. 2014;21(9):924-32.

51. World Health Organization Fact Sheet. Cardiovascular diseases. [Internet]. 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

52. Thurston RC, Aslanidou Vlachos HE, Derby CA, Jackson EA, Brooks MM, Matthews KA, et al. Menopausal vasomotor symptoms and risk of incident cardiovascular

disease events in SWAN. Journal of the American Heart Association. 2021;10(3):e017416.

53. Coulter SA. Epidemiology of cardiovascular disease in women: risk, advances, and alarms. Tex Heart Inst J. 2011;38(2):145-7.

54. Kanis J, Cooper C, Rizzoli R, Reginster J. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2019;30(1):3-44.

Annex 8 - Summary of changes to the risk management plan over time

Table Annex 8-1: Significant changes to the risk management plan over time

Version	Approval Date Procedure	Change
1.1	N/A	This is the first version submitted together with the initial MAA.
1.2	N/A	[redacted]
1.3	N/A	[redacted]

EMA: European Medicines Agency, EU RMP: European Union Risk Management Plan; MAA: Marketing Authorization Application; N/A: Not Applicable