18 September 2025
EMA/CHMP/299122/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynkuet

International non-proprietary name: Elinzanetant

Procedure No. EMEA/H/C/006298/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AET	Adjuvant endocrine therapy
BCS	Biopharmaceutics Classification System
BDI-II	Beck Depression Inventory
CEP	Certificate of Suitability of the EP
CQA	Critical Quality Attribute
DoE	Design of experiments
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EQ-5D-5L	European Quality of Life 5-dimension 5-level questionnaire
EZN	Elinzanetant
FDA	Food and Drug Administration
GC-HS	Headspace Gas Chromatography
GMP	Good Manufacturing Practice
HF	Hot Flash
HFDD	Hot Flash Daily Diary
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
ISI	Insomnia severity index
KF	Karl Fischer titration
MENQOL	Menopause Specific Quality of Life Scale
MO	Major Objection
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
PE	Polyethylene
PET	Polyethylene terephthalate
PCTFE	Polychlorotrifluoroethylene
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PROMIS SD SF 8b	Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b
PVC	Polyvinyl chloride

QbD	Quality by design
QTTP	Quality target product profile
RH	Relative Humidity
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
TEAE	treatment-emergent adverse event
US	United States
UV	Ultraviolet
VAS	Visual analog scale
VMS	Vasomotor symptoms
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer AG submitted on 11 October 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Lynkuet, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 February 2023.

The applicant applied for the following indication:

Lynkuet is indicated for the treatment of moderate to severe vasomotor symptoms (VMS):

- associated with menopause
- caused by adjuvant endocrine therapy

in women who are not candidates for hormone replacement therapy (HRT) (see section 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision(s) CW/1/2015 on the granting of a class waiver. Pursuant to Article 7(1) of Regulation (EC) No 1901/2006, the application additionally included an EMA Decision(s) on the granting of a product-specific waiver for elinzanetant (EMEA-003500-PIP01-23).

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request for consideration

1.5.1. New active Substance status

The applicant requested the active substance Elinzanetant contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
10 December 2020	EMEA/H/SA/4673/1/2020/III	*Rosalia Ruano Camps, Peter Mol*
15 December 2022	EMA/SA/0000110628	*Minne Casteels, Peter Mol*
30 March 2023	EMA/SA/0000126188	*Karri Penttila, Adriana Ammassari*
17 October 2024	EMA/SA/0000222856	*Andreas Kirisits, Mario Miguel Coelho da Silva Rosa*

The Scientific advice pertained to the following quality, non-clinical and clinical aspects:

- the rationale for starting material selection; the strategy to develop a titanium dioxide (TiO2)-free formulation
- the overall non-clinical study programme
- the clinical pharmacology programme, TQT study and dose selection
- the two proposed confirmatory Phase 3 studies including their primary and secondary endpoints, the proposed statistical analysis approach, the proposed selection and/or planned analysis of safety parameters and the safety database to support the MAA
- design of a discrete choice experiment with opt-out to elicit treatment preferences (treatment preference study) including definition and levels of benefit and risk attributes, study population, sample size, statistical analyses

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	11 October 2024
The procedure started on	31 October 2024
The CHMP Rapporteur's first Assessment Report was circulated to all	20 January 2025

CHMP and PRAC members on	
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 January 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 February 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 February 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 May 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	24 July 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	03 September 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lynkuet on	18 September 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	18 September 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Post-menopause, also called "menopause" in several guidelines, is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathologic or physiologic cause. It occurs at a median age of 51.4 years and is a reflection of complete, or near complete, ovarian follicular depletion, with resulting very low estradiol levels due to decreased ovarian function, and a resulting increase in gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus leading to high luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations (*Freeman et al. 2005*).

In menopause, VMS are one of the most common, debilitating and distressing symptoms (*Pachmann et al. 2010*) and the leading cause for seeking medical attention during this stage of a woman's life (*Whiteley et al. 2013, Williams et al. 2007*).

2.1.2. Epidemiology and risk factors

VMS are reported by up to 80% of women at some point during the menopausal transition and last for a median duration of 7.4 years (*El Khoudary et al. 2019*). The prevalence of VMS was found to differ between racial/ethnic groups, with Black or African American women reporting the highest number and longest duration of VMS, and Asian women having the lowest prevalence (*Gold et al. 2006, Avis et al 2015*). Other risk factors for VMS during menopause include higher BMI and smoking (*Koo et al. 2017, Anderson et al. 2020*).

2.1.3. Biologic features, aetiology and pathogenesis

The menopausal transition is the stage leading up to a woman's final menstrual period, usually beginning when women are in their mid-forties (*Roberts and Hickey 2016*). The menopausal transition is typically marked by irregular menstrual bleeding and ultimately amenorrhea. During the transition, ovarian function declines resulting in lower estrogen production. As estrogen secretion declines, a corresponding increase in follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels occurs due to increased gonadotrophin releasing hormone (GnRH) (*Davis et al. 2015*). Most women experience multiple symptoms associated with the menopausal transition that often extend into the postmenopausal stage.

2.1.4. Clinical presentation

VMS are transient (lasting between 1-5 minutes) episodes of flushing, perspiration, and intense heat sensation (*Bansal and Aggarwal 2019*). They are one of the most common, debilitating and distressing symptoms experienced by women during the menopausal transition (*Pachmann et al. 2010*) and are the leading cause for seeking medical attention during this particular phase of a woman's life (*Whiteley et al. 2013, Williams et al. 2007*). VMS can have a significant impact on the health-related quality of life of an individual, including impact on sleep and emotional well-being (*Fisher and Thurston 2016, Vigeta et al. 2012, Dare 2011, Nappi et al. 2023*).

2.1.5. Management

Hormone replacement therapy (HRT)

Hormone replacement therapy (HRT), also referred to as hormone therapy (HT) or menopausal hormone therapy (MHT), is currently the recommended first-line treatment for moderate to severe VMS associated with menopause according to international guidelines (*Neves-E-Castro et al. 2015, ACOG 2014, NAMS 2022, NICE 2019, Yuksel et al. 2021*). Estrogen-only preparations are given to postmenopausal women without a uterus. In women with a uterus, estrogen should be combined with a progestogen to protect the endometrium from development of hyperplasia and potential endometrial cancer *(Baber et al. 2016, de Villiers et al. 2016, Stuenkel et al. 2015, Yuksel et al. 2021*). The efficacy of HRT for the treatment of moderate to severe VMS has been demonstrated for multiple products, typically in placebo-controlled trials, and HRT has been considered the most effective treatment for VMS. HRT is also effective in preventing osteoporosis and genitourinary syndrome. The approved products offer a range of application forms and dosage strengths allowing for adjustment of treatment schemes for the individual woman (*Flores et al. 2021*).

The use of HRT decreased substantially after the publication of the WHI trial results in 2002 (*Rossouw et al. 2002*), where HRT was associated with adverse CV outcomes and increase in breast cancer incidence. The use of HRT decreased further in the EU after the publication of results regarding the increased risk of breast cancer observed in the UK Million Women study in 2003 (*Beral et al, 2003*). Further analysis of the results has shown that the demographic characteristics of the population included in the trial did not allow the generalization of the results, and the benefit-risk of HRT is favourable for healthy women with no contraindications to HRT, with less than 60 years of age and within 10 years after the last menstrual period.

Non-hormonal treatment

Up until recently, the only non-hormonal treatment option approved for the treatment of VMS in some EU countries and UK was *clonidine*, a centrally acting a2-adrenergic agonist. Other non-hormonal medications, such as selective *serotonin or serotonin and norepinephrine reuptake inhibitors (SSRIs/SNRIs)*, are included as alternative treatment options in international and European clinical guidelines (*Neves-E-Castro et al. 2015, British Menopause Society 2024, NICE 2019, ACOG 2014, NAMS 2022*) for management of VMS despite not being approved by European regulatory authorities, and thus being used off-label (*Mintziori et al. 2015*). Paroxetine (a SSRI) is only approved in the US for the treatment of VMS.

Since 2023, *fezolinetant*, an oral NK-3 only receptor antagonist has been approved for the treatment of moderate to severe VMS associated with menopause in Europe (EU, Switzerland, UK), USA, Australia and other countries. Fezolinetant has shown high efficacy for VMS treatment.

Phytoestrogen supplements have also been proposed as alternatives to HRT for the treatment of VMS. Phytoestrogens are found in soybeans (isoflavones), hops (Humulus lupulus), flaxseed (lignans), fruits, vegetables, whole grains and legumes. However, data on efficacy of these compounds are inconsistent and safety data are limited (*Chen et al. 2015, Lethaby et al. 2013*). None of these preparations has obtained regulatory approval for treatment of VMS.

Medical need

Despite its high efficacy, the majority of women seeking treatment for menopausal symptoms is not treated with HRT (*Biglia et al. 2019*), with a recent survey showing that 83% of women in Europe experiencing menopausal symptoms had never received HRT (*Nappi et al. 2021*). Non-candidates for HRT include women with medical contraindications (e.g. breast cancer, venous thromboembolism, coronary heart disease, stroke, transient ischemic attack), women who experienced tolerability issues with HRT and women who are not interested in considering HRT (*Manson et al. 2015*).

2.2. About the product

Mode of action/ development rationale

Menopause is characterized by decreased estradiol levels due to decreased ovarian function, and a resulting increase in gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus leading to high luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations (*Freeman et al. 2005*). A group of sex steroid-responsive neurons has been characterized as important upstream regulators of GnRH. These are localized in the hypothalamic infundibular (arcuate) nucleus and co-express kisspeptin, neurokinin B, as well as dynorphin, being known as kisspeptin/NKB/dynorphin neurons or KNDy neurons (*Navarro et al. 2009, Navarro et al. 2015, Rance et al. 2009*). KNDy neurons express, besides other neuromodulator ligands/receptors, substance P/NK-1 and NKB/NK-3 (*Rance et al. 2013, Navarro et al. 2015, Hrabovszky et al. 2013*). Morphologic studies indicate that KNDy neurons from postmenopausal women are hypertrophied and this hypertrophy is accompanied by elevated gene expression, including NKB, kisspeptin and substance P gene expression.

The development of elinzanetant was based on the rationale that VMS associated with menopause are caused by overactivity of the kisspeptin/neurokinin B (NKB)/dynorphin (KNDy) neurons in the hypothalamus. Elinzanetant is a selective, non-hormonal neurokinin 1 (NK-1) and 3 (NK-3) specific receptors antagonist that blocks increased NK-1 and NK-3 receptor signalling on KNDy neurons to modulate neuronal activity involved in thermo- and sleep regulation. This results in an improvement of menopausal symptoms including VMS, sleep disturbances and menopause related quality of life.

NK-3 and vasomotor symptoms:

KNDy neurons in the hypothalamus have been identified as playing a role in thermoregulation that is responsive to both estrogen and ambient temperature (*Rance et al. 2013*). In the menopausal state (in natural menopause or caused by medical intervention) the KNDy neurons are in a state of hyperactivation, which disrupts baseline thermoregulation and triggers VMS. The oral NK-3 receptor specific antagonist fezolinetant has been approved for treatment of moderate to severe VMS associated with menopause in 2023 by centralized procedure.

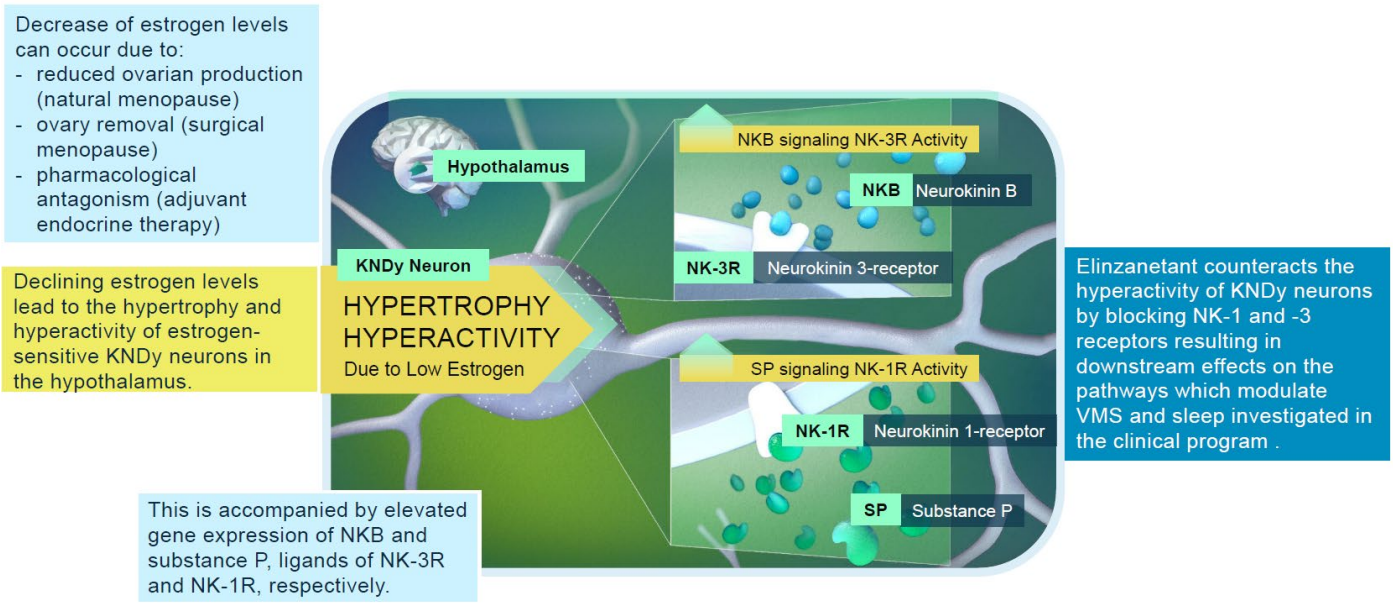
NK-1 and vasomotor symptoms:

It is hypothesized that the dual specificity of elinzanetant, thus antagonizing NK-1 and NK-3 receptors, has beneficial effects on the treatment of menopausal symptoms. As substance P immunoreactive fibers have been demonstrated in the hypothalamus of postmenopausal women (*Borsay et al. 2014*), SP and NK-1 receptors may additionally have a role in peripheral vasodilatation (*Wong and Minson 2006*).

NK-1 and sleep disturbances:

VMS during the night affect sleep quantity and quality but there is evidence of sleep disturbances experienced during menopause that are independent of VMS (*Woods et al. 2016*). It is hypothesized that additional biological mechanisms beyond reduced estrogen receptor signalling and night-time awakening due to VMS may contribute to sleep disturbances during the menopausal period.

Figure 1 Etiology of menopause and VMS and mechanism of action



2.3. Type of Application and aspects on development

The overall clinical development program of the VMS indications consists of 24 clinical pharmacology studies, 2 Phase 2 studies, and 4 Phase 3 studies.

Three Phase 3 studies, OASIS 1, 2, and 3, in postmenopausal women have been performed to investigate the efficacy and safety of elinzanetant 120 mg for the "*treatment of moderate to severe VMS associated with menopause*".

OASIS 1 and OASIS 2 are the pivotal efficacy studies for the proposed indication moderate to severe VMS associated with menopause. Both studies are randomized, placebo-controlled, 12-week double-blind studies, followed by a 14-week treatment extension period for up to 26 weeks where placebo group switched to elinzanetant 120 mg.

OASIS 3 provides additional efficacy and safety data. This is a is a randomized, double-blind, placebo-controlled safety and efficacy study with a duration of 52 weeks.

OASIS 4 is pivotal for the indication "*moderate to severe vasomotor symptoms (VMS) caused by adjuvant endocrine therapy (AET) related to breast cancer"*. Part A (Week 1 to 26 of the study) and Part B of OASIS 4 (Week 27 to 52 of the study) have been completed presenting the final data on the primary and key secondary endpoints, while Part C (optional, 2 further years) is currently ongoing.

The EMA scientific advice has been generally followed by the applicant.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as soft capsules containing 60 mg of elinzanetant.

Other ingredients are:

Capsule filing:

all-rac-α-tocopherol (E 307), caprylocaproyl macrogolglycerides, glycerol monocaprylocaprate, glycerol mono-oleate (E 471), polysorbate 80 (E 433).

Capsule shell:

gelatin, sorbitol liquid partially dehydrated (E 420) - glycerol (E 422) blend, iron oxide red (E 172), iron oxide yellow (E 172), medium-chain triglycerides, phosphatidyl choline solution 53% in medium-chain triglycerides, titanium dioxide (E 171).

Printing ink:

macrogol 400 (E 1521), polyvinyl acetate phthalate, propylene glycol (E 1520), titanium dioxide (E 171).

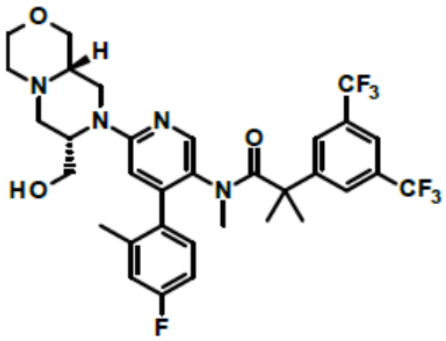
The product is available in a PVC/PCTFE-Aluminium/PET/paper blister containing 12 soft capsules (6 × 2 as unit dose), as described in section 6.5 of the SmPC. The agreed pack sizes are 24, 60 or 180 soft capsules.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of elinzanetant is 2-[3,5-bis(trifluoromethyl)phenyl]-N-{4-(4-fluoro-2-methylphenyl)-6-[(7S,9aS)-7-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl]pyridin-3-yl}-N,2-dimethylpropanamide corresponding to the molecular formula $C_{33}H_{35}F_7N_4O_3$. It has a relative molecular mass of 668.7 g/mol and the following structure:

Figure 2 Active substance structure



The chemical structure of elinzanetant was elucidated by a combination of IR, UV, Raman spectroscopy, 1H-NMR & 13C-NMR, MS, & elemental analysis. The solid-state properties of the active substance were measured by XRPD.

The active substance is a white to off-white to yellowish solid, and it is slightly hygroscopic. It is practically insoluble in aqueous media; however, at low pH conditions (pH 1) the active substance becomes slightly soluble. The active substance is considered to be BCS class II.

Elinzanetant exhibits stereoisomerism due to the presence of two chiral centres. The active substance is present in the 7S and 9aS configuration. The chiral centres originate in one of the proposed starting materials. Chiral purity is controlled in the specification of the relevant starting material and in the specification of the active substance.

One polymorphic form has been observed for elinzanetant (crystalline form I) along with an amorphous form. The active substance produced is the crystalline form I. It is dissolved during the finished product manufacturing process and therefore the polymorphic form does not impact the performance of the finished product.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at one manufacturing site. Satisfactory information concerning GMP has been provided.

Elinzanetant is synthesised in five main steps using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis and critical steps have been adequately defined. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The route of synthesis is the same between the commercial and pivotal clinical batches. Process optimisations introduced for the commercial manufacturing process have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of Quality by design (QbD) such as risk assessment and design of experiment (DoE) studies. Based on these studies, design spaces have been proposed for each of the five main manufacturing process steps of the active substance. The design spaces have been shown to be scale independent and information at laboratory scale and production scale experimentation was used to demonstrate this, the design spaces are therefore considered verified for the intended commercial process. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

The active substance is packaged in a clear PE bag which complies with Commission Regulation (EU) 10/2011, as amended. The bag is then placed into a secondary container such as a drum.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), water (KF), residual solvents (GC-HS), impurities (HPLC), chiral impurities (chiral HPLC) assay (HPLC).

Impurities are controlled according to ICH Q3A and no impurities are present above the relevant qualification threshold.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data which includes six commercial scale batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three pilot scale batches of the active substance from the clinical manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Stability data from three commercial scale batches from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Supportive stability data from clinical trial batches stored for up to 48 months at the long term and accelerated conditions were also provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions of thermal, oxidative, and hydrolytic stress were also provided on one batch.

The parameters tested are the same as for release, with the addition of tests for identity (XRPD) and microbiological quality (Ph. Eur.). The analytical methods used were suitable for the intended purpose and were stability indicating.

At long term and accelerated conditions, all tested parameters were within the specifications and no trends were observed. The active substance is sensitive to light and an out of specification result for the assay test was observed during photostability results.

The active substance showed degradation under the thermal and oxidative stress testing conditions chosen with decreases in assay values and consequent increases in impurity values observed. No significant degradation was observed under the hydrolytic stress conditions.

With respect to ongoing studies any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months with the instruction of protect from light in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a soft capsule containing 60 mg of elinzanetant. It is an opaque red oblong soft capsule which is approximately 24 mm long and 11 mm in diameter, with white printing of "EZN60".

The objective of formulation development was to provide a safe and efficacious oral solid formulation containing elinzanetant with immediate release properties. The intended Quality Target Product Profile (QTPP) was provided as outlined in Table 1.

Table 1 Summary of Quality Target Product Profile (QTPP)

QTPP-Element	Target
Intended use in clinical setting	Non-hormonal treatment of moderate to severe vasomotor symptoms associated with menopause
Route of administration	Oral
Dosage form	Immediate release solid oral dosage form
Dose regimen	Once daily 120 mg (free base equivalents)
Unit dose strength	Suitable for administration as not more than 2 units per dose
Shape and size	Easy to handle and to swallow by the patient
Appearance	Differentiation from other commercial products to avoid medication errors
Identity	Positive for Elinzanetant
Uniformity of dosage units	According to Ph. Eur., USP
Dissolution	Meets immediate release profile, controlled by stage testing according to Ph. Eur., USP
Degradation products	Meets ICH criteria
Assay	Meets ICH criteria
Microbiological purity	According to Ph. Eur., USP
Intended markets	Global
Shelf life (Climatic zones I – IVb)	Not less than 24 months
Primary packaging materials	Suitable protection to achieve target shelf-life and maintain dosage form integrity during shipping and transportation

From the QTPP a number of relevant critical quality attributes (CQAs) were identified. These encompassed the following attributes: appearance, identity, uniformity of dosage units, dissolution, degradation products, assay and microbiological limits.

The active substance is practically insoluble in aqueous media over a wide pH range, only in acidic conditions (pH 1) is the active substance slightly soluble. The active substance has improved solubility in organic solvent systems and is freely soluble in a number of organic solvents such as ethanol and polyethylene glycol 400. The active substance is considered to be BCS class II. During the manufacture of the finished product the active substance is fully dissolved in the liquid fill mass for the capsules and the solid state properties of the active substance therefore do not impact the finished product.

All excipients are well known pharmaceutical ingredients and where relevant their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. A sensitivity to oxidation was observed for the active substance in the liquid fill medium for the capsules, and as a result of this an antioxidant was required. The applicant tested a number of potential antioxidants, and the proposed all-rac-α-tocopherol was identified as appropriate for further development to determine the optimal concentration. A number of potential concentrations were tested, and an optimal concentration was then defined in line with the EMA note for guidance on inclusion of antioxidants and antimicrobial preservatives in medicinal products.

The manufacturing process development has been described. The process has been subject to scale-up during the clinical program. The information gained was used to inform the proposed commercial process parameters and in-process controls.

During early development the applicant investigated potential suspension formulations, tablet formulations, and hard gelatin capsule formulations. These formulations resulted in high pharmacokinetic variability and therefore a soft capsule formulation was selected for further clinical development. Differing strengths of soft capsules were tested during clinical development, and the proposed commercial 60 mg soft capsule formulation is the same as was used in the phase 3 clinical programme.

The discriminatory power of the dissolution was initially not considered acceptable and further information was requested during assessment. A major objection (MO) was raised on this aspect, requesting the applicant to justify the selection of the method and the discriminatory power. To resolve this the applicant sufficiently justified the selected parameters for the dissolution method including the concentration of surfactant used and the stirring speed. The applicant also justified that the method was suitably discriminatory and provided data showing the method can discriminate specific quantitative differences in the formulation.

The primary packaging is PVC/PCTFE-Aluminium/PET/paper blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory information with respect to GMP aspects has been provided.

The manufacturing process consists of six main steps: melting, mixing, preparation of shell mass, encapsulation, drying and packaging. The process is considered to be a standard manufacturing process.

The description of the manufacturing process is acceptable, and relevant information has been provided concerning process parameters and in-process controls. The proposed bulk hold time is suitably justified by relevant stability data.

As the process is considered standard, the applicant has presented a prospective process validation scheme outlining the validation to be conducted on the commercial scale batches. This is acceptable. The in-process controls are adequate for this type of manufacturing process & pharmaceutical form.

2.4.3.3. Product specification

The finished product release & shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identity (HPLC, UV), uniformity of dosage unites (Ph. Eur.), dissolution (HPLC), degradation products (HPLC), assay (HPLC), microbiological quality (Ph. Eur.).

The applicant's initial proposal for the dissolution limit to be applied during quality control testing was not accepted because the limit had not been sufficiently set in line with the dissolution performance of the clinical batches. As the applicant had not sufficiently justified their approach, an MO was raised requesting the applicant to tighten the limit in line with the results of the clinical batches. To resolve the MO the applicant suitably tightened the dissolution limit in line with the request.

Degradation products which are present at levels above the ICH Q3B qualification threshold have been appropriately qualified based on toxicological studies.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The risk assessment provided by the applicant concerning potential nitrosamine impurities was initially not considered acceptable as not all relevant risk factors had been considered. The applicant had not sufficiently ruled out the presence of nitrosamine impurity formation based on theoretical considerations and as a result confirmatory testing was requested in order to demonstrate the absence of potential nitrosamine impurities. An MO was raised requesting this testing data, and in response the applicant provided confirmatory testing data for a number of potential nitrosamine impurities including those which could be derived from the active substance. The data which included aged-finished product batches demonstrate that the potential nitrosamine impurities in question are not present and all results were below 10% of their respective acceptable intakes. The response however did not fully account for all potential nitrosamine impurities. The applicant was therefore requested by way of a further MO to extensively discuss the potential for the formation of nitrosamines from certain secondary amines present in the active substance that had not been sufficiently discussed in their risk assessment. The applicant updated their risk assessment and provided information concerning the outstanding potential nitrosamine impurities. This included the results of screening conditions attempting to form corresponding nitrosamines from the specific secondary amines. No further potential nitrosamine impurities were identified and the information provided confirms that the applicant has sufficiently investigated the potential formation of nitrosamine impurities. In line with the updated nitrosamine risk assessment, it was agreed that there is no risk of nitrosamine impurities in the finished product and therefore no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results for a number of batches manufactured throughout the clinical development program were provided, including three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 30 months under long term conditions (25 ºC / 60% RH), 30 months under intermediate conditions (30 ºC / 65% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition, stability data from production scale batches stored for up to 12 months under long term and intermediate conditions as well as for up to six months under accelerated conditions were also provided.

Samples were tested in line with the shelf-life specification in Table 6 with an additional test for the assay of antioxidant (HPLC). The analytical procedures used are stability indicating. During the stability studies, increases in degradation products and decreases in assay values were observed over time at all the tested conditions, however the product remained within specification. The changes observed were therefore not regarded as significant.

With respect to ongoing stability programs, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not considered photosensitive.

Based on available stability data, the proposed shelf-life of 30 months and storage conditions 'This medicinal product does not require any special temperature storage conditions. Store in the original blister in order to protect from moisture' as stated in the SmPC (section 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. A valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the active substance. The design spaces have been adequately established and verified.

During the procedure three major objections concerning quality were raised, these related to the development of the method for dissolution testing of the finished product, the risk assessment for

nitrosamine impurities, and the limit proposed for dissolution testing for the finished product. To resolve the MO concerning the development of the dissolution method for the finished product the applicant provided information justifying the selected parameters for the method and demonstrated that the method was suitably discriminatory. The MO on nitrosamine impurities was resolved by the provision of testing data demonstrating that no nitrosamine impurities are present, the methods used were suitably sensitive relative to the acceptable intakes for the impurities. The applicant also updated their risk assessment to account for all potential nitrosamine impurities and the information provided confirms there is no risk of nitrosamine impurity formation in the finished product. To resolve the MO on the dissolution limit for the finished product the applicant suitably tightened this proposed limit in line with the dissolution profiles observed for the clinical batches.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

A comprehensive non-clinical program including pharmacology and safety pharmacology studies, pharmacokinetic as well as toxicology studies was conducted to characterize the efficacy and safety profile of elinzanetant and its principle human metabolites according to current testing guideline standards and regulatory requirements for the long-term use of elinzanetant.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The suggested mechanism of action of elinzanetant involves antagonism of both NK-1 and NK-3 receptors. Several *in vitro* studies have been performed to support this MoA.

Elinzanetant's affinity for the NK-1 receptor was studied using competitive binding assays using either overexpression (human and baboon) as well as endogenous expression in brain tissue (gerbil, guinea pig, rat). For all species except rat, affinities were very high (pK_i 9.9-10.2). Affinity for rat NK-1 receptor was

lower than for the other four species (pK_i 8.4). Elinzanetant's affinity for NK-3 receptor was lower than for NK-1 receptor for human, gerbil and guinea pig (pK_i 7.5-8.0).

These findings were confirmed in another competitive binding assay, where only native tissue was used from human, gerbil and guinea pig. Although lower than reported above, affinities were high and comparable for NK-1 receptor from all three species (pK_i 8.7-9.0) and were lower for gerbil and guinea pig NK-3 receptor (pK_i 7.8-8.2).

A third competitive binding assay using overexpressed human NK-1 and NK-3 receptors confirmed high affinity of elinzanetant for NK-1 receptor (pK_i 9.6), with lower affinity observed for NK-3 receptor (pK_i 8.7).

A fourth competitive binding assay using overexpressed human NK-1, NK-2 and NK-3 receptors revealed high affinities for NK-1 and NK-3 receptor (pK_i 8.7-9.3), with clearly lower affinity reported for NK-2 receptor (pK_i 6.0).

The type of binding of elinzanetant was investigated in a saturation binding study using overexpressed human NK-1 receptor where K_d and maximal binding (B_{max}) of the NK-1 receptor agonist [^{3}H]-substance P were determined in the presence of increasing amounts of elinzanetant. A statistically significant decrease B_{max} was observed, whereas K_d remained unchanged upon addition of elinzanetant. Therefore, elinzanetant binding to human NK-1 receptor is insurmountable.

Several functional assays confirmed the antagonistic properties of elinzanetant, where the substance showed insurmountable antagonistic properties for the human NK-1 and human and marmoset and guinea pig NK-3 receptors.

Several relevant metabolites of elinzanetant have been identified. These include M18/21, M22 (possible degradation product), M27 and M30/34. A series of binding assays and functional assays revealed that all four showed affinities and activities for human NK-1 and NK-3 receptors similar to elinzanetant.

Ex vivo autoradiography studies on brain tissue were aimed at determining receptor occupancy and receptor binding.

In studies with elinzanetant administered orally, brain slice autoradiography revealed that elinzanetant enters the CNS of male Mongolian gerbils, where it binds to NK-1 and NK-3 receptors depending on the dose and concentration.

Brain slice autoradiography of male guinea pigs dosed intraperitoneally with different doses of elinzanetant revealed dose dependent increases of NK-1 receptor occupancy. The presence of haloperidol did not affect the receptor occupancy of NK-1 receptor, with values of 97 and 99% (+haloperidol) for the 30 mg/kg dose and 99 and 98% (+haloperidol) for the 100 mg/kg dose. Receptor occupancies of NK-3 receptor were 37 and 74% (+haloperidol) for the 30 mg/kg dose and 78 and 85% (+haloperidol) for the 100 mg/kg dose. There was a statistically significant difference for haloperidol presence for the 30 mg/kg dose for NK-3 receptor, however the difference was not statistically significant for the 100 mg/kg dose. The blood concentrations of elinzanetant 1.5 h post-dose for 30 and 100 mg/kg were 40 and 191 mg/mL, and in the presence of haloperidol were 77 and 181 ng/mL, respectively. The brain concentrations of elinzanetant for 30 and 100 mg/kg were 97 and 378 mg/g, and in the presence of haloperidol were 177 and 269 ng/g, respectively.

The affinity of elinzanetant for human NK-1 receptor was determined using autoradiography of human putamen slices from one human donor. A competition binding assay using a known NK-1 receptor antagonist revealed an elinzanetant pK_i of 9.44.

In summary, the mechanism of action of elinzanetant has been sufficiently described. Elinzanetant is shown to act as an insurmountable antagonist with high affinity for NK-1 and NK-3 receptors, with a preference for the NK-1 receptor. Upon oral or intraperitoneal dosing, elinzanetant was shown to enter the CNS and result in NK-1 and NK-3 receptor binding, with the highest receptor occupancies observed for the NK-1 receptor.

Several *in vivo* studies have been performed to investigate the effect of elinzanetant on pharmacodynamic effects of NK-1 and NK-3 receptor agonists.

In a Mongolian gerbil foot tapping model, elinzanetant at intracerebroventricular doses of 1, 3 and 10 mg/kg reduced GR-73632 (NK-1 receptor agonist) induced foot tapping, a behaviour associated with NK-1 receptor agonists. Elinzanetant decreased the foot tapping behaviour dose dependently, with statistically significant differences to vehicle treated controls for all three dose levels. Elinzanetant blood concentrations 1 h post dose were 6.4, 22 and 87 ng/mL for the 1, 3 and 10 mg/kg dose levels. Corresponding brain concentrations were <15, 35 and 126 ng/g.

In a follow-up study, Mongolian gerbils were dosed with 10 mg/kg elinzanetant and were dosed with GR-73632 (NK-1 receptor agonist) at 1, 24, 48 or 72 h post-dose and assessed for foot tapping behaviour. Animals that did not receive GR73632 were assessed for *ex vivo* striatal NK-1 and cortical NK-3 receptor occupancy at the same timepoints. Foot tapping was inhibited completely up to 24 hours post dosing and was inhibited by 90% at 48 hours after dosing. By 72 hours after dosing, inhibition had decreased to 31%. The corresponding blood concentrations were 287 ng/mL (1 hour), <8.2 ng/mL (24 hours), and <5 ng/mL (48 and 72 hours). Corresponding brain concentrations were 393 ng/g (1 hour), 8.4 ng/g (24 hours) and <3 ng/g (48 and 72 hours). Receptor occupancies for the NK-1 receptor were 94.1% (1 hour), 91.5% (24 hours), 72.3% (48 hours), and 42.3% (72 hours). For the NK-3 receptor, occupancies were 89.9% (1 hour), 39.1% (24 hours), 0.7% (48 hours), and 1.0% (72 hours). This study demonstrates a close correlation between NK-1 receptor occupancy and reduction of foot tapping behaviour, demonstrating that elinzanetant acts as a potent antagonist of the NK-1 receptor in Mongolian gerbils.

In a guinea pig study, injections of elinzanetant inhibited wet dog shake behaviour, which is associated with NK-3 receptor agonism. Guinea pigs were administered 2.6, 8.5 or 25.5 mg/kg elinzanetant intraperitoneally, followed by intracranioventricular administration of senktide (NK-3 receptor agonist) 1-hour post-dose. Blood and brain concentrations of elinzanetant were determined after a 30-minute observation for wet dog shaking. Statistically significant reductions in wet dog shaking were observed for the 8.5 and 25.5 mg/kg dose levels. The observed concentrations in blood were 17, 27 and 91 ng/mL for the low, mid and high dose, respectively. Corresponding brain concentrations were 12, 28 and 92 ng/g. Associated receptor occupancies were not investigated. These observations demonstrate that elinzanetant acts as a NK-3 receptor antagonist in guinea pigs.

In a guinea pig microdialysis model using aimed at investigating monoaminergic transmission in the mammalian brain, elinzanetant (dosed intraperitoneally at 3, 10 or 30 mg/kg) was shown to induce statistically significant increases in the medial prefrontal cortex levels of noradrenaline at the 10 and 30 mg/kg dose levels, as well as the levels of 5-HT at the 10 mg/kg dose level. Levels of dopamine were not changed for any of the dose levels. In the dorsal hippocampus, levels of noradrenaline were increased at the low and high dose (not at the mid dose), and no changes were observed for 5-HT, although a trend might have been present. Together, elinzanetant has been shown to affect noradrenaline and 5-HT transmission in the forebrain structure of guinea pigs.

A subsequent study with microdialysed guinea pigs was designed to investigate the effects of elinzanetant on the dopamine efflux in the nucleus accumbens after haloperidol or amphetamine administration.

Administration of elinzanetant alone did not result in increases in dopamine efflux, whereas amphetamine and haloperidol resulted in statistically significant increases in dopamine efflux. Pre-treatment with elinzanetant at 10, 30 or 100 mg/kg resulted in similar dopamine efflux as haloperidol or amphetamine alone, indicating the elinzanetant did not modulate basal or stimulated dopamine efflux in guinea pigs.

NK-1 receptor occupancy in two baboons was investigated using positron emission tomography (PET) with a known NK-1 receptor selective radioligand. After performing a baseline scan, intravenous infusion of elinzanetant at 0.01, 0.1 and 2 mg/kg for 60 minutes resulted in a dose dependent decrease in signal for the radioligand across all brain structures. The resulting elinzanetant ED_{50} (dose associated with 50% receptor occupancies) was estimated at 0.21 mg/kg, and the EC_{50} (plasma concentration associated with 50% receptor occupancy) was estimated at 9.93 ng/mL. No data are available for NK-3 receptor occupancy due to lack of a suitable radioligand.

In summary, the Applicant has provided studies in several species that support the mechanism of action *in vivo* for elinzanetant, as it has been shown that elinzanetant acts as an antagonist of both NK-1 and NK-3 receptors.

2.5.2.2. Secondary pharmacodynamic studies

In a selectivity screen for 29 receptor binding and 9 enzyme assays, elinzanetant at 1 µM (~0.67 µg/mL) showed no inhibition >16% for receptor binding or >4% for enzymatic assays, indicating no relevant effects for any of these receptors or enzymes.

A second screen using concentration curves of elinzanetant in a panel of 44 molecular target assays including functional and binding assays was performed. There were no targets with an IC_{50} <1 µM. In another radioligand binding assay, K_i values for estrogen receptor and progesterone receptor were 6.4 µM and 0.51 µM, respectively. The IC_{50} for the progesterone receptor coactivator was >30 µM.

Also, no relevant stimulation or inhibition of either monoamine oxidase (MAO-A), dopamine D1 or opiate d1 receptors was observed for elinzanetant concentrations >10 µM.

In human volunteers receiving multiple doses, the highest reported C_{max} was 3520 ng/mL. Since plasma protein binding in humans is reported at 99.7%, the corresponding free fraction of 0.3% is ~10.6 ng/mL (~0.016 µM). This leads to at least a 30-fold lower concentration in humans than for any of the results presented above (K_i of 0.51 µM for progesterone receptor), therefore no relevant clinical effects are anticipated for any of the tested targets.

For the three metabolites M27, M30/34 and M18/21, K_i values for the progesterone receptor were 1.08, 0.96 and 1.35 µM, respectively. The K_i of M30/34 for the estrogen receptor was reported at 4.72 µM. Reported C_{max} values in human volunteers at day 14 after multiple dosing for M27, M30/34 and M18/21 were 628, 954 and 515 ng/mL, respectively (study 21703). After correcting for the protein plasma binding (free fraction <1% for all three metabolites as mentioned in clinical PK summary), the corresponding free fraction of these three metabolites (0.0074-0.0139 µM) is well below the K_i values reported above, indicating low risk for clinical effects.

In vivo studies included a test for anxiolytic properties of elinzanetant. In short, elinzanetant was dosed orally at 1, 3 and 10 mg/kg and subsequently at 3, 10 and 30 mg/kg in a crossover marmoset human threat test 1 h prior to testing. In the first experiment, the number of postures in response to close proximity of the human observer was reduced with statistical significance at 10 mg/kg, which was confirmed in the

subsequent experiment at the 10 and 30 mg/kg doses with no evidence for sedation for these doses, implying an anxiolytic effect of elinzanetant indeed.

In a study with aged Rhesus monkeys, delayed matching-to-sample testing (DMTS) was performed 1 h after receiving an oral dose of 0.38, 1.27, 3.8, 12.7 or 38.0 mg/kg elinzanetant. Elinzanetant produced a trend for improvement of DMTS accuracy, which appeared to be dose-dependent, with improvement observed mainly for the 3.8 mg/kg and 38.0 mg/kg dose levels, with no effect for the 12.7 mg/kg dose level. When selecting the dose that showed to most beneficial effect for each of the six animals (1 at 1.27 mg/kg, 2 at 12.7 mg/kg and 3 at 38.0 mg/kg), a statistically significant effect was observed for the medium delay interval group, with a trend observed for the short and long delay interval.

A similar experiment was performed in young adult Rhesus monkey receiving a single oral dose of 0.38, 1.27, 3.8, 12.7 or 38.0 mg/kg elinzanetant. In a series of non-distractor trails, there was no significant effect of treatment with elinzanetant on accuracies. However, in a series of distractor trials, elinzanetant improved accuracies of the short and medium delay groups with statistical significance. When selecting the dose that showed to most beneficial effect for each of the six animals (3 at 0.38 mg/kg and 3 at 12.7 mg/kg), a statistically significant effect was observed for the main effect of treatment on task accuracy. In summary, elinzanetant was shown to have the potential to improve working memory.

In a guinea pig hyperdopaminergic model of psychosis, intraperitoneal administration of 9.5, 29 and 95 mg/kg elinzanetant 1 hour before dosing with amphetamine resulted in dose-dependent decreases in rearing, a behaviour associated with psychosis. Statistically significant decreases were observed for the highest dose level only. Receptor occupancies associated with increasing dose levels were 98%, 98% and 99% for the NK-1 receptor and 63%, 66% and 91% for the NK-3 receptor. These findings confirm the antipsychotic potential of elinzanetant, which appears to be driven by the NK-3 receptor mainly.

In a group of three Rhesus monkeys, elinzanetant did not antagonize the discriminative stimulus effects of cocaine, although effects varied among the three animals that were used. The attenuation of rate-decreasing effects of cocaine appeared to vary among animals tested as well, with some attenuation of elinzanetant observed at the higher cocaine doses. In another study focusing on cocaine self-administration behaviour or food-maintained responding behaviour, 10-100 mg/kg elinzanetant administration did not result in any statistically significant changes.

2.5.2.3. Safety pharmacology programme

In a GLP-compliant study where HEK cells transfected with hERG cDNA were used to record hERG tail current, the maximum soluble concentration of elinzanetant of 1.91 µM (~1.27 µg/mL) resulted in similar decreases in hERG tail current as those recorded for vehicle treated cells, indicating no effect of elinzanetant on hERG tail current. In human volunteers receiving multiple doses, the highest reported C_{max} was 3520 ng/mL. Since plasma protein binding in humans is reported at 0.3%, the corresponding free fraction is ~10.6 ng/mL (~0.016 µM), at least 120-fold lower than the concentration used in the hERG assay, and therefore no relevant clinical effects are anticipated.

In another (non-GLP) study, CHO cells expressing hERG were tested for peak tail currents with elinzanetant concentrations up to 50 µM. pIC_{50} values were below 4.52 (*i.e.* >30 µM (~20.0 µg/mL)) for all samples, confirming the low risk of elinzanetant-associated hERG inhibition in humans.

The metabolites M27, M30/M34 and M18/M21 were also tested for their inhibitory effects on specific human cardiac ion channels: the hERG potassium channel, the hNav1.5 sodium channel, the hCav1.2 L-type calcium channel, the hKvLQT1 potassium channel, the hKv4.3 potassium channel, and the hKir2.1 potassium channel. Automated patch clamp analysis revealed that for all three metabolites, there were no IC_{50} values below 10 µM for any of the investigated channels, except for M30/M34, with an IC_{50} for the hCav1.2-mediated Ca^{2+} current of 6.5 µM. Since the free fraction of all three metabolites ranges between 0.0074-0.0139 µM in humans, there is at least a 400-fold difference between IC_{50} values and free fraction C_{max}, confirming the low risk of elinzanetant-associated inhibition in humans.

In a GLP-compliant study on the cardiovascular system in Cynomolgus monkey, arterial pressures, heart rate, electrocardiographic (ECG) parameters and body temperature were monitored for up to 5 days after a dose of 6, 20 or 60 mg/kg elinzanetant. A dose of 6 mg/kg did not produce any abnormal changes in arterial pressures, heart rate, body temperature or ECG intervals, whereas a dose of 20 mg/kg produced a mild, reversible decrease in body temperature (up to 0.32°C) from approximately 3 to 5 hours after dosing. A dose of 60 mg/kg produced a mild, reversible increase in heart rate (up to 12 beats/minute or 15%) from approximately 11 to 17 hours after dosing and a mild, reversible decrease in body temperature (up to 0.63°C) from approximately 3 to 6 hours after dosing. This dose did not produce any effects on arterial pressures or any abnormal changes in ECG interval durations and did not produce any evidence of ECG waveform abnormalities or arrhythmias. The C_{max} values on day 1 in a 4-week Cynomolgus toxicology study with 6 mg/kg dosing were 0.371 µg/mL (0.55 µM) for males and 0.199 µg/mL (0.30 µM) for females, corresponding to a free fraction of ~0.016 µM (males) and 0.0013 µM (using 2.96% and 0.434% plasma protein binding in male and female Cynomolgus monkey, see non-clinical pharmacokinetics). These concentrations are similar to or below the C_{max} observed at the human recommended dose (~0.016 µM), with exposure multiples at ~1 or ~0.081, indicating clinically relevant exposure. However, even for the 60 mg/kg dose level (showing effects of elinzanetant dosing) exposures were still clinically relevant, as the exposure multiples based on C_{max} were ~5 for males and ~0.37 for females (free C_{max} for 60 mg/kg dose level was 0.082 µM for males and 0.0059 µM for females).

In a GLP-compliant study in SD rats, neuro-behavioural effects (modified Irwin assay) and body temperature were investigated after an elinzanetant dose of 5, 25 or 100 mg/kg. No relevant effects on any of the investigated parameters (neuro-behavioural and body temperature) were observed for any of the dose levels. The C_{max} values on day 1 in a 4-week SD rat toxicology study with 100 mg/kg dosing were 5.15 µg/mL (7.7 µM) for males and 5.37 µg/mL (8.0 µM) for females, corresponding to a free fraction of ~0.15 µM (males) and 0.067 µM (using 1.91% and 0.843% plasma protein binding in male and female SD rat, see non-clinical pharmacokinetics). These concentrations are above the C_{max} observed at the human recommended dose (~0.016 µM), with exposure multiples at ~9 for males or ~4 for females, indicating a low risk for clinical effects.

In a GLP-compliant study in SD rats, effects on respiratory function were studied using whole body plethysmography after an elinzanetant dose of 5, 25 or 100 mg/kg. Ventilatory function (respiratory rate, tidal volume and minute volume), airway resistance (total pulmonary resistance) and body temperature were monitored for up to approx. 72 hours after dosing. There were no elinzanetant-related effects on any of these parameters for any of the dose levels. The C_{max} values on day 1 in a 4-week SD rat toxicology study with 100 mg/kg dosing were 5.15 µg/mL (7.7 µM) for males and 5.37 µg/mL (8.0 µM) for females, corresponding to a free fraction of ~0.15 µM (males) and 0.067 µM (using 1.91% and 0.843% plasma protein binding in male and female SD rat, see non-clinical pharmacokinetics). These concentrations are above the C_{max} observed at the human recommended dose (~0.016 µM), with exposure multiples at ~9 for males or ~4 for females, indicating a low risk for clinical effects.

2.5.2.4. Pharmacodynamic drug interactions

No studies were performed; this was agreed.

2.5.3. Pharmacokinetics

Elinzanetant (NT-184) was investigated in a range of *in vitro* and *in vivo* pharmacokinetic (PK) and toxicokinetic (TK) studies in mice, rats, rabbits, dogs, and monkeys. Sprague Dawley (SD) rats and Cynomolgus monkeys, were the nonclinical safety species selected. These studies were conducted to define the absorption, distribution, metabolism, and excretion (ADME) of elinzanetant. Oral administration, which is the route of clinical administration, was selected for the pharmacokinetic studies in animals. Data from these studies were used to characterize the PK and TK properties of elinzanetant to support nonclinical toxicology evaluations and to support its intended clinical use.

Analytical methods

The bioanalytical methods used in support of GLP studies in rat and Cynomolgus monkey were validated in accordance with European Medicines Agency (EMA), *Guideline on bioanalytical method validation*.

The bioanalytical methods for elinzanetant employed in all pharmacokinetic and toxicokinetic studies involved extraction of elinzanetant and its metabolites from plasma by protein precipitation using acetonitrile optional containing 1% formic acid. Elinzanetant was analysed using anisotopically double labelled internal standard ([$^{2}H_{6}{}^{13}C_{2}$]elinzanetant) by LC-MS/MS using a TurboIon Spray™ interface and multiple reaction monitoring.

GLP methods (for mouse, rabbit, rat and Cynomolgus monkey) were validated for elinzanetant and metabolites M27, M30/34 and M18/21 with respect to within-run and between-run precision, accuracy, selectivity, sensitivity, linearity, reproducibility, carry over, matrix effect and stability. There were no major differences between the methods, and the results of the different methods appear comparable and therefore relevant for the current development.

In the fully validated assays, the lower and upper limits of quantitation (LLOQ and ULOQ) used to determine elinzanetant plasma concentrations in mouse, rat, rabbit, and monkey GLP studies were adjusted according to the expected concentrations and ranged from 1.0 and 10 µg/L (LLOQ) to 1000 and 10,000 µg/L (ULOQ). LLOQ and ULOQ for metabolites of fully validated assays for mouse, rat, rabbit and monkey plasma in GLP studies ranged from 0.1 µg/L to 1000 µg/L, respectively.

Short term stability of elinzanetant and its metabolites in rabbit plasma was at least 33 days at -20°C, in mice 101 days at -20°C. In rat plasma long term stability was up to 202 days at -20°C and -80°C and freeze-thaw stability up to 5 cycles from -20°C or -80°C to room temperature. In Cynomolgus monkey, elinzanetant plasma stability was up to 193 days at -20°C and -80°C and freeze-thaw stability up to 3 cycles from -20°C and -80°C to room temperature.

For Cynomolgus monkey plasma samples, incurred sample reanalysis (ISR) was conducted for elinzanetant and metabolites M27, M30/34 and M18/21 (report R-13895) and at least 73.8% of the ISR results had a relative % difference within ±20% what is within the acceptance criteria (>66.7% of the samples within 20% difference). For rat plasma, ISR was conducted as part of the 2-year carcinogenicity study in rats (report B003186). The individual difference was within 20% for all samples for all analytes and the acceptance criteria for ISR were fulfilled.

The possible conversion of M22, the degradation product of elinzanetant, back to elinzanetant during sample preparation was investigated in human plasma. No hint on back-conversion of M22 to elinzanetant was found, although this observation is considered less relevant for PK studies in animals as metabolite M22 is not a main metabolite *in vitro* nor *in vivo*.

Absorption

Single dose PK studies after intravenous (IV) solution (in 2%, 5% or 10% DMSO in saline (v/v), or oral (PO) suspension (in 1% aqueous methylcellulose (w/v), table 3-8) administration were conducted in mice, Sprague Dawley (SD) rats, New Zealand White (NZW) rabbits, dogs, marmoset monkeys and Cynomolgus monkeys as non-GLP studies. Repeated dose toxicokinetic studies after oral administration were conducted under GLP.

In summary, the pharmacokinetic profile of elinzanetant shows differences between species with regard to clearance and bioavailability. Pivotal PK/TK studies in rats and monkeys were conducted with elinzanetant free base and absorption of elinzanetant free base was similar to that of elinzanetant tosylate salt. After intravenous administration, the volume of distribution (V_{ss}) was 2.4- 3 L/kg in Cynomolgus monkeys and dogs, respectively, which is 4-5 times the total body water indicating significant tissue distribution.

The clearance of elinzanetant was low to moderate (male 0.78 L/(h.kg), female 1.1 L/(h.kg)) in rats (~30% of liver blood flow), moderate (male 1.2 L/(h.kg)) in Cynomolgus monkeys (~50% of liver blood flow), but high (1.8 L/h.kg) in male dogs (near liver blood flow). The half-life ($T_{1/2}$) after IV administration was 6.3, 7.8, 1.8, 10 and 1.7 hours in male rats, female rats, dogs, marmoset monkeys and Cynomolgus monkeys, respectively.

After oral administration elinzanetant was rapidly and extensively absorbed with a t_{max} between 0.5 and 2 hours in mice, rats, dogs and monkeys, but slow in rabbits (t_{max} 8-11 h), resulting in moderate bioavailability in rats (male 47%, female 77%) and marmoset monkeys (male 34%) but low bioavailability in cynomolgus monkeys (male 19%) and dogs (male 19%). The highest exposure in terms of dose-normalized AUC and C_{max} was achieved in rats and marmoset monkeys, whereas a lower exposure was observed in dogs. Overall, plasma exposure increased dose proportional with increasing dose and moderate accumulation (2 to 3-fold) was observed in rats and cynomolgus monkeys. There were sex differences observed in rats with a 4 to 5-fold higher exposure in females.

Based on a 1.5 times lower clearance (CL_{blood} 1.2 vs 1.8 L/(h.kg), 1.5 times higher exposure (AUC_{norm} 0.86 vs 0.57 kg.h/L), 2.5 time longer half-life ($T_{1/2}$ 6.7 vs 2.7 h), a similar C_{max} (C_{max_norm} 0.046 vs 0.048 kg/L) and similar bioavailability (19% both species) of elinzanetant in monkeys as compared to dogs, the monkey was considered the most suitable non-rodent species for investigation of effects of elinzanetant in long-term toxicological studies.

Pharmacokinetics of metabolite M27 was assessed in female rats. M27 mean C_0, C_{max} and AUC_{0-t} values increased with the increase in dose level, were non-linear and greater than dose proportional. The mean V_{ss} values increased with the increase in dose and ranged from 1.46 to 1.87 L/kg and were greater than the total body of water in rats (~0.67 L/kg), indicating that M27 is highly distributed in tissues. Due to the limited dataset, estimation of the elimination phase half-life was not calculated for M27.

Distribution

In vitro plasma protein binding data, brain tissue binding data and blood distribution data were obtained in mouse, gerbil, rat, guinea pig, dog, marmoset, Cynomolgus monkey and human. The extent of binding of elinzanetant to plasma proteins was moderate to high with certain variability between species or genders. In human plasma as well as in female SD rat and female Cynomolgus monkey plasma the protein binding was high with less than 1% free fraction. A moderate protein binding was found in mouse, male SD rat, rabbit, dog and male Cynomolgus monkey plasma.

The f_u´s ranged between 0.27% in male human plasma (0.33% in female human plasma), in male rats 1.9% and in female 0.84%, 2.5% in mice, 1.2% in female dogs, in cynomolgus monkeys 2.9% and 0.43% (male and female, respectively) and 4.6% in female NZW rabbit plasma. No concentration dependence (range of 500 µg/L to 5000 µg/L) of the unbound fraction of elinzanetant was observed. The main binding protein was serum (human) albumin with a f_u of 0.41%. The binding to human liver microsomes (HLMs) was low (59% free fraction at 0.01 mg/mL HLM) and dependent on the HLM protein concentration (30% free fraction at 1 mg/mL HLM).

The partitioning of elinzanetant into blood cells versus plasma (B/P) was determined *in vivo* in the rat and *in vitro*. Elinzanetant was distributed with a C_b/C_p of 0.6 in mouse, rat, dog and male human blood, up to 0.7 in Cynomolgus monkey, guinea pig and female human blood, indicating elinzanetant is distributed mainly in plasma.

The protein binding of the principal human metabolites of elinzanetant M27, M30/34 and M18/21 was moderate to high in an almost similar range compared to elinzanetant. The f_u´s for M27 ranged between 0.07% in male human plasma and 3.4% in NZW rabbit plasma. The f_u´s for M30/34 ranged between 0.5% in male human plasma and 3.4% in NZW rabbit plasma. The f_u´s for M18/21 ranged between 0.1% in female human plasma and 10% in NZW rabbit plasma.

The extent of protein binding of elinzanetant towards the major binding partner HSA was affected by sodium oleate (SO) resulting in a factor of 2 lower f_u with increasing SO concentration, indicating that the protein binding of elinzanetant is affected by free fatty acid concentrations.

Organ and Tissue Distribution

In vivo brain penetration of elinzanetant was studied in the mouse, rats and monkey yielding brain to blood ratios of 0.5, 0.1 to 0.5 and 0.6 respectively. Elinzanetant is bound to homogenized mouse brain tissue what resulted in a low free fraction in brain of 0.28%. Elinzanetant is a substrate of human P-glycoprotein (P-gp) and a role for P-gp in limiting the brain penetration of elinzanetant was observed in rat and mouse. Co-administration of elinzanetant with elacridar (GF120918) a non-specific inhibitor of P-glycoprotein in rats or in mdr1a$^{(-/-)}$ P-gp knockout male mice relative to mdr1a$^{(+/+)}$ wild type mice, resulted in a significant increase (~5-fold) in brain:blood ratio, indicating active contribution of efflux transport to elinzanetant brain exposure.

Transport activity did not fully prevent elinzanetant brain penetration, as it was determined in rats, mouse and monkey as well as by clinical PET studies after both single and repeated oral administration to baboons and humans. Dose-dependent (0.01, 0.1 and 2 mg/kg) NK1 receptor occupancy was found by PET in the brain of male baboons. The ED_{50} (dose administered leading to 50% occupancy of the NK1 receptor) was 0.21 mg/kg, and the EC_{50} (plasma concentration associated with 50% RO) was 9.9 ng/mL.

The *in vivo* tissue distribution of [^{14}C]elinzanetant was investigated in the male albino SD rat, in male partially pigmented (Lister Hooded) rats, in partially pigmented Long Evans rat and in pregnant SD rats after oral administration of 10 (3.7 MBq/kg) or 2 mg/kg (5.6 MBq/kg), or intravenously 1 mg/kg (2.8 MBq/kg) administration and using quantitative whole body autoradiography (QWBA) at 1h up to 168 h (2 mg/kg PO, albino SD) and up to 840 h (35 days Lister Hooded, 10 mg/kg PO and 1 mg/kg IV) post dosing. Tissue distribution in non-pigmented (Sprague Dawley) rats was generally comparable to that in the pigmented (Lister Hooded) male rats and comparable between 10 mg/kg oral versus 1 mg/kg intravenous administration.

[^{14}C]elinzanetant was extensively distributed in male and female rat independent of the route of administration (PO or IV) with levels in the majority of tissues (except CNS) being higher than those in blood, consistent with observed high volume of distribution. The highest radioactivity levels were generally observed in abdominal and brown fat, the liver, gastro-intestinal mucosa, kidney, mammary gland region, harderian gland, adrenal gland, pancreas, mucous gland, bulbo-urethral gland, exorbital lacrimal gland and found at 2 to 8 hours post dose. Thereafter, radioactivity decreased in most tissues but remained elevated (tissue to blood ratio (T/B) >10) at 24 and 72 hours after administration in abdominal and brown fat, Harderian gland, intestinal mucosa (T/B=7 at 72h), liver, pigmented skin (T/B=9 at 72h), adrenal gland, preputial gland and uveal tract/retina.

Tissue to blood ratio was generally found to be <4 for all tissues during the first 8 hours post dose except in adipose tissue (8.7), mammary gland tissue (6.8), adrenal gland (5.3) and Harderian gland (5.0). Levels in the brain were notably low, with brain:blood ratios of between 0.1 (brain total 0.054/ blood cardiac 0.54) and 2.4 (hypophysis 1.27/ blood cardiac 0.54) consistent with dedicated brain penetration studies in rat and mouse. Levels of radioactivity generally declined with time, but by 35 days post-dose, radioactivity was still quantifiable in some tissues following both routes of administration, with highest levels generally present in brown fat, uveal tract/retina, spleen and adrenal cortex. The persistence of radioactivity in the uveal tract/retina and skin in Lister Hooded rats might suggest an association of drug-related material with melanin, however, the radioactivity level in non-pigmented skin was higher 35 days post-dose than pigmented skin. In addition, in Long-Evans rats no difference in exposure was found between highly pigmented and low pigmented skin, tempering the role of melanin in tissue exposure of elinzanetant.

In pregnant rats [^{14}C]elinzanetant-derived radioactivity was widely distributed from blood to most peripheral organs, tissues, and the tissues of foetuses to a lesser degree. The maximum concentration in most maternal and foetal tissues was reached 2 to 5 h post dose. Foetal and associated tissue concentrations were generally much lower than maternal blood, except for amnion and placenta.

Elinzanetant was detected in the milk of lactating Sprague Dawley rats. Milk to plasma concentration ratios determined for each time point ranged from 1.8 at 1 h to 4.0 at 32 h. The milk/plasma ratio for $AUC_{0\text{-tlast}}$ was 2.5. At C_{max} of both matrices (8 h), the milk/plasma ratio was 2.1. The cumulative sum percent of administered dose secreted into milk from 0 to 48 h was 6.1%, suggesting that elinzanetant penetrates from circulating blood into milk of lactating female rats. Metabolites were also excreted with milk but at more than 100-fold lower concentration for M27 and M18/21 and at least 3-fold lower concentration for M30/34, as compared to elinzanetant.

Metabolism

In vitro, the intrinsic clearance (CL_{int}) of elinzanetant was low to moderate in liver microsomes of all species tested (mouse <0.5, rat 0.6, dog 1.1, human 2.2 and monkey 4.3 and mL/min/g liver) as well as moderate in human and monkey hepatocytes (1.9 and 1.7 mL/min/g liver, respectively). Studies in human liver microsomes and hepatocytes with selective CYP inhibitors and with recombinant human CYP enzymes indicated that CYP3A4 is the primary CYP isoform involved in the oxidative metabolism of elinzanetant.

The main route of metabolism in non-clinical species and human *in vitro* was hydroxylation leading mainly to metabolites M27, M30/34, and M18/21. Further routes detected include N,O-dealkylation of morpholine ring and dehydrogenation. In general, metabolite profiles in hepatocytes of non-clinical species and humans were qualitatively similar and no human specific metabolites were observed.

In vivo elimination of elinzanetant in the rats, monkeys and humans was mainly by metabolism and the predominant routes of metabolism appear to be oxidations similar to those seen in hepatocytes (hydroxylation, N,O-dealkylation of morpholine ring, dehydrogenation) as well as minor glucuronidation, either alone or in combination with oxidation.

Following single oral administration of [^{14}C]elinzanetant to rats, monkeys and human, parent compound was the major component in plasma of rat and monkey (>50% of total radioactivity AUC) as well as in human.

In mass balance studies using [^{14}C]elinzanetant, the unchanged parent covered 39% of total radioactivity in human plasma, 41% in monkey and 43% in rat. In faeces, unchanged elinzanetant was 50% in human, 7% in monkey and 11% in rat. Mono-hydroxylated metabolites M30/34 accounted for 13.7% in human, 5.8% in monkey and >8.8% in rat and M27 accounted for 7.6% in human, 1.5% in monkey and 3% in rat. Double hydroxylated metabolite M18/21 accounted for 4.9% in human, <1% in monkey and 2.1% in rat. M14 (O-glucuronidation of elinzanetant) accounted for 10.8% in monkey, <1% in rat and was not present in human. Dehydrogenation metabolite M39 was only present for 10.8% in rat but was not detected or at low levels in monkey or human. Only metabolite M30/34 exceeded 10% of total radioactivity AUC in human plasma, whereas all other metabolites contributed to less than 10% of total drug-related radioactivity. Therefore, M30/34 has to be considered as major human metabolite. As all three principal metabolites M27, M30/34, M18/21 exhibit similar pharmacological activity as elinzanetant itself on the human receptor, exposure to all three metabolites was analysed and confirmed in toxicology studies and clinical studies.

After repeated dosing in rats (26 weeks) and monkeys (39 weeks) the major human metabolite M30/34 was present in high amounts in particular in Cynomolgus monkeys (100% of elinzanetant exposure based on AUC), and lower in rats (10/25% (f/m) of elinzanetant exposure), as confirmed in the toxicokinetic studies with exposures in the range or above the human therapeutic exposure. The other metabolites were present at low amounts; M18/21 in rat ~3% and in Cyno ~ 6%, M27 in rat 1/10% (f/m) and in Cyno ~5%.

Excretion

In rats, following a single oral administration of [^{14}C]GSK1144814 tosylate (10 mg free base/kg) to intact male Sprague-Dawley rats, the major route of elimination of drug-related material was via the faeces (94% of the dose after 168 hrs). Urinary elimination was very minor (0.9% of the dose). The total recovery of radioactivity at 168 h post-dose (including cage washings and tissues) was 96.6%. In bile duct-cannulated (BDC) male rats following oral administration, the major route of elimination was via the bile (61% of the dose after 48 hrs), with faecal and urinary excretion accounting for 29% and 0.9% of the dose, respectively. Total recovery of radioactivity (including cage washings, gastrointestinal tract and the residual carcass) was 96.6% at 48 h post-dose. At least 66% of the dose was absorbed by these animals, as judged by the radioactivity recovered in bile, urine and the residual carcass (minus the gastrointestinal tract).

In Cynomolgus monkeys, following a single oral dose of [^{14}C]GSK1144814 tosylate (5 mg free base/kg), the major route of elimination was via the faeces (85.6% of the dose during 168 h after dosing). Urinary elimination was very minor, only accounting for 0.1% of the dose. The total recovery of radioactivity (including cage washes and cage debris) was 86.2% of the dose.

In human, the amount of [^{14}C]elinzanetant excreted into faeces was ~90% whereas the radioactivity excreted into urine accounted for on average only 0.4% of the dose.

In conclusion, following oral administration, elinzanetant was primarily cleared upon metabolism via biliary excretion and faecal elimination in the tested preclinical species (rat and cynomolgus monkey). Renal clearance appears to play a minor role.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Information on acute toxicity was derived from the rat micronucleus assay. Rats were orally administered with 1000 or 2000 mg/kg/day elinzanetant. There was no mortality, but at both dose levels animals lost body weight and clinical signs of toxicity were seen, including piloerection and hunched posture. In summary, the oral lethal dose (LD) was >2000 mg/kg/day in male and female rats.

Further single dose toxicity studies were conducted with elinzanetant in stand-alone acute toxicity studies, which is not needed. Acute toxicity could have been evaluated in repeated dose toxicity with rats and monkeys following the first dosing.

In rats, no adverse effects were described during the single dose study and elinzanetant was well tolerated at 100 mg/kg in the three males Crl:CD (SD) tested.

Non-rodent acute dose toxicity was further tested with escalating doses of elinzanetant in orally dosed marmosets and cynomolgus monkeys. In two tested (1f/1m) marmosets, elinzanetant did not produce any notable findings up to the highest tested dose of 1000 mg/kg. In the two tested (1f/1m) cynomolgus monkeys, clinical signs of loose/watery faeces were observed from ≥100 mg/kg. Additionally, animals showed emesis after 1000 mg/kg.

Another single dose toxicity study was conducted to investigate if via IV administration sufficiently high exposure levels for the dependence/abuse liability studies in monkeys could be reached. Except for severely reduced food intake during the first (morning) and second feeding (overnight), both female cynomolgus monkeys treated with 6.5 mg/kg elinzanetant (maximum soluble dose in the vehicle) tolerated the treatment.

2.5.4.2. Repeat dose toxicity

Pivotal GLP-compliant repeated dose studies were conducted in Sprague Dawley (SD) rats and Cynomolgus monkeys and comprised studies of 4, 13 (two studies), and 26 weeks duration in rats and 4, 13 (two studies) and 39 weeks duration in monkeys. The monkeys were initially aged 3 to 7 years (4-week study), 4.5-5 years (13-week study), 2.2-2.5 years (second 13-week study) and 27-29 weeks (39-week study).

Mortality

The highest dose level of 100 mg/kg led to preterm euthanasia in rats (one female) on day 12 of dosing in the 4-week study, due to the number and severity of clinical signs, which is most likely related to the high exposure (40-fold the clinical exposure). In the 13-week rat study with recovery, there was mortality/premature sacrifice in all high dose males. No TK evaluation was done for these males. No males were found dead at exposures of 9.1-fold the clinical exposure. The number of earlier euthanized females due to welfare reasons was dose-related and started at ≥20 mg/kg/day (no safety margin) after showing dose-related clinical signs evident of a poor condition or as they had CNS-related clinical signs including spams and abnormal involuntary contractions. The poor condition of the animals was correlated with low food intake and body weight loss, especially in high dosed males. Acute degeneration/necrosis of the skeletal muscles was considered to be the likely cause of death in most animals. Notably, the animals euthanized prematurely appeared to have higher plasma elinzanetant levels compared to term animals with less clinical signs.

In the 4-week monkey study, at 60 mg/kg, one male and one female were euthanized for humane reasons. Elinzanetant-related body weight loss and deteriorating clinical condition were noted, in addition to adverse kidney toxicity. In addition, there were effects secondary to inanition or stress on the pancreas, liver, gastrointestinal tract, heart, thymic cortex and adrenal cortex.

Reproductive organs

In the 4-week rat study, adverse NK-3 pharmacology-related microscopic findings indicative of abnormal diestrus (mucification of the vaginal epithelium with a moderate inflammatory infiltrate and/or atrophy of the uterus and persistent corpora lutea in the ovary) were present in the reproductive tract. In the 39-week monkey study, there was an elinzanetant-related lack of cyclical activity in the ovaries, with an absence of corpora lutea or maturing follicles and correlating with a reduction in reproductive organs weight, despite the young age of the monkeys. Also in the rat carcinogenicity study, an elinzanetant related increase in corpora lutea absence, hyperplasia of sex cord stromal/granulosa cells and decreased mucification vagina epithelium were observed. No adverse PD related reproductive findings were observed in rats up to 25 mg/kg and in monkeys up to 30 mg/kg, corresponding to a safety margin of 10 and 0.3, respectively, based on total exposure (AUC0-24).

Skeletal muscle

Acute degeneration/necrosis of the skeletal muscles was considered to be the likely cause of death in most high dose animals that died or were euthanized prematurely in the 13-week rat recovery study. These histopathological findings correlated with the clinical chemistry changes, in particular the large increases in LDH, CK and AST recorded mainly in prematurely sacrificed males. This finding was not observed in any other studies on elinzanetant in rats or monkeys, however, it can be agreed that skeletal muscles may be considered targets of toxicity. As demonstrated in the mechanistic study, elinzanetant accumulation in skeletal muscle tissue may play a role. For skeletal muscle necrosis, there is a safety margin of 9.1 for males and 18 for females based on total exposure (AUC0-24). Skeletal muscle toxicity is therefore not expected to occur in humans.

Central nervous system

In the 13-week rat recovery study, elinzanetant-related clinical signs were observed in animals of each elinzanetant treatment group and included tremors, rigidity of the whole body, spasms, abnormal involuntary muscle contractions/convulsions and stiff tail. Generally, the animals appeared disoriented and showed weakness, irritability or aggressive behaviour in the period around dosing in association with the signs. Some animals also showed salivation. There were no related histopathological changes, and the effects were not dose-dependent. However, given the nature of the compound and its known CNS activity, it was concluded by the study director that it is possible due to primary or secondary pharmacologic action of the compound. Therefore, the CNS should be considered as target organ.

Gastrointestinal toxicity

In the 39-week monkey study, loose or liquid faeces and weight loss or reduced body weight gain were noted in all treatment groups, but predominantly in females given 80 mg/kg. Females given 80 mg/kg showed inflammatory cell infiltrate in the mucosa or mucosal hyperplasia of the large intestine. Moreover, mild hyperplasia of the mucosa of the caecum and colon was present in one female which had received long-term antibiotic therapy due to severe diarrhoea. Given the severity of the clinical findings in females, gastrointestinal toxicity was adverse in this study. The NOAEL for GI effects in monkey can be agreed to be 60 mg/kg/day, corresponding to a safety margin of 2-fold the human therapeutic exposure. This appears to be a higher exposure than for 80 mg/kg and therefore the data appear to indicate a local effect. Although local elinzanetant concentrations in the GI tract in monkeys dosed with 40 mg/kg are approximately 20 times higher than in humans (2 mg/kg), suggesting that no severe GI effects are expected, adverse gastrointestinal reactions are reported in clinical studies and can therefore not be excluded.

Other elinzanetant-related findings

In the majority of the repeated dose toxicity studies, hypertrophy in the adrenal glands were observed, correlating with increased adrenal weight in rats. In addition, thymus atrophy, reduced thymus weight or lymphoid depletion of the thymus were noted. The effects observed in adrenal glands and thymus were discussed to be related to treatment-induced stress and non-adverse. While it is understood that these effects could be secondary to stress or malnutrition rather than a direct elinzanetant-related finding, it is not agreed that for these animals it is not adverse. However, it often occurs in toxicity studies and is most likely not relevant to humans.

Liver findings, including hypertrophy of the hepatocytes, increased liver weight, minor perturbations of chemistry markers (increased transaminases and glutamate dehydrogenase in monkeys, as well as increased total bilirubin in rats) were seen. The liver findings were discussed to represent an adaptive response relating to enzyme induction to facilitate the clearance of test item and therefore, the liver findings in both rats and monkeys were considered to be non-adverse, which can be agreed since there is no sign of necrosis/ degeneration. In contrast, in the rat carcinogenicity study, increased incidences and/or severities of biliary hyperplasia, biliary cysts, and multinucleated hepatocytes in the liver were observed at ≥ 60 mg/kg (margin of exposure (MoE) 29 based on total AUC exposure). However, no adverse effects were observed at 20 mg/kg (MoE of 7.5). Clinically, adverse liver effects were only noted in a few cases. Therefore, the overall risk for liver toxicity seems low based on non-clinical data.

In preterm euthanized high-dose monkeys in the 4-week study, microscopic findings of dilation of the collecting ducts (moderate) in the kidney of both monkeys, associated with intra-luminal accumulations of birefringent crystals in the male monkey, were observed, which was considered an adverse elinzanetant-related finding, corresponding to safety margin of 0.8- (males) and 1.2- (females) fold the clinical exposure based on total AUC.

2.5.4.3. Genotoxicity

The GLP-compliant *in vitro* Ames test and the evaluation of gene mutations and chromosomal damage in L5178Y mouse lymphoma cells, conducted according to OECD guidelines 471 and 476, respectively, were clearly negative. *In vivo*, a micronucleus test was conducted in polychromatic erythrocytes from rat bone marrow according to OECD guideline 474. Animals were treated at dose levels of 0, 1000 and 2000 mg/kg/day for two consecutive days. For TK satellite animals, the blood was sampled on day 1. There was no notable decrease in the proportion of polychromatic erythrocytes in the total erythrocyte count (%PCE) at any of the doses tested when compared with vehicle control, indicating no bone marrow toxicity. The number of micronucleated polychromatic erythrocytes (MPCE) per 2000 PCE for rats dosed at 1000 and 2000 mg/kg/day, were similar to the vehicle control and fell within the range of the laboratory historical control data. Therefore, elinzanetant was considered to have given a negative result for micronucleus induction. Based on the results of two *in vitro* and one *in vivo* test, elinzanetant is concluded to be not genotoxic.

2.5.4.4. Carcinogenicity

Elinzanetant's potential for carcinogenicity was assessed in a six-month carcinogenicity transgenic mouse model (tg RasH2) study in addition to one long-term two-year rat study.

No dose-dependent elinzanetant-related neoplastic or non-neoplastic findings were observed in mice at doses up to 70 mg/kg (females) or 85 mg/kg (males) (exposure margin of 2.8/2.0 for males/females based on total exposure or 21/18 based on unbound exposure). Mice were also sufficiently exposed to the main metabolites. Based on this study, no risk for carcinogenicity is expected at clinical exposures.

In rats, elinzanetant-related neoplastic findings included a significantly increased incidence of uterine neoplasms in females administered ≥60 mg/kg/day. The uterine neoplasms consisted of adenocarcinoma and squamous cell carcinoma with concomitant, increased severity/incidence of cystic glandular hyperplasia, endometrial hyperplasia with atypia and/or non-proliferative findings of squamous metaplasia of the endometrium. In addition, an increase in the incidence of malignant lymphoma of the hematolymphoid system was noted with statistical significance for females administered 80 mg/kg/day but with incidences outside historical control data from ≥ 60 mg/kg/day. There was an elinzanetant related decreased incidence of mammary gland neoplasia and benign pituitary adenomas of the pars distalis, which have been previously reported with perturbation of the prolactin axis and may have been the underlying mechanism for the incidences noted in these animals (*Harleman et al., 2012; Keenan et al., 1995; Rao,1996*). Based on these findings in rats, the dose level of 20 mg/kg/day has no evidence of an increase in carcinogenic effect due to elinzanetant. This dose level corresponds to a safety margin of ~7-fold or ~21-fold the clinical exposure based on total AUC0-24 or unbound AUC0-24, respectively.

2.5.4.5. Reproductive and developmental toxicity

Male fertility:

No dedicated male fertility study was conducted. Instead, male reproductive organs were assessed in a repeated dose toxicity study, which is acceptable. At the high dose, there was a decrease in seminal vesicles and prostate weights. These effects occurred at a dose resulting in an exposure margin of 80, with a safety factor of 56 at the NOAEL, when unbound exposure is compared to human exposure. This is sufficiently high to conclude there is a low risk of effects on fertility in males from treatment with elinzanetant.

Female fertility:

In female rats treated up to 100 mg/kg/day in the FEED study, there were increased pre and post implantation losses, resulting in reduced litter size, and decreased foetal body weight at the high dose. These effects coincided with maternal toxicity and are likely related. No TK measurements were performed in this study, but extrapolation from other studies indicate that these effects occur at least at a 16-fold exposure margin compared to human exposure at the intended dose. These effects were not observed following dosing resulting in 4-fold the human therapeutic dose. There were no further effects on fertility, including no effect on oestrus cycle. Effects on the oestrus cycle however were evident in the 4-week repeated dose toxicity study at the same high dose of 100 mg/kg/day. Further, data from monkey repeated dose toxicity studies indicate a similar effect on oestrus cycle, with a lack of cyclical activity in the ovaries, no evidence of corpora lutea or maturing follicles and a reduction in reproductive organ weight. The effects in monkeys occurred at clinically relevant exposures, without a safety margin. This suggests that rats are less sensitive to an effect of elinzanetant on fertility than monkeys and presumably humans.

In the embryofoetal toxicity study in rats there was some evidence of maternal toxicity at the high dose of 100 mg/kg/day in terms of reduced body weight gain and food consumption during the first few days of dosing. There were no effects on the foetus. The NOAEL for embryofoetal development in the rat is therefore the high dose of 100 mg/kg/day. No TK measurements were performed in this study, but extrapolation from the PPND rat study indicate that there is a safety margin of around 23-fold for total or 64-fold for unbound exposure compared to human exposure at the intended dose.

In rabbits dosing was limited due to maternal toxicity. At the high dose in the pivotal study still 4 females died due to body weight loss and reduced food consumption. However, there were no effects on embryofoetal development at any dose. The high dose of 140 mg/kg/day is considered the be the NOAEL. When comparing total exposure, there is no safety margin at the high dose as exposure is in the range of clinical exposure. However, when differences in protein binding are taken into account, there is a safety margin of 19. This is considered sufficient to conclude that elinzanetant has a low risk of embryotoxicity during the embryofoetal development stage, based on the EFD studies.

Pre- and postnatal development was studied in rats. In a DRF study with the same doses in the EFD study, the high dose was not well tolerated in the dams evidenced by maternal toxicity, which resulted in stillborn pups, increased post-implantation loss and decreased pup body weight. These effects on the F1 were not seen in the EFD study at the same dose and could therefore be due to an effect that occurs between GD17 and birth. The NOAEL for effects during gestation is therefore 25 mg/kg/day, resulting in a safety margin of 6.7-fold for total and 19-fold for unbound exposure.

Already at the lowest dose tested of 5 mg/kg/day resulting in clinically relevant exposures, there was litter loss from PND 0 to 4. It appears that the pups were not nursing, as there was no milk in the stomachs. In the surviving F1 animals, there were no further effects on development and reproductive capacity, and there were no effects detected in the F2 generation.

2.5.4.6. Toxicokinetic data

A substantial amount of toxicokinetic data has been collected in the pivotal animal species rat and monkey. Exposure multiples were calculated based on AUC0-24 values, both for total and unbound exposure of the parent. Exposure multiples based on total exposure were used in the discussion on the relevance of toxicological findings. As these are lower than exposure multiples based on unbound exposure and therefore worst case, this is acceptable. Numerous repeat-dose studies, with different dosages ranging from 5-300 mg/kg, were performed in rats. Exposure multiples based on total exposures from 0.7-40 were achieved in rats. In pregnant rats (dosed 1.5-15 mg/kg) exposure margins were 0.2-4.2. Based on unbound exposure, exposure multiples from 4.3-101 were achieved in rats and 0.7-12 in pregnant rats.

The pivotal cynomolgus monkeys repeat-dose studies were performed with doses ranging from 6-80 mg/kg. The use of higher doses was not possible due to dose-limiting toxicity observed in dose range finding studies. Exposure multiples in the pivotal cynomolgus monkey studies were 0.1-3.6 and 0.1-46 for total exposure and unbound exposure, respectively. Exposure multiples of 0.1-2.8 and 1.0-21 for total exposure and unbound exposure, respectively, were achieved in the pivotal 26-week carcinogenicity study in transgenic RasH2 mice. Exposure multiples of 0.1-1.2 and 2.3-19 for total exposure and unbound exposure, respectively, were achieved in pregnant rabbits.

In human mass balance studies, M30/34 was found to be a major and principle human plasma metabolite of elinzanetant (13.7% of total radioactivity AUC(0-144)), while M27 (7.6%) and M18/21 (4.9%) are principal human plasma metabolites. Since M30/34 is a major metabolite in humans, the exposure in animal species used in the pivotal toxicity studies should be high enough to be sufficiently toxicologically qualified. The exposure margins for M30/34 in pivotal rat studies range from 5.9-8.3, from 1.5-1.6 in transgenic RasH2 mice, from 1.9-3.0 in cynomolgus monkeys and was 2.4 in pregnant rats. Only in the supporting pregnant rabbit TK study, M30/34 was not sufficiently covered (0.3). However, since the plasma concentrations of elinzanetant in this study at the high dose of 140 mg/kg were 50% lower than those in the embryofoetal development study in rabbits on gestation day 11, it can be assumed that M30/34 was also covered in the embryofoetal development study in rabbits. Overall, the major metabolite M30/34 is sufficiently qualified in pre-clinical species.

Interspecies comparison and exposure margins to clinical exposure

The *in vivo* PK/TK studies with elinzanetant (BAY 3427080) were conducted via oral administration, which is the intended route of administration in humans, in rats and Cynomolgus monkeys which were used for toxicology studies.

In all species oral absorption was fast and elinzanetant was rapidly and extensively absorbed with a T_{max} between 0.5 and 2 hours, resulting in moderate bioavailability in rats (male 47%, female 77%) and marmoset monkeys (male 34%) but low bioavailability in dogs (male 19%) and cynomolgus monkeys (male 19%). The highest exposure in terms of dose-normalized AUC and Cmax was achieved in rats and monkeys, whereas a lower exposure was observed in dogs. Gender differences were seen in rats (2-3 fold higher exposure in females), but not in Cynomolgus monkeys. A rapid and extensive distribution to tissues was seen, which is in line with the high plasma volume of distribution. Terminal elimination half-life ($t_{1/2}$) values after intravenous dosing was ~7h in rats and less than 2h in dogs and Cynomolgus monkeys. Upon multiple dosing for 4 up to 39 weeks in the safety studies dose linear PK was observed and no apparent accumulation of elinzanetant was found.

In plasma, a moderate to high protein binding was found (95% in rabbit, >98% in rat, 97/>99% (m/f) in Cynomolgus monkey and >99% in human). This means that the unbound elinzanetant concentration (Fu) is about 3-6 fold higher in rat and up to 10-fold higher in male Cynomolgus monkeys compared to human. A similar metabolism was seen in rat, monkey and human; mainly mono-hydroxylated metabolite M30/34 (5-10%), mono-hydroxylated metabolite M27 and di-hydroxylated metabolite M18/21 (both below 5%) and other metabolites formed via dealkylation and N-demethylation. After oral administration, the excretion of elinzanetant was found to be largely via the biliary/faecal route (>90%), partly as unchanged parent (rat 11%, monkey 7%, human 50%) and as numerous metabolites. Renal excretion was minor route in rat (1%), monkey and human (<1%).

2.5.4.7. Local Tolerance

No dedicated local tolerance studies were conducted with elinzanetant. As elinzanetant is administered orally, this was agreed.

2.5.4.8. Other toxicity studies

Dependence

To evaluate the dependence potential of elinzanetant, GLP-compliant drug abuse liability studies in monkeys were conducted that evaluated self-administration, drug discrimination and physical dependence. According to ICH M3, non-human primates should be reserved only for those limited cases where there is clear evidence that they would be predictive of human abuse liability and the rodent model is inadequate. Notably, the advantages of the PK profile in the monkey are not very convincing, and although data on the NK-1 and NK-3 selectivity were not submitted, data on sequence homology across these species were considered supportive for the use of monkey. Brain penetration of elinzanetant is not considered markedly, but slightly higher in monkeys as compared to rats (brain to blood ratios of 0.6 and 0.1 to 0.5, respectively, also see PK section).

In a physical dependence study, elinzanetant tolerance to behavioural and withdrawal effects was assessed during a repeated dosing period of 29 days and a discontinuation phase and compared to positive control methamphetamine. There were no withdrawal signs observed after treatment with elinzanetant up to the highest tested dose of 80 mg/kg/day (orally) or 3.9 mg/kg/day (IV) as indicated by the absence of significant behavioural, cardiovascular, or physiological marker consistent with known withdrawal syndrome induced by common drugs-of-abuse. The highest unbound C_{max} on day 28 was 24.1 µg/L, corresponding to ~5 fold the clinical unbound C_{max} ~4.5 µg/L.

In a drug-discrimination test, monkeys given elinzanetant up to doses of 40 mg/kg (orally) were evaluated for drug discrimination in a 2-choice (elinzanetant versus vehicle) 2-lever operant discrimination task for food reinforcement. As there are presently no published drug discrimination studies using NK antagonists as a reference stimulus, elinzanetant was chosen as the training drug in this study following FDA recommendation. Elinzanetant did not evoke trainable interoceptive cues that could serve as discriminative cue in food-motivated monkeys trained to respond under a two-lever operant conditioning paradigm, since the responses to food rewards were lower compared to vehicle. However, failure of elinzanetant administration to serve as a clear discriminative stimulus is consistent with limited abuse potential. The highest unbound C_{max} was expected to be 3.7 µg/L, which is just below clinical unbound Cmax.

One self-administration study was conducted to evaluate the reinforcing potential of elinzanetant. Monkeys that were successfully trained to self-administer cocaine were divided in groups including 4 animals per each treatment, which were then tested with the positive control (0.032, 0.056, 0.1, and 0.32 mg/kg/injection cocaine), and/or elinzanetant (0, 0.01, 0.05, and 0.195 mg/kg/injection), administered during 1 hour access periods over the course of 3 consecutive days. Animals did not exhibit active self-administration of elinzanetant.

Together, the available data suggests that elinzanetant has a low potential for abuse based on studies of self-administration, physical dependence and drug discrimination.

Studies on metabolites

M27 was initially presumed to be a major human metabolite. A GLP-compliant study was conducted in SD rats with M27 for up to six months. There were no M27-related adverse findings up to the highest tested dose of 20 mg/kg. There were increases in leucocyte subpopulation counts, but this was considered non-adverse since in the majority of cases there was no clear dose-response, the extent of the difference from control was slight and there were no associated histopathological findings. Additionally, minor increases of plasma sodium, calcium and phosphorus concentration and higher plasma bilirubin levels were not related to microscopic findings and were therefore not adverse in this study. The NOAEL of 20 mg/kg corresponds to a safety margin for M27 of 15.3 for females and 5.5 for males based on the AUC0-24 of human M27 exposure at the therapeutic dose.

Additionally, *in vitro* GLP genotoxicity studies with M30/34, M27 and M18/21 were conducted. The *in vitro* Ames tests for M27, M30/34 and M18/M21 were negative. The in *vitro* human lymphocyte micronucleus assay for M27 and M30/34 and the *in vitro* micronucleus test in Chinese hamster V79 cells for M18/21 revealed no biologically relevant increases in micronuclei. These results indicate that M27, M30/34 and M18/21 have no potential for inducing clastogenic or aneugenic effects.

In conclusion, there are no indications for genotoxic effects of M27, M30/34 and M18/21 *in vitro*.

Phototoxicity studies

Since elinzanetant absorbs light in the visible part of the spectrum, an *in vitro* 3T3 neutral red uptake (NRU) phototoxicity assay was conducted. The highest tested concentration was 31.6 µg/mL, as higher concentrations were limited by solubility. As the mean photo effect (MPE) of 0.442, elinzanetant was considered phototoxic (value $\geq$0.15). The highest concentration with no phototoxicity, as indicated by a decrease in Neutral Red uptake, was 0.316 µg/mL, which is 73-fold the unbound clinical C_{max} (4.3 µg/L). Therefore, it can be agreed that there is a low potential for phototoxicity at clinically relevant concentrations.

Mechanistic studies

Based on the 13-week rat study, the skeletal muscle may be considered a target organ of toxicity. A non-GLP 14-day rat study was conducted to investigate muscle disposition potentially underlying the skeletal muscle findings, after repeated dosing at 50 mg/kg/day (25 mg/kg bid), 200 mg/kg/day (100 mg/kg bid) or 200 mg/kg/day as a once daily dose. No elinzanetant-related microscopic changes in the skeletal muscle were noted up to 200 mg/kg.

However, minimal focal degeneration of the skeletal muscle observed in 1/10 rats at 200 mg/kg once daily and in 3/10 rats at 100 mg/kg bid could be early signs of skeletal muscle pathology (degeneration/ necrosis) observed in the 13-week rat study. In addition, elinzanetant concentrations were approx. 8 to 10-fold higher in muscle tissue in comparison to plasma indicating accumulation of elinzanetant in the skeletal muscle. Thus, elinzanetant shows accumulation in the skeletal muscle and initial, minimal signs of skeletal muscle degeneration after repeated dosing in single rats. However, it can be agreed that since there is a safety margin of 9.1 for males and 18 for females for skeletal muscle degeneration in the 13-week rat study, skeletal muscle toxicity is unlikely to occur in humans. Skeletal muscle effects in rats are reflected in the SmPC and Part II: Module SII - Non-clinical part of the safety specification of the RMP.

2.5.5. Ecotoxicity/environmental risk assessment

Table 7 Summary of main study results

Substance (INN/Invented Name): elinzanetant			
CAS-number: 929046-33-3			
PBT/vPvB screening			
Study type	**Test protocol**	**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	log D_{ow} 4.53 at pH 4log D_{ow} 5.25 at pH 5 log D_{ow} 5.31 at pH 7 log K_{ow} 5.28 at pH 9	Potential PBT: Y
PBT/vPvB assessment			
Property	**Parameter**	**Result**	**Conclusion**
Bioaccumulation	log K_{ow}	5.28	
	BCF_{KgL}	61.1 L/kg_{ww}	not B
Persistence	Ready biodegradability	N	
	$DT_{50,system}$ at 12ºC	308 d, >1000 d	vP
Toxicity	$NOEC_{aquatic}$	0.43 µg/L	T
PBT-statement:	Elinzanetant is considered to be not PBT, nor vPvB		
Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
$PEC_{sw, default}$	0.60	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)	potentially endocrine active substance		Y

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	12.28 $mg \cdot L^{-1}$ at pH 4 2.97 $mg \cdot L^{-1}$ at pH 5 1.71 $mg \cdot L^{-1}$ at pH 7 1.55 $mg \cdot L^{-1}$ at pH 9	column
Dissociation in Water	OECD 112	Undissociated at pH 5-9	
Adsorption-Desorption Soil 1 = loamy sand	OECD 106	$K_{Foc, soil\ 1}$ = 3653 L/kg_{oc}	
Soil 2 = loam		$K_{Foc, soil\ 2}$ = 6175 L/kg_{oc}	
Soil 3 = silt loam		$K_{Foc, soil\ 3}$ = 12897 L/kg_{oc}	
Sludge 1 = urban		$K_{Foc, sludge\ 1}$ = 6633 L/kg_{oc}	
Sludge 2 = rural		$K_{Foc, sludge\ 2}$ = 5388 L/kg_{oc}	
Ready Biodegradability Test	OECD 301F	2 % (28 d) not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = silt loam	OECD 308	$DT_{50, water\ 1}$ = 6.29 d $DT_{50, sediment\ 1}$ = 543 d $DT_{50, whole\ system\ 1}$ = 152 d CO_2 = 1.5 % NER_{total} = 23 %	19.5 °C CO_2 and NER values at test end

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Sediment 2 = sand		$DT_{50,\ water\ 2}$ = 28.9 d $DT_{50,\ sediment\ 2}$ = >1000 d $DT_{50,\ whole\ system\ 2}$ = >1000 d CO_2 = 0.7 % NER_{total} = 16 %			19.5 °C CO_2 and NER values at test end
Transformation products		>10% = N			
Phase II Aquatic Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*R. subcapitata*	OECD 201	NOEC	≥450	µg/L	growth rate
Daphnia magna, Reproduction Test	OECD 211	EC_{10}	114	µg/L	reproduction
Fish, ZEOGRT draft OECD protocol /*Danio rerio*	-	NOEC	0.43	µg/L	fertilisation rate
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10}	$>1x10^6$	µg/L	respiration
Phase II Sediment Effect studies					
Sediment dwelling organism/ *C. riparius*	OECD 218	EC_{10}	398	mg/kg_{oc}	emergence normalised to 10% o.c.
Phase II Secondary poisoning					
Bioaccumulation/*Danio rerio*	OECD 305	BCF_{KgL}	61.1	L/kg_{ww}	%lipids: 8.2
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	3.46 µg/L	>100 000 µg/L	$<3x10^{-5}$		No risk
Surface water	0.34 µg/L	0.043 µg/L	7.9		Risk
Sediment	0.0.43 mg/kg_{dw}	3.98 mg/kg_{dw}	0.11		No risk

* e = emergence, m = mortality, fw = fresh weight, pht = phytoxicity.

A risk to the surface water compartment is anticipated based on the prescribed use of elinzanetant.

All required studies on Phase II A have been submitted and found reliable for use in the risk assessment. The applicant's PEC calculations are endorsed.

Following the Phase II A risk assessment, using an unrefined PECsw, no risk is anticipated for the sewage treatment plant and the sediment compartment. A potential risk is identified for the surface water compartment.

For the Phase II, the applicant's refinement of PECsw is correct. The refined PEC_{sw} is 0.34 µg/L. A risk is anticipated for the surface water compartment after refinement of PECsw.

The logarithmic partition coefficient of elinzanetant is 53 at environmentally relevant pH values. At pH 5-9, elinzanetant is considered to be predominantly neutral. The log Kow value at this pH exceeds the trigger value of 4.5, therefore elinzanetant is potentially bioaccumulative. A further PBT/vPvB assessment is deemed necessary.

Based on evaluation of the available data, elinzanetant meets the vP and T criterion and does not meet the B criterion.

Considering the above data of the definitive hazard assessment, elinzanetant is not a PBT nor vPvB substance.

Considering the data from Phase I and Phase II, elinzanetant may pose a risk to the aquatic environment. This was reflected adequately in the Product information.

2.5.6. Discussion on non-clinical aspects

Primary pharmacodynamics

The suggested mechanism of action of elinzanetant involves antagonism of both NK-1 and NK-3 receptors. Several *in vitro* studies have been performed to support this MoA. For all species except rat, affinities for the NK-1 receptor were very high. Affinity for rat NK-1 receptor was lower than for the other four species. Elinzanetant's affinity for NK-3 receptors was lower than for NK-1 receptor for human, gerbil and guinea pig. Additional data on sequence homology across species was considered supportive for the use of cynomolgus and mouse.

Elinzanetant was shown to act as an insurmountable antagonist for human NK-1 receptor. Several functional assays confirmed these antagonistic properties of elinzanetant for the human NK-1 and human and marmoset NK-3 receptors. Elinzanetant also displayed insurmountable antagonistic properties for guinea pig NK-3 receptor. In contrast, elinzanetant displayed (weak) surmountable antagonism for rat NK-3 receptor.

Ex vivo autoradiography studies on brain tissue were aimed at determining receptor occupancy and receptor binding. In two studies with Mongolian gerbils, elinzanetant entered the CNS of Mongolian gerbils, where it bound to NK-1 and NK-3 receptors dose and concentration dependently. Similarly, two studies with guinea pigs showed dose dependent increases of NK-1 and NK-3 receptor occupancies. Blood and brain concentrations increased dose-dependently as well. In one of these studies, brain slice autoradiography in male guinea pigs after dosing of elinzanetant in the presence or absence of haloperidol revealed that haloperidol did not affect receptor occupancy of NK-1 receptor.

The primary PD characteristic of elinzanetant was complemented by data describing the effect of this NK3 receptor antagonist on sex hormone levels. Trends in sex hormones measured (follicle-stimulating hormone, testosterone, estrogen, and dehydroepiandrosterone sulfate), including their clinical significance are described in SmPC section 5.1.

In summary, the Applicant has provided studies in several species that support the mechanism of action *in vivo* for elinzanetant, as it has been shown that elinzanetant acts as an antagonist of both NK-1 and NK-3 receptors.

Secondary pharmacodynamics

Multiple selectivity screens revealed no relevant inhibition for any of the selected targets. Therefore, no relevant clinical effects are anticipated for any of the tested targets.

In vivo, elinzanetant showed an anxiolytic-like profile in a marmoset human threat test, trends toward improved working memory and attentive processing in Rhesus monkeys, inhibition of amphetamine-induced rearing in guinea pigs, and no effects on cocaine drug administration and self-administration in Rhesus monkeys.

For the three metabolites M27, M30/M34 and M18/21, K_i values for the progesterone and estrogen receptor were determined and were concluded to indicate low clinical risk.

Safety pharmacology

A hERG assay for elinzanetant as well as an automated patch clamp analysis for the metabolites M27, M30/M34 and M18/M21 revealed no relevant inhibition of hERG (elinzanetant) as well as cardiac ion channels (metabolites), confirming the low risk of elinzanetant- or metabolite-associated inhibition in humans.

In a GLP-compliant study on the cardiovascular system in Cynomolgus monkey, a dose of 60 mg/kg produced a mild, reversible increase in heart rate from approximately 11 to 17 hours after dosing and a mild, reversible decrease in body temperature from approximately 3 to 6 hours after dosing, whereas all other parameters were unchanged. Exposures associated with the 60 mg/kg dose were clinically relevant.

In two GLP-compliant studies in SD rats, neuro-behavioural effects (modified Irwin assay) and body temperature as well as respiratory function were investigated after an elinzanetant dose of 5, 25 or 100 mg/kg. No relevant effects on any of the investigated were observed for any of the dose levels.

Pharmacokinetics

The possible conversion of the degradation product M22 of elinzanetant back to elinzanetant during sample preparation was investigated in human plasma with no hint on back-conversion of M22 to elinzanetant. The pharmacokinetic profile of elinzanetant shows differences between species, mice, rats, rabbits, dogs, marmoset monkeys and Cynomolgus monkeys with regard to clearance and bioavailability. In addition, sex differences were observed in rats with higher exposure in females. Rats, rabbits and Cynomolgus monkeys were considered the most suitable species for investigation of effects of elinzanetant in toxicological studies.

Toxicology

Pivotal GLP-compliant repeated dose studies were conducted in Sprague Dawley (SD) rats and Cynomolgus monkeys. Recovery groups were included in one of the 13- week rat studies but unfortunately not in Cynomolgus monkeys. SD rats and Cynomolgus monkeys were selected as species for the investigation of systemic toxicological effects based on pharmacological responsiveness (potency, sequence homology, and pharmacologic effects on the NK receptors) as well as based on the pharmacokinetic and metabolic profile. Elinzanetant antagonizes rat NK-1 receptor and NK-3 receptor activity but is less potent, especially compared to human NK-3 (approx. 30-fold). Although data on the NK-1 and NK-3 selectivity were not submitted, data on sequence homology across these species were considered supportive for the use of monkey (see 3.2.6 PD). In addition, the substantiation based on the pharmacokinetic and metabolic profile behind the choice for the monkey as non-rodent species, instead of dogs, is based on the high clearance in dogs (1.8 L/h.kg, near liver blood flow) compared to monkey (moderate clearance, ~50% of liver blood flow). After oral administration elinzanetant showed a low bioavailability in cynomolgus monkeys and dogs. However, a higher exposure in terms of dose-normalized AUC was achieved in monkeys (0.17 l*h/kg) compared to dogs (0.11 kg*h/L), while the dose normalized C_{max}, was similar in monkey (0.046 kg/L) and dog (0.048 kg/L).

In general, the skeletal muscles, reproductive organs, the CNS and the gastrointestinal tract may be targets of toxicity of elinzanetant.

In the 4-week monkey study, at 60 mg/kg, one male and one female were euthanized due to elinzanetant-related body weight loss and deteriorating clinical condition. In addition, adverse kidney toxicity was noted, although it was not discussed whether this was the underlying cause of morbidity. In addition, there were effects secondary to inanition or stress on the pancreas, liver, gastrointestinal tract, heart, thymic cortex and adrenal cortex. The 60 mg/kg dose corresponds to a MoE of 4.7- and 3.6- fold the clinical exposure in males, and females respectively, which were not reached in subsequent longer toxicity studies, although monkeys were dosed up to 80 mg/kg. Nevertheless, there is a low safety margin for morbidity in the monkey (0.8 and 1.2 for males and females, respectively, based on total AUC). Both cases were likely related to severe

dehydration due to severe diarrhoea. These effects do not appear to be linked to higher C_{max} levels reached in these short-term studies compared to the chronic tox studies. Since severe diarrhoea in humans would lead to cessation of treatment before marked dehydration, body weight loss and deteriorating general condition appears, the clinical relevance of this finding is considered low.

Although in the dedicated fertility studies no effects on fertility in rats was observed, the effects on reproductive organs of the females in both rat and monkey repeated dose toxicity studies were considered to be a pharmacological effect. In monkeys, effects on the reproductive organs occurred at clinically relevant exposures.

Elinzanetant exerted CNS-related clinical signs including convulsions and has a known CNS activity. However, it does not interact with pharmacological targets known to be seizure-related, only at concentrations far exceeding the human therapeutic protein-unbound plasma concentration, and no clear pattern was observed across species. Therefore, it is unlikely that convulsions are expected in patients treated with elinzanetant.

Adverse gastrointestinal reactions were reported in the 39-week monkey study. The NOAEL for GI effects in monkey is 60 mg/kg/day, corresponding to a safety margin of 2-fold the human therapeutic exposure. The gastrointestinal disorders are mentioned in the Product Information.

The kidney findings in rats do not indicate a primary effect of elinzanetant on the kidneys, but rather a secondary effect of the general well-being of the animal. In monkeys, the effects were likely secondary to severe dehydration. No effects were seen in mice. In addition, no effects on the kidney were observed in patients, therefore the clinical relevance of these findings are considered low.

Elinzanetant was shown to be not genotoxic.

No carcinogenic potential was observed in a six-month carcinogenicity transgenic mouse model (tg RasH2).

Among early sacrifice animals in the 2-year rat carcinogenicity study, moderately to markedly higher white blood cell count was noted in a few animals, due to the presence of immature hematopoietic cells (including blasts), likely reflecting hematopoietic neoplasia but this occurred only in animals with malignant lymphomas. Since the observed changes were observed at doses at least 29-fold higher than the therapeutic exposure in humans, it is not a relevant risk to humans.

Elinzanetant-related neoplastic findings in the 2-year rat carcinogenicity study included a significantly increased incidence of uterine neoplasms and malignant lymphomas of the haematolymphoid system in females administered ≥60 mg/kg/day. The dose level of 20 mg/kg/day has no evidence of an increase in carcinogenic effect due to elinzanetant. This dose level corresponds to a safety margin of ~7-fold or ~21-fold the clinical exposure based on total AUC0-24 or unbound AUC0-24, respectively. As a safety margin of ~7-fold is relatively low, the Applicant conducted its own assessment on the findings in the rat carcinogenicity study and concluded that there is no safety risk for humans. Overall, it is acknowledged that the alteration of normal reproductive ageing in rats due to chronic drug induced hyperprolactinemia as a result of NK-1 receptor antagonism and subsequent reduced prolactin release is a plausible mechanism which is not relevant for humans. Literature indicates that Wistar rats, but not SD rats, are sensitive for the increased uterine tumours associated with reduced levels of prolactin. Still, it was argued that the association was potentially less strong for SD rats due to the lower numbers of included SD rats as well as due to differences in background incidences between SD rats and Wistar rats. Based on literature, it was stated that both reproductive aging and cyclical arrest, along with the resulting estrogen/progesterone ratios, may be similarly affected in Wistar and SD rats under conditions of drug-induced hypoprolactinemia. A direct contribution of

elinzanetant to the formation of uterine tumour is unlikely since there was no evidence of primary estrogenic and genotoxic/mutagenic activity of elinzanetant throughout the non-clinical studies.

There was an increase in malignant lymphomas of the haematolymphoid system. However, the findings are not clinically relevant, based on the fact that the incidences of malignant lymphomas were observed at doses exceeding the MTD (based on severe body weight loss), observed at exposures at least 29-fold the human AUC and only significant at 33-fold the human AUC, the absence of tumorigenic potential in transgenic mice and the absence of genotoxicity, chronic inflammation or immunosuppressive activity based on the available toxicology data. Overall, it can be agreed that there is a low risk for malignant lymphomas in women being treated with elinzanetant.

Taking into account that elinzanetant is proposed to be used in subjects under AET therapy, who are at high risk for developing cancer, it was investigated whether findings related to carcinogenicity potential observed in the non-clinical development program should not be considered relevant for humans. In the 2-year carcinogenicity study, a shift in incidences of commonly occurring tumours of hormone-sensitive tissues with increased incidences of uterine neoplasms was observed at the two high doses of 60 and 80 mg/kg/day. The observed changes included increased incidences of uterine adenocarcinoma and squamous cell carcinoma as well as one uterine adenoma. Moreover, increase in endometrial hyperplasia with atypia was observed. The Applicant assumed that since elinzanetant has no intrinsic estrogenic activity, the possible mechanism responsible for the observed increased incidences can be rat-specific, not relevant for humans, drug-induced hypoprolactinemia via its NK-1 receptor antagonistic activity. With respect to malignant lymphoma, in the 2-year carcinogenicity study increased incidences of malignant lymphoma were noted at the high doses of 60 or 80 mg/kg/day with drug accumulation and high multiples of exposure of 29 or 33 in terms of total AUC in comparison to human therapeutic exposure. The increase of lymphomas was only statistically significant at 80 mg/kg/day, while the incidence at 60 mg/kg/day was exceeding the Historical Control Data of 0-5% only by one case. This finding seems to be of spontaneous origin. In the clinical studies OASIS 1, 2, 3 and 4 no cases of malignant lymphoma were reported. With respect to the recurrence of breast cancer, in the 2-year carcinogenicity study in rats, incidences of breast-cancer (mammary tumours) were markedly reduced in comparison to controls. It is agreed that non-clinical data on elinzanetant do not indicate a cancer risk for women under AET therapy.

The effects in rat and monkey included a lack of cyclical activity in the ovaries, no evidence of corpora lutea or maturing follicles and a reduction in reproductive organ weight. In monkeys, effects on the reproductive organs occurred at clinically relevant exposures. For women not of reproductive potential, these findings are not relevant. However, as elinzanetant is also proposed to be indicated for the treatment of moderate to severe vasomotor symptoms (VMS) caused by adjuvant endocrine therapy, who may be premenopausal women, the risk of infertility in premenopausal females taking elinzanetant and the possible reversibility of such an effect was addressed. Although data on the menstrual cycle after long-term treatment of women with elinzanetant as well as fertility (e.g., pregnancy) are lacking, the available non-clinical data do not indicate a strong effect on fertility. It is agreed that the lack of cyclical activity after chronic treatment in monkeys after treatment with NK-3 antagonists is reversible after cessation of treatment. In addition, there was no effect on the primordial follicle pool in monkeys. Short-term data from pre-menopausal women demonstrated prolongation of the menstrual cycle, but no cyclic arrest. Therefore, is agreed that the risk of infertility in women during and after elinzanetant treatment is likely low.

The NOAEL for embryofoetal development in the EFD rat study was 100 mg/kg/day, resulting in a safety margin of around 23-fold for total or 64-fold for unbound exposure compared to human exposure at the intended dose. In contrast, in the PPND study in rats, a dose of 100 mg/kg/day was not well tolerated

resulting in maternal toxicity and effects on the F1 (stillborn pups, increased post-implantation loss and decreased pup body weight). This discrepancy has been explained by the differences in dosing period and role of the NK-1/3 receptor during this period. As NK-1 receptor agonism can induce rat uterine contractions, it is plausible that antagonism of the receptor can cause a delay in contraction and therefore increased gestation time. It is likely that interference in this process during late pregnancy also has an effect on the foetuses, while such an effect during the EFD stages up to GD 17 are not anticipated. Indeed, the earliest time-point at which maternal toxicity resulted in death was at GD 18. The clinical relevance of this finding has not been further discussed by the applicant and can therefore not be ruled out. It is clear that NK1 and NK3 receptors play a role in the regulation of uterine function during pregnancy and parturition. The Applicant proposed a CI pregnancy for elinzanetant to prevent any risk, e.g. for a potential pregnancy in peri-menopausal women. This was agreed.

At clinically relevant doses, there was total litter loss from PND 0-4 in the PPND study in rats due to lack of nursing. This lack of nursing is explained by the applicant by a possible reduced oxytocin level in the dams, leading to diminished milk ejection. Although oxytocin levels have not been measured in the study, literature data indicates that NK-1 agonism leads to release of oxytocin while antagonism countered this effect. This explanation appears plausible and can be accepted. The clinical relevance cannot be ruled out.

There was no phototoxicity and abuse potential of elinzanetant at clinically relevant concentrations. The main metabolites and drug substance impurities are sufficiently characterized.

Due to the identified potential environmental risk, the Product Information includes statements to limit the environmental impact.

2.5.7. Conclusion on the non-clinical aspects

The mechanism of action of elinzanetant has been sufficiently described. Elinzanetant is shown to act as an insurmountable antagonist with high affinity for NK-1 and NK-3 receptors, with a preference for the NK-1 receptor. Elinzanetant was shown to enter the CNS and result in NK-1 and NK-3 receptor binding, with the highest receptor occupancies observed for the NK-1 receptor.

The absorption, distribution, metabolism, and excretion (ADME) of elinzanetant was adequately evaluated in *in vitro* systems (PPB, metabolism) and using *in vivo* PK studies (PO, IV) in the mouse, rat, rabbit, dog and monkey. In addition, the *in vivo* multiple-dose TK of elinzanetant was conducted via oral administration to Sprague-Dawley rats, New Zealand White rabbits and cynomolgus monkeys, which were used as part of the non-clinical safety program.

The repeat dose toxicity studies showed that skeletal muscles, reproductive organs, the CNS and the gastrointestinal tract may be targets of toxicity of elinzanetant. Elinzanetant was shown not to be genotoxic. There were no elinzanetant-related neoplasms in the 6-month transgenic mouse carcinogenicity study. In the rat carcinogenicity study, there were no elinzanetant-related tumours up to exposures 7-fold the clinical exposures. In reproductive toxicity studies (FEED and PPND), elinzanetant caused pre-and post-implantation loss, associated with lower foetal weights, pup body weights and pup viability. There was no phototoxicity and abuse potential of elinzanetant at clinically relevant concentrations. The main metabolites and drug substance impurities were sufficiently characterized.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacology of elinzanetant was assessed in healthy volunteers and patients with vasomotor symptoms. Dedicated healthy volunteer studies assessed the effect of food, absolute oral bioavailability, relative bioavailability, intrinsic factors (race, renal impairment and hepatic impairment), and several drug-drug interactions (DDI) on the pharmacokinetics of elinzanetant. Furthermore, a mass-balance study characterised absorption, metabolism and excretion of elinzanetant. In addition, DDI studies with elinzanetant as perpetrator were performed. Table 8 provides an overview of the clinical PK studies.

Table 2 Summary of studies supporting the clinical pharmacokinetics of elinzanetant

study	description	dosing regimen
		PK studies in healthy subjects
21673	PK and PD and safety	Part A single oral dose of 10 mg, 30 mg, 60 mg, 120 mg or 160 mg Part B single oral dose of 3 mg, 7.3 mg, 9 mg, 10 mg, 16 mg, 70.4 mg or 115.3 mg
21670	PK and safety	single oral dose of 240 mg, 360 mg, 480 mg or 600 mg
21678	PK (incl. food effect) and safety	single oral dose of 40 mg, 80 mg, 120 mg or 160 mg and multiple oral dose of 40 mg, 80 mg, 120 mg or 160 mg once daily for 7 days
21703	PK of parent and metabolites	multiple oral dose of 120 mg once daily for 14 days
21664	mass balance	single oral dose of 120 mg
21772	absolute oral bioavailability	single oral dose of 120 mg + after 1 h IV infusion of 100 µg
21675	food effect	single oral dose of 100 mg under fasted or fed conditions or 200 mg under fasted conditions
21676	alcohol effect	single oral dose of 200 mg
21680	effect on hormones	multiple oral dose of 40 mg, 80 mg or 120 mg once daily for 22 days
22653	PK and safety	Treatment A 120 mg elinzanetant was given on Days 1-5 and zopiclone placebo on Days 1 and 5 Treatment B 240 mg elinzanetant was given on Days 1-5 and zopiclone placebo on Days 1 and 5

		Treatment C 7.5 mg zopiclone was given on Days 1 and 5 and elinzanetant placebo on Days 1-5 Treatment D elinzanetant placebo was given on Days 1-5 and zopiclone placebo on Days 1 and 5.
21665	food effect and relative bioavailability between 40 mg and 60 mg soft capsule	single oral dose of 120 mg either 1 or 3 hours after a meal
21677	food effect and relative bioavailability between 25 mg soft gel and 100 mg (2 x 50 mg) hard gel capsule	single oral dose of 25 mg under fasted or fed conditions or 100 mg under fasted conditions
22050	relative bioavailability between 120 mg (3 x 40 mg) and 120 mg (2 x 60 mg) soft capsule	single oral dose of 120 mg multiple oral dose of 120 mg
	PK studies in patients with vasomotor symptoms	
21681	PK and PD	single oral dose of 50 mg, 100 mg, 150 mg or 300 mg multiple oral dose of 50 mg, 100 mg, 150 mg or 300 mg once daily for 14 days
	PK studies in special populations	
21669	renal impairment	single oral dose of 120 mg
21668	hepatic impairment	single oral dose of 120 mg multiple oral dose of 120 mg once daily for 6 days
21756	PK in Chinese women	single oral dose of 120 mg multiple oral dose of 120 mg once daily for 6 days
21774	PK in Japanese women	Part A single oral dose of 120 mg under fasted conditions and 40 mg, 80 mg, 120 mg, 160 mg under fed conditions Part B multiple oral dose of 120 mg once daily under fed conditions
	DDI studies	
21666	effect of elinzanetant on PK of rosuvastatin	single oral dose of 5 mg rosuvastatin on Day 1, Day 8 and Day 13 multiple oral dose of 120 mg elinzanetant once daily on Day 4 to 15
21840	effect of elinzanetant on PK of midazolam	Period 1 single oral dose of 1 mg midazolam on Day 1 Period 2 single oral dose of 1 mg midazolam and 120 mg elinzanetant on Day 1 Period 3 multiple oral dose of 120 mg elinzanetant once daily on Day -13 to 1, single oral dose of 1 mg midazolam on Day 1
22004	effect of elinzanetant on PK of tamoxifen	Period 1 single oral dose of 20 mg tamoxifen Period 2 multiple oral dose of 120 mg elinzanetant once daily on Day -6 to 22 single oral dose of 20 mg tamoxifen on Day 1
22081	effect of elinzanetant on PK of dabigatran etexilate	Period 1 single oral dose of 75 mg dabigatran etexilate Period 2 single oral dose of 120 mg elinzanetant

		single oral dose of 75 mg dabigatran etexilate
21667	effect of carbamazepine on PK of elinzanetant and midazolam	Period 1 single oral dose of 1 mg midazolam on Day -1 and Day 1 single oral dose of 120 mg elinzanetant on Day 1 Period 2 multiple oral dose of carbamazepine 200 mg on Day -15 and -14, and 400 mg on Day -13 and -12 and 600 mg on Day -11 to 6 single oral dose of 1 mg midazolam on Day -1 single oral dose of 120 mg elinzanetant on Day 1
21679	effect of itraconazole on PK of elinzanetant	Period 1 single oral dose of 40 mg elinzanetant Period 2 single oral dose of 40 mg elinzanetant single oral dose of 200 mg itraconazole
21772	effect of esomeprazole on PK of elinzanetant	multiple oral dose of 40 mg esomeprazole on Day -4 to 1 single oral dose of 120 mg elinzanetant on Day 1

Furthermore, several *in vitro* studies were performed investigating the permeability, plasma protein binding, blood-to-plasma ratio, metabolic stability in human liver microsomes and human hepatocytes and if elinzanetant was a substrate of CYP enzymes and transporters. Furthermore, *in vitro* studies were performed to investigate whether elinzanetant was an inhibitor or inducer of CYP enzymes or transporters. In addition, *in vitro* inhibition studies were conducted for the human metabolites M27, M30/34 and M18/21 towards CYPs, UGTs and transporters.

Elinzanetant has 2 chiral centres and is in the 7S and 9aS configuration. No inter-conversion occurs *in vivo*. Based on *in vitro* studies in Caco2 cells, elinzanetant is most likely a highly permeable compound.

Analytical methods

Several bioanalytical methods have been developed and partially validated or validated to determine plasma and urine concentrations of elinzanetant and M18/21, M27 and M30/34 (main metabolites). In addition, one validated analytical method was developed for M22. LC-MS/MS with internal standards were used to measure plasma and urine concentrations. Analytical procedures differed in extraction method and liquid chromatography and mass spectrometry equipment and settings. The major analytical methods were VPT4371 V05 and SBQ-20320. Analytical methods GSK1144814 HUPL VALA (studies 21673 and 21675) and NT81HPP V01 (study 21703) were used to determine the PK in healthy volunteers. The number of PK studies using these analytical methods is limited and therefore the impact of no cross-validation is limited.

Modelling

Population PK (PopPK) modelling
Two PopPK models were developed and aimed at describing the overall pharmacokinetic profile of elinzanetant and its metabolites (first PopPK analysis) and quantifying the variability and influences of intrinsic and extrinsic factors in the relevant patient population (second PopPK analysis). Generally, model development, covariate analysis and model validation and application seem robust and are adequately summarised.

For the first model, it seems that the absorption phase was not well estimated by the first PopPK model. Sufficient data from clinical studies are available, the effects of formulation, fed status and circadian rhythm on elinzanetant pharmacokinetics can be investigated using these studies. The second PopPK model is

deemed fit for purpose to simulate the exposure in healthy volunteers and VMS patients. Vasomotor symptom status was found to be a significant covariate.

Physiologically-based pharmacokinetic (PBPK) modelling
A physiologically-based pharmacokinetic (PBPK) model for elinzanetant and its major metabolite M30/34 was developed to predict the influence of strong, moderate and weak CYP3A4 inhibitors on the exposure of elinzanetant and M30/34. Generally, simulations for model evaluation of the predicted versus observed concentration-time data of multiple clinical studies show good agreement for elinzanetant and M30/34. The PBPK model is suitable to predict the effect of moderate and weak CYP3A4 inhibitors on the PK of elinzanetant.

Exposure-response modelling
The relationship between exposure ($C_{trough,ss}$) and hot flashes frequency and severity could be described using an E_{max}-model. Two significant covariates were found. Participants aged ≤54 years had a stronger steady-state placebo effect compared to participants >54 years. Also, participants experiencing their vasomotor symptoms at baseline as less bothersome according to MENQVM (score ≤6) showed a slightly stronger steady-state placebo effect compared to patients with a higher symptom burden (score >6). A covariate search for drug effect parameters showed that none of the investigated covariates had a significant impact on drug effect parameters. Overall, the model was acceptable and fit for purpose. Fixing the EC_{50} to the estimated EC_{50} 71.8 µg/L from the frequency model could also describe to exposure-dependent effect for severity. Baseline values and time after first dose were found to be highly significant covariates. The placebo-effect was more pronounced in study 21810 compared to studies 21651 and 21652 and the improvement of hot flushes severity over time was more pronounced in study 21810.

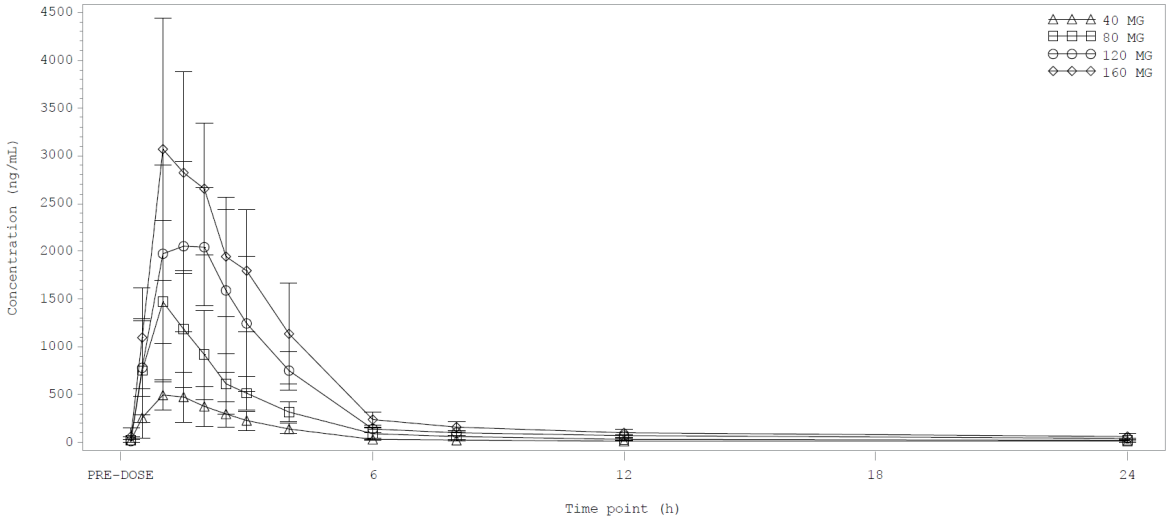
No exposure-response model was developed to describe the relationship of elinzanetant exposure with abnormal elevation of AST or ALT levels (3x ULN), because no difference between placebo and treatment effect could be detected. A logistic regression model was used to describe the exposure-safety relationship of elinzanetant exposure with adverse events of special interest (somnolence, fatigue, and dizziness). Treatment with 120 mg daily elinzanetant is associated with a 3-4-fold increased risk for AESI (somnolence, fatigue, and dizziness). From the updated model, it seems like this does also apply for the separated AESIs, and that there is no significant change between daily doses with 40-160 mg, or that it increases slightly with doses >120 mg. However, as the model is less well informed with data of doses other than 120 mg and lower number of separated AESIs, no certain conclusions could be drawn.

Absorption

The pharmacokinetics of elinzanetant in healthy adult subjects was investigated in the dose range of 10 to 600 mg after a single oral dose and of 40 to 160 mg once daily following repeated dosing. The absolute oral bioavailability of elinzanetant is 52%. Elinzanetant soft gel capsules show a dose-proportional increase in C_{max} in the dose range of 25 to 600 mg. The AUC increases dose-proportional in the dose range 25 to 120 mg and greater than dose proportional in the dose range 160 to 600 mg. The greater than dose proportional increase in exposure may be explained by saturation of metabolism.

After a single oral dose of 120 mg under fasted conditions, elinzanetant is absorbed with a median t_{max} of 1.0-1.8 hours. The intended commercial formulation further demonstrated a mean C_{max} of 1216-1870 ng/mL and mean $AUC_{0\text{-}inf}$ of 5180-7200 ng × h/mL after a single dose of 120 mg. The concentration-time profile following a single dose is shown in Figure 5.

Figure 5 Plasma elinzanetant concentrations (ng/mL) after a single dose of 40 mg, 80 mg, 120 mg and 160 mg elinzanetant on a linear scale (study 21678)



The median t_{max} after multiple doses was 1.0-1.5 hours under fasted conditions and was comparable with the t_{max} after a single dose. The intended commercial formulation further demonstrated a mean C_{max} of 1830-2350 ng/mL and mean AUC_{0-24} of 8690-10300 ng × h/mL after repeated dosing with 120 mg once daily. The accumulation ratio for elinzanetant is 1.2-1.6 for the C_{max} and 1.6-2.1 for AUC after multiple doses with 120 mg. Steady state after multiple doses of 120 mg elinzanetant as soft gel capsules once daily was achieved by 5 to 8 days. In addition, a time dependency was observed with a linearity factor (R_{lin}) of 1.4, suggesting some degree of metabolic auto-inhibition.

Following a single oral dose, the inter-individual variability ranged from 27 to 120% for the C_{max} and from 17 to 77% for the AUC. Following repeated oral dosing, the inter-individual variability ranged from 26 to 58% for the C_{max} and from 17 to 64% for the AUC. The inter-individual variability in C_{trough} ranged from 28 to 75% at steady state at the clinical dose of 120 mg elinzanetant. Furthermore, in the PopPK model the residual error for elinzanetant observations was between 58-78%, indicating a high intra-individual variability in measured plasma concentrations.

It was observed that the pharmacokinetics of elinzanetant are subject to circadian fluctuations with higher exposure when administered in the evening compared to the morning. This is probably caused by changes in clearance over time due to the fluctuation in fraction unbound by changes in the free fatty acid plasma concentrations affecting the binding of elinzanetant to albumin.

It is difficult to compare the food effect across studies because of the high inter-individual variability of elinzanetant and the different study conditions. The C_{max} and AUC_{0-24} are lower under fed conditions. When comparing the AUC extrapolated to infinity, the exposure is shown to be comparable between fed and fasting conditions. The food effect is not expected to be of clinical relevance for efficacy.

Different formulations (oral solution, film-coated tablet, hard gel capsule, and soft gel capsule) were used in the clinical studies. The intended commercial formulation is a 60 mg soft gel capsule. During the clinical program, the most extensively used formulations were the commercial formulation of the 60 mg soft gel capsules and 40 mg soft capsules. The soft gel capsules of 40 mg and 60 mg and 50 mg hard gel capsules have sufficiently comparable exposure to elinzanetant and the clinical data with these formulations can be bridged. The pharmacokinetic data derived with the suspension and tablet formulations should be interpreted with caution, because the data indicate a lower C_{max} compared to the soft gel capsule formulation.

Distribution

The *in vitro* plasma protein binding of elinzanetant was investigated over a concentration range of 706 to 6739 µg/L using the Transil method. The blood plasma protein binding is high (>99%). The *in vitro* blood-to-plasma ratio ranged from 0.57 to 0.66, indicating that elinzanetant does not accumulate in red blood cells.

Elinzanetant has a volume of distribution (Vz) of 241 L (CV%=30; ranging from 157-365 L) indicating that elinzanetant has extensive extravascular distribution. This is in line with a Vd of 168-233 L predicted with the PopPK model. Furthermore, positron emission tomography (PET) showed that elinzanetant is able to pass the blood-brain-barrier and penetrate into the brain.

Elimination

The majority of the radioactivity is eliminated via faeces (~90%) and only a very limited amount is eliminated via urine (<1%). The elimination time of the radioactivity is in-line with the observed terminal elimination half-life of elinzanetant and its metabolites. In clinical studies, an elimination half-life of 11.2 to 33.8 h was observed following a single oral dose of 120 mg elinzanetant. Based on the accumulation ratio's the effective $t_{1/2}$ can be calculated ($t_{1/2,eff}$ = tau*ln(2)/ln[R_{ac}/(R_{ac}−1)]). The calculated $t_{1/2,eff}$ is 17 to 26 hours.

Special populations

Dedicated clinical studies were conducted to investigate the effect of renal (moderate and severe) and hepatic (mild and moderate) impairment. Furthermore, PK studies were conducted in healthy Caucasian, Japanese and Chinese women to identify the effect of ethnic factors on the PK. In addition, the PopPK model was used to investigate the effect of gender, ethnic factors, body weight and BMI on the PK.

- *Renal impairment.* In subjects with normal and severe renal impairment the exposure to elinzanetant is similar, but higher in subjects with moderate renal impairment. However, the unbound exposure to elinzanetant is ~2-fold higher in subjects with moderate and severe renal impairment compared to subjects with normal renal function.
- *Hepatic impairment.* Total exposure to elinzanetant was increased ~1.3-fold in subjects with mild hepatic impairment and 2.3-fold in subjects with moderate hepatic impairment compared to normal hepatic function. Unbound exposure of elinzanetant was marginally increased in participants with mild and moderate hepatic impaired function. The effect of severe hepatic impairment on the PK of elinzanetant was not investigated.
- *Gender.* The exposure to elinzanetant is lower in male subjects compared to female subjects, but not statistically significant. However, since the intended patient population for elinzanetant is women with vasomotor symptoms due to menopause, gender differences are not of importance.

- *Ethnic factors.* Two dedicated PK studies were conducted to investigate the PK of elinzanetant in Chinese and Japanese women. In Caucasians, the PK was investigated under fasted and different fed conditions and at different dosing times (morning versus evening). In Chinese women, the PK was investigated under semi fed conditions (3 h after a meal) following a dose in the evening. In Japanese women, the PK was investigated under fed conditions following a dose in the morning. Clinical studies have shown that the PK of elinzanetant depends on the time of dosing with higher exposure following evening dosing compared to morning dosing. Additionally, the Applicant conducted PopPK modelling to estimate the exposure to elinzanetant dosed in the evening following once daily dosing with 120 mg. The estimated exposure in Chinese women following once daily dosing with 120 mg elinzanetant once in the evening is higher than that of Caucasian of Japanese women. In contrast the estimated exposure in Japanese women following once daily dosing with 120 mg elinzanetant once in the evening is lower than that of Caucasian women. Furthermore, the effect of ethnic factors on the PK was also investigated using the PopPK model (Black versus others and White versus others). No significant influence of ethnic factor on the exposure of elinzanetant was detected with a slightly lower exposure in subjects of Black ethnic origin versus others (~0.85-fold) and a slightly higher exposure in subjects of White origin versus others (~1.2-fold). However, the incidence of adverse events up to Week 52 was numerically higher in women of White race compared to women of Black or African American race (52.8% vs 36.8%), in particular in such adverse events as headache (7.9% versus 3.7%), fatigue (5.9% versus 2.2%) and dizziness (3.2% versus 1.5%).
- *Body weight and BMI.* The effect of body weight and BMI on the PK of elinzanetant was investigated using the PopPK model. Increasing body weight and BMI is associated with higher exposure. $AUC_{0\text{-}24,ss}$ increases by approximately 535 µg × h/L for each increase of 10 kg in body weight and increases by approximately 1060 µg × h/L for each increase of 5 kg/m^2 in BMI.
- *Age*. A 10% increase was observed with age from 48 years to 61 years using PopPK modelling. The patient population is adult women with vasomotor symptoms due to menopause. Therefore, the patient population will most likely not consist of women >65 years.

Pharmacokinetic interaction studies

Elinzanetant as victim

In vitro studies indicated that elinzanetant is a substrate of CYP3A4 and to a more limited extent to CYP3A5 and UGTs. Furthermore, elinzanetant is a substrate of P-glycoprotein.

Clinical DDI studies were conducted to investigate the effect of CYP3A4 and P-glycoprotein inhibition and induction on the PK of elinzanetant. The exposure to elinzanetant was increased when co-administered with a strong CYP3A4 and P-glycoprotein inhibitor (C_{max} increased 3.3-fold and AUC increased 6.3-fold). PBPK modelling indicated that co-administration with the moderate CYP3A4 inhibitor erythromycin leads to a 2.0-fold increase in C_{max} and a 3.0-fold increase in AUC. PBPK modelling also showed that co-administration with the weak CYP3A4 inhibitor cimetidine leads to a 1.3-fold increase in C_{max} and a 1.5-fold increase in AUC.

Furthermore, the exposure to elinzanetant was decreased when co-administered with a strong inducer of CYP3A4 and P-glycoprotein (C_{max} decreased 1.8-fold and AUC decreased 2.8-fold).

The effect of increased gastric pH on the PK of elinzanetant was also investigated in a clinical DDI study with the proton pump inhibitor esomeprazole. The exposure to elinzanetant was not affected by increased gastric pH. Thus, elinzanetant can be given with proton pump inhibitors or other medicinal products that increase the gastric pH.

Elinzanetant as perpetrator
In vitro studies indicated that at maximal intestinal concentrations elinzanetant is an inhibitor of CYP3A4 and the transporters P-glycoprotein and BCRP. At maximal portal vein concentrations, elinzanetant is an inhibitor of OATP1B1 and 1B3. At maximal systemic concentrations, elinzanetant is a direct and time-dependent inhibitor of CYP3A4 and an inhibitor of the transporters P-glycoprotein, BCRP, OATP1B3, and MATE1. Elinzanetant is not an inducer via AhR, CAR, or PXR at clinically relevant concentrations.

Clinical studies were performed investigating the inhibition potential of elinzanetant towards CYP3A4 (single and repeated dosing with elinzanetant) and the transporters P-glycoprotein (dabigatran etexilate) and BCRP, OATP1B1 and 1B3 (rosuvastatin). Elinzanetant is a weak inhibitor of CYP3A4 using midazolam as index substrate (C_{max} increased 1.1- to 1.5-fold and AUC increased 1.4- to 1.8-fold). Elinzanetant did not affect the PK of dabigatran etexilate which was used as reference substrate of P-glycoprotein. Elinzanetant increased the PK of rosuvastatin (substrate of BCRP, OATP1B1 and 1B3) 1.2- to 1.3-fold.

In addition, a clinical study was conducted to investigate the effect of elinzanetant on the PK of tamoxifen (a common medicinal product to treat breast cancer). In the clinical DDI study with tamoxifen (CYP2D6 and 3A4 and UGT substrate), tamoxifen C_{max} increased 1.2-fold and AUC increased 1.5-fold following a single dose of tamoxifen. For N-desmethyl-tamoxifen, C_{max} decreased 2.0-fold and AUC decreased 1.1-fold. Endoxifen C_{max} decreased 2.3-fold and AUC decreased 1.4-fold. N-desmethyl-tamoxifen and endoxifen are the pharmacologically active metabolites of tamoxifen. In study OASIS-4, sparse blood samples were collected and concentrations of tamoxifen and its metabolites (N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen) were investigated. No effect on the steady state plasma concentrations of tamoxifen and its metabolites (N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen) were observed when co-administered with elinzanetant.

No effect on the plasma concentrations of anastrozole was observed in the OASIS-4 study (baseline concentrations were similar to the concentrations after treatment with elinzanetant). It is therefore unlikely that elinzanetant will lead to a DDI with anastrozole when given concomitantly.

In vitro studies indicated that elinzanetant is an inhibitor of MATE1 at clinically relevant concentrations. No dedicated clinical DDI study was conducted towards MATE1. However, no effect on creatinine clearance was observed in a clinical study at supratherapeutic dosages of 600 mg. Overall, this indicates that the observed *in vitro* interaction potential is clinically not relevant.

Pharmacokinetics in patients with vasomotor symptoms

One clinical PK study was performed in adult women with moderate to severe vasomotor symptoms with full blood sampling for PK in which subjects received a once daily dose of 50 mg, 100 mg, 150 mg or 300 mg elinzanetant. A clinical PK study in patients was not performed with the clinical dose of 120 mg. The PK results in patients with the 50 mg, 100 mg, and 150 mg dose were compared with the PK in healthy volunteers over a dose range of 40 mg to 160 mg. In addition, five clinical studies were conducted in patients with moderate to severe vasomotor symptoms, but with sparse blood sampling for PK. PopPK modelling was used to predict the PK in patients from these 5 clinical studies. According to the simulated PopPK data, VMS patients have higher exposure compared to healthy volunteers after single dose and at steady state. The (biological) reason for differences in elinzanetant exposure between healthy volunteers and VMS patients is not known. The results of the simulations for a single dose of 120 mg elinzanetant show that the exposure to elinzanetant is 1.4-fold, 1.3-fold and 1.9-fold higher in VMS patients in terms of $AUC_{0\text{-}24h}$, C_{max} and C_{trough}, respectively. The results of the simulations for multiple doses of 120 mg daily elinzanetant show that the exposure to elinzanetant is 1.7-fold, 1.4-fold and 2.3-fold higher in VMS patients in terms of $AUC_{0\text{-}24h}$, C_{max} and C_{trough}, respectively. It seems that the results of the simulations with the model, based on PK data for a large number of subjects, are more reliable than directly comparing the NCA data between studies. Therefore, the worst-case situation that VMS patients may have a higher elinzanetant exposure compared to healthy volunteers is agreed.

A dose of 37 mg can be considered as the lowest dose of elinzanetant to achieve clinically meaningful efficacy (a reduction of 2 in HF/day compared to placebo). Furthermore, a dose of 160 mg can be considered as the highest dose of elinzanetant not leading to clinically relevant safety issues, since no higher dose was investigated. The therapeutic window is 46.6-2810 µg/L for total and 0.155–9.33 µg/L for unbound. This corresponds to an $AUC_{0\text{-}24,ss}$ range of 2690–21900 µg × h/L for total and 8.93-72.7 µg × h/L for unbound.

2.6.2.2. Pharmacodynamics

Mechanism of action

As a consequence of estrogen decline in menopause, kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the hypothalamus are hyperactivated. Elinzanetant is a selective, non-hormonal neurokinin 1 (NK-1) and 3 (NK-3) specific receptor antagonist that blocks increased NK-1 and NK-3 receptor signalling on KNDy neurons to modulate neuronal activity involved in thermo- and sleep regulation.

<u>NK-3 and vasomotor symptoms</u>

KNDy neurons in the hypothalamus have been identified as playing a role in thermoregulation that is responsive to both estrogen and ambient temperature (*Rance et al. 2013*). In the menopausal state (in natural menopause or caused by medical intervention) the KNDy neurons are in a state of hyperactivation, which disrupts baseline thermoregulation and triggers VMS. NK-3 receptor specific antagonists, including fezolinetant, have provided direct clinical evidence that NK-3 receptor blockade can reduce both the frequency and the severity of HFs. The oral NK-3 receptor specific antagonist fezolinetant has been approved for treatment of moderate to severe VMS associated with menopause in 2023 by centralized procedure.

NK-1 and vasomotor symptoms

It is hypothesized that the dual specificity of elinzanetant, thus antagonizing NK-1 and NK-3 receptors, has beneficial effects on the treatment of menopausal symptoms. As substance P immunoreactive fibers have been demonstrated in the hypothalamus of postmenopausal women (*Borsay et al. 2014*), SP and NK-1 receptors may additionally have a role in peripheral vasodilatation (*Wong and Minson 2006*).

NK-1 and sleep disturbances

VMS during the night affect sleep quantity and quality but there is evidence of sleep disturbances experienced during menopause that are independent of VMS. It is hypothesized that additional biological mechanisms beyond reduced estrogen receptor signalling and night-time awakening due to VMS may contribute to sleep disturbances during the menopausal period. Improvements in wakefulness after sleep onset (WASO) in primary insomnia had been shown for a NK-1 specific receptor antagonist (*Ratti et al. 2013*), but not for sleep disturbances associated with menopause.

Primary and Secondary pharmacology

Primary pharmacology

NK-1 receptor occupancy

The extent of NK-1 receptor occupancy was assessed in a single dose Study 21673 and a repeat dose Study 21674 in healthy participants using PET scanning with the NK-1 specific PET ligand [11C]GR-205171.

Study 21673 (MNK111321): First in human, single ascending dose placebo-controlled study to investigate safety, PK (Part A), and NK-1 receptor occupancy (Part B). See also PK section.

- Part A evaluated safety, tolerability and PK of ascending single doses of elinzanetant (tosylate salt in a suspension formulation) in 14 healthy male participants. Part A was divided in 2 cohorts. Subjects in cohort 1 received 10 mg and 30 SD, subjects in Cohort 2 received 60, 120, 160 mg and individualized doses (160 mg, 200 mg, 230 mg (each dose one participant) and 250 mg (4 participants). In Cohort 2, doses were split into two or three divided doses given 2 to 3 hours apart to account for the higher than anticipated maximum plasma concentrations observed in Cohort 1.
- Part B was conducted in 7 healthy male participants to assess NK-1 receptor occupancy in the human brain following a single oral administration of elinzanetant, using PET scanning with NK-1 radiotracer ligand [11C]GR205171.

PD results (i.e. Part B)

NK-1 receptor occupancy

NK-1 receptor occupancy by elinzanetant was investigated in the human brain, for which positron emission tomography (PET) with the NK-1 radiotracer [11C]GR-205171 was employed. The results demonstrated an elinzanetant dose-dependent decrease in the volume of distribution (VT) of the PET ligand in the brain regions with a high concentration of NK-1 receptors. The VT values from frontal cortex and an area virtually devoid of NK-1 receptors (cerebellum) were used to calculate the frontal cortex binding potential (BPND) of the PET ligand, and to estimate the NK-1 receptor occupancy by elinzanetant. Results indicate a dose-dependent NK-1 receptor occupancy by elinzanetant. Based on the PET data, a plasma concentration of approximately 19 µg/L at C_{trough} would be required to achieve 95% NK-1 receptor occupancy. Based on *in vitro* binding affinity and *in vitro* functional potency, a plasma concentration of approximately 190 µg/L at C_{trough} would be required to achieve 95% NK-3 receptor occupancy.

NK-3 receptor occupancy

The absence of suitable PET ligands for NK-3 precludes a direct assessment of the occupancy of the NK-3 receptor. Therefore NK-3 receptor occupancy predictions were made from the NK-1 data.

Total testosterone

For total testosterone, decreases in mean values from Day −1 to 24 hours post-dose, were greatest at the highest dose levels of 160 mg (change from 22.6 to 14.6 nmol/L) and individualized dose levels of up to 250 mg elinzanetant (20.9 to 12.9 nmol/L), compared with mean increases following placebo (23.5 to 24.3 nmol/L) and the lower elinzanetant doses (e.g. 18.4 to 21.0 nmol/L for 10 mg dose level).

Study 21674 (MNK111587): Multiple ascending dose study to investigate safety and PK, effect of elinzanetant on CYP3A4; NK-1 receptor occupancy, and cognition. See PK section for results PK. This study consisted of two parts:

- Part A was a multiple ascending dose to evaluate safety, tolerability and PK of ascending doses study (30, 90, 200 mg suspension) of elinzanetant (tosylate salt in a suspension formulation) in 37 healthy male participants.
- Part B was conducted in four healthy male participants to assess the elinzanetant NK-1 receptor occupancy after repeated oral dosing by PET scanning with the NK-1 radiotracer ligand [11C]GR205171.

PD results (i.e. part B)

NK-1 receptor occupancy

NK-1 receptor occupancy by elinzanetant was investigated in the human brain by positron emission tomography (PET) scanning with the NK-1 radiotracer [11C]GR-205171. The frontal cortex was used as a representative region to estimate the binding of elinzanetant to the NK-1 receptor due to its high expression of NK-1 receptors. A dose-dependent decrease in VT of the PET ligand was observed following administration of elinzanetant.

The EC50 for NK-1 receptor occupancy was estimated as 0.97 µg/L (95% CI: 0.47 – 1.46) from an Emax model assuming full occupancy could be achieved (using receptor occupancy results from all doses with elinzanetant plasma concentrations), see Figure 4 Study 21674 – Receptor Occupancy of a Representative Cortical Area (Frontal Cortex) Derived as a Function of Elinzanetant Plasma Concentration and Emax (Model Fitted to Estimate the EC_{50})Figure 4 below. The relationship between the plasma concentration and NK-1 receptor occupancy is consistent with a direct model. In addition, based on EC_{50} values the concentration required to approach >95% NK-1 receptor occupancy is estimated as 18.4 µg/L (95% CI: 8.93 – 27.4).

Assuming a 5 to 10-fold lower affinity of elinzanetant for NK-3 compared to NK-1 receptors, EC50 and EC95 of elinzanetant for NK-3 receptor occupancy should be in the range of 4.5 - 9.7 µg/L and 95 – 190 µg/L, respectively.

Total and free testosterone

Total and free testosterone was analyzed in Part A of the study. Data collected at pre-dose were compared with data collected on Day 15 (Cohorts 1 and 2) and on Day 14 (Cohort 3).

Participants receiving 200 mg elinzanetant showed reductions in free and total testosterone levels on Day 14 and Day 30 when compared to baseline. Six participants had total testosterone levels below the reference range (9.90 to 27.80 nmol/L) (four on Day 14 only, one on Day 30 only and one on Day 14 and 30) during the study period, and 1 participant had total testosterone above the reference range on Day 30.

PD conclusions

- A dose-dependent NK-1 receptor occupancy by elinzanetant was observed. The EC_{50} was estimated at: 0.97 µg/L (95% CIs: 0.47 – 1.46). These data were consistent with those predicted from the single dose occupancy study (EC50 = 0.88 µg/L). The EC_{50} of elinzanetant from the single dose and repeated dose PET studies were consistent, indicating a direct relationship.
- Assuming a 5 to 10-fold lower affinity of elinzanetant for NK-3 compared to NK-1 receptors, EC_{50} and EC_{95} of elinzanetant for NK-3 receptor occupancy should be in the range of 4.5 - 9.7 µg/L and 95 – 190 µg/L, respectively.
- A reduction in total and free serum testosterone was noted after administration of the 200 mg dose.

Study 21680 (814-1-05): Effect of repeat doses of elinzanetant on estradiol, progesterone, LH, and FSH concentrations in healthy female participants aged 19 to 45 years.

In the randomized single-blind, placebo-controlled phase 1 study aimed to determine effects of elinzanetant at doses of 40 mg, 80 mg, 120 mg, and 160 mg once daily (using 40 mg soft gel capsules) for approximately 21 days on GnRH pathway hormones i.e. change from baseline in LH, FSH, estradiol and progesterone in 33 healthy female participants (19-45 years). The secondary objective was to evaluate the safety of elinzanetant.

PD results

- **LH:** clear dose-related reduction in overall LH concentrations (i.e. average across the menstrual cycle) was observed following treatment with elinzanetant, see figure below.
- **FSH**: No clear pattern of effect on overall FSH concentrations was observed following treatment with elinzanetant
- **Estradiol**: clear dose-related reduction in overall estradiol concentrations (average across the cycle) following treatment with elinzanetant, see figure below.
- **progesterone**: there was a dose-related reduction in median progesterone concentrations during the luteal phase (Day 21/22) following treatment with elinzanetant between 80 mg and 120 mg (cycle 2), see figure below.

  Median menstrual cycle length increased by 7.0 days following treatment (cycle 2) in the elinzanetant 120 mg group. Smaller changes in menstrual cycle length were observed in the placebo, elinzanetant 40 mg and elinzanetant 80 mg groups, without relevant differences between groups.

PD conclusions: Administration of elinzanetant once daily for 21 days in women of reproductive age resulted in dose-related changes in female sex hormones (LH, oestradiol, progesterone) that were consistent with the anticipated pharmacological effects of elinzanetant on hypothalamic kisspeptin, neurokinin B, and dynorphin neurons. The effect was greatest at the highest dose tested (120 mg) once daily dose.

Study 21681 (RELENT-1): PK, safety and PD in post-menopausal women with VMS

For an extensive description of this study, see the section on dose response studies

This phase 1b study aimed to evaluate the PD, PK and safety profile of multiple dose levels (50 to 300 mg) of elinzanetant compared to placebo, by once-daily administration of a hard gel capsule for 14 days. 76 post-menopausal women with VMS were randomized to this study. A total of 18 participants were randomized to placebo and 58 participants to elinzanetant.

Effect on LH

LH AUC(0-8) values were generally similar across the treatment groups at baseline (Day -1). On Day 1, LH AUC(0-8) was reduced in the 100, 150 and 300 mg groups (mean [±standard deviation] change from Day -1: -10.0 [±21.9], -31.1 [±38.3] and -24.6 [±32.4] h·U/L, respectively), whereas small increases were observed in the placebo and 50 mg groups (14.4 [±31.3] and 4.7 [±35.8] h·U/L). On Day 7, there was a similar pattern of changes to those observed on Day 1 but the changes from baseline were smaller and the differences for the 100, 150 and 300 mg groups compared to placebo were not statistically significant.

Table 3 Absolute and Change in Luteinizing Hormone Levels (FAS)

	Placebo (N = 18)	NT-814 50 mg (N = 15)	NT-814 100 mg (N = 15)	NT-814 150 mg (N = 15)	NT-814 300 mg (N = 13)
LH AUC_{0-8} (h•U/L) [Mean±SD (Median)]					
Day -1	295.4±82.64 (287.2)	295.5±85.22 (288.3)	290.8±85.83 (291.3)	309.5±104.38 (304.0)	261.1±65.53 (267.4)
Day 1	309.8±76.97 (284.4)	300.3±88.88 (307.0)	280.7±77.78 (276.2)	278.4±95.55 (278.7)	236.5±69.55 (240.2)
Day 7	307.8±90.54 (284.1)	318.4±103.37 (293.5)	301.0±76.66 (292.7)	297.4±114.28 (293.8)	256.7±63.51 (259.8)
Change from Day -1 to Day 1	14.4±31.33 (11.7)	4.7±35.80 (4.8)	-10.0±21.90 (-6.2)	-31.1±38.28 (-18.8)	-24.6±32.36 (-33.7)
Change from Day -1 to Day 7	12.4±57.46 (20.9)	22.9±37.07 (17.9)	10.2±20.49 (12.5)	-12.1±47.30 (-1.3)	-4.4±33.43 (-4.7)
Statistical Analysis of Change from Week -1 Versus Placebo					
Change from Day -1 to Day 1					
LS mean±SE (90% CI)	14.9±7.34 (2.6, 27.1)	5.2±8.04 (-8.2, 18.6)	-10.1±8.04 (-23.5, 3.3)	-29.1±8.08 (-42.5, -15.6)	-28.0±8.73 (-42.6, -13.5)
p-value within treatment	0.0467	0.5215	0.2125	0.0006	0.0020
Difference in LS means±SE (90% CI)	NA	-9.7±10.88 (-27.8, 8.5)	-25.0±10.89 (-43.1, -6.8)	-43.9±10.90 (-62.1, -25.8)	-42.9±11.43 (-61.9, -23.8)
p-value versus placebo	NA	0.3768	0.0248	0.0001	0.0004
Change from Day -1 to Day 7					
LS mean±SE (90% CI)	12.6±9.96 (-4.0, 29.2)	23.1±10.91 (4.9, 41.2)	10.2±10.90 (-8.0, 28.4)	-11.3±10.95 (-29.5, 7.0)	-5.8±11.85 (-25.5, 14.0)
p-value within treatment	0.2091	0.0380	0.3535	0.3067	0.6268
Difference in LS means±SE (90% CI)	NA	10.4±14.76 (-14.2, 35.1)	-2.4±14.77 (-27.1, 22.2)	-23.9±14.79 (-48.6, 0.7)	-18.4±15.50 (-44.2, 7.4)
p-value versus placebo	NA	0.4819	0.8694	0.1105	0.2390

Source data: Table 14.2.4.1 and Table 14.2.4.2. AUC0-8 = area under the concentration time curve from time zero to 8 hours; CI = confidence interval; LH = luteinizing hormone; LS = least squares; NA = not applicable; SD = standard deviation; SE = standard error.

Effect on other sex hormones (estradiol, FSH, testosterone)

While an increase from baseline was observed for ***estradiol*** levels in the placebo and 50, 100 and 150 mg elinzanetant groups, the magnitude decreased with increasing dose and a reduction was observed in the 300 mg group (mean [±standard deviation] of 13.2 [±80.7] pmol/L in the 50 mg group to -9.02 [±87.5] pmol/L in the 300 mg group versus 22.4 [±142] pmol/L in the placebo group).

Overall, small changes from baseline in ***FSH*** and ***testosterone*** levels were observed across all the treatment groups, with no meaningful differences between any of the active treatment groups and placebo (range of mean [±standard deviation] change from baseline: FSH -2.29 [±20.9] to 8.92 [±13.4] IU/L; testosterone -0.087 [±0.474] to 0.155 [±0.269] nmol/L).

PD conclusions:

In postmenopausal women, statistically significant reductions were observed for LH compared to placebo in the 100, 150 and 300 mg groups on Day 1. The reductions were less evident on Day 7, and the differences were not statistically significant. There was an increase observed in placebo and doses up to 150 mg, but the magnitude decreased with higher doses. However, the changes were small and of doubtful clinical relevance. There were no clinically relevant changes from baseline in mean FSH or testosterone concentrations.

Secondary pharmacology

Cognitive Effects - Study 21674 (MNK111587): for the design of this study, see primary pharmacology/ PD.

An exploratory endpoint of this study was to test differences between elinzanetant and placebo-treated participants in terms of cognitive function by using methods described in the table below.

Table 10 Cognitive effects observed in study 21674

Code	Main Outcome
Groton Maze Learning Task	Total error rate
One Card Learning Task	Accuracy of performance = arcsine transformation of the proportion of correct responses
Detection Task	Speed of performance = mean of the $\log_{10}$ transformed reaction times for correct responses
Identification Task	Speed of performance = mean of the $\log_{10}$ transformed reaction times for correct responses

The only statistically significant difference compared to placebo was an increased speed in the Identification task in the 90 mg elinzanetant dose group at 13 days post-dose. The effect was not confirmed at other time points or with different elinzanetant doses. However, no correction for multiplicity was performed, as the PD variables were evaluated in an explorative manner only.

An exploratory endpoint of this study was to test for differences between elinzanetant and placebo-treated participants in terms of cognitive function; Groton Maze Learning Task, One Card Learning Task, Detection Task and Identification Task). No relevant effect of elinzanetant on cognition was observed after repeated daily doses of 30 mg, 90 mg and 200 mg.

Alcohol interaction - Study 21676 (MNK113476)

This was a single-blind, randomised, placebo-controlled, 2-period crossover, single-dose study which investigated whether the psychomotor and cognitive effects of alcohol are exacerbated by elinzanetant (200 mg as 2 x 100 mg IR tablets) up to 8 hours post dosing in 20 healthy male participants.

Alcohol was administered alone (blood alcohol concentration 0.05%) and together with 200 mg elinzanetant as IR tablets (Study 21676). Plasma exposures with a 200 mg dose (2 x 100 mg) of the IR tablet formulation were similar to a 120 mg dose (2 x 60 mg) with the to-be-marketed soft capsule formulation.

Results

In comparison to alcohol + placebo, administration of alcohol + elinzanetant was associated with a 3% decrease of peak velocity and a 4% increase in reaction times of saccadic eye movements, a reduction in adaptive tracking performance (1.7%), an average increase of 15% in the response in the Body Sway measure, a 2 point increase (max 24 points) of the sleepiness (Epworth scale) and a 2.6 point decrease of alertness (Bond Lader scale), and a worsening of recognition score and recognition times in the Visual Verbal Learning Test (VVLT). Changes in the PD endpoints correlated with the PK of elinzanetant. Overall, administration of elinzanetant in the presence of alcohol was generally well tolerated and the observed cognitive effects were small and not likely to produce clinically relevant additional impairments after alcohol consumption. (*te Beek et al 2013*)

Somnolence - Study 21670: Safety and PK of single ascending supratherapeutic doses of elinzanetant in healthy male and female volunteers

In the supratherapeutic Study 21670 the safety and tolerability of single supratherapeutic oral doses between 240 mg and 600 mg of elinzanetant given as soft gel capsules were investigated. Investigation of the QTc interval prolonging potential of elinzanetant was an exploratory endpoint, see further below.

Results

In the supratherapeutic dose, somnolence and dizziness (SOC: Nervous system disorders) of mild to moderate intensity were reported as adverse events by 22.2% of participants after administration of the 480 mg dose, however in none of the lower or higher dose groups.

Other CNS-related symptoms within this SOC included mild to moderate headache, dizziness and orthostatic intolerance were also reported by 11.1 to 22.2% of the participants in the 480 mg dose group only. Disorientation (SOC: Psychiatric disorders) of mild intensity was reported by 11.1% of the participants in the 480 mg dose group.

Driving ability - Study 22653: Effects of elinzanetant on simulated driving performance and cognitive function in healthy women

Safety data from completed Phase 1 and 2 clinical trials and on-going phase 3 trials with elinzanetant showed mild to moderate somnolence and fatigue as commonly reported AEs. Although elinzanetant should be taken at night before bedtime, there is a possibility of residual central nervous system (CNS)-impairing effects in the morning, which could pose a safety risk to patients. In particular, somnolence and fatigue could impair the ability to drive a motor vehicle. Therefore, this Phase 1 study was designed to investigate the effects of elinzanetant on simulated driving performance and cognitive function. Driving performance was assessed at 9 hours after bedtime administration of elinzanetant 120 mg and 240 mg (two times the recommended dose) over 5 days in a randomized, double-blind, placebo- and active-controlled (Zopiclone 7.5 mg on day 1 and day 5), four-period crossover study in 64 healthy women (mean age 52.1 years) using a computer-based driving simulation. Washout period was 14 days. Driving simulations using the CRCDS-MiniSim™ to assess driving performance, CogScreen® SDC test to assess cognitive function, KSS to assess subjective sleepiness, and self-rating assessments to assess the participants' self-reported readiness to drive, motivation, and appraisal of driving performance were performed in the morning on Day 2 (after the initial night dose) and Day 6 (after 5 consecutive night of dosing, at presumed steady state), approximately 9 hours following the previous evening dose. The primary outcome measure was the difference from placebo in the Standard Deviation of Lateral Position (SDLP). Driving performance was evaluated using a validated threshold of 4.4 cm established in a population with blood alcohol concentration of 0.05% in previous simulator studies with the CRCDS-MiniSim™.

Results

The mean SDLP did not reach the threshold for driving impairment after administration of elinzanetant 120 or 240 mg. Compared to placebo, minor differences in mean SDLP, not exceeding the predefined threshold for driving impairment, were seen with both doses after 1 day but not after 5 consecutive days of elinzanetant administration. Compared to placebo, minor effects were found on driving or cognitive performance and on subjective sleepiness following an initial nighttime dose of 120 mg or 240 mg. These mild effects were no longer apparent when participants were evaluated after 4 additional nights of dosing.

Cardiac Safety - Study 21670 (CPMX50129): Concentration-QTc analysis of elinzanetant in supratherapeutic doses (>102 mg)

In this PK-PD study, investigation of the QTc interval prolonging potential of elinzanetant was an exploratory endpoint.

The relationship between the elinzanetant plasma concentration and ΔQTc was evaluated based on clinical data from this Phase 1 supratherapeutic safety study (study 21670) with a linear mixed-effects concentration-response modelling approach. In this study, single doses of up to 600 mg were investigated in healthy male and female participants.

Results

Mean changes from baseline ranged between -4.0 to 1.9 msec in 240 mg elinzanetant arm, -8.0 to 3.6 msec in 360 mg elinzanetant arm, -3.5 to 4.7 msec in 480 mg elinzanetant arm, -7.0 to 1.4 msec in 600 mg elinzanetant arm and -5.3 to 6.4 msec in placebo arm during the first 24 h after administration of study intervention. No absolute values of QTcF >450 msec or QTcF changes of >30 msec from baseline were recorded.

Part 2 of the study was designed to demonstrate the sensitivity of the ECG assay using a single dose of 400 mg moxifloxacin as a positive control. As anticipated, prolongation of mean QTcF interval was seen after 400 mg moxifloxacin administration when considering participants who received both 400 mg moxifloxacin and placebo (PDS2): the baseline mean QTcF value was 386.8 msec and the maximum measured mean value 2 h after administration was 399.4 msec (change 12.6 msec).

For the plasma concentration effect curve, the estimated slope calculated with scaled elinzanetant plasma concentration values (*CONC_SCAL*) was -0.02403. Thus, for the original plasma concentration values, the slope is -0.00024. This slightly negative slope was not statistically significant ($p > 0.5$). The highest individual plasma concentration of 12916 µg/L was measured in the 600 mg dose group.

The elinzanetant concentration-ΔQTc analysis showed no relevant change in ΔΔQTcF up to the maximum tested plasma concentration of 12900 µg/L. The highest plasma concentration in this cQTc analysis exceeds the steady state maximum concentration of the clinically effective dose of 120 mg with soft gel capsules by at least 5-fold. Therefore, the risk of exceeding the +10 ms QTc prolongation threshold of regulatory concern can be excluded even in high exposure scenarios.

Cardiac Safety - Study 21774 (CPMX50187) Concentration-QTc analysis of elinzanetant based on single ascending dose / multiple dose study 21774 in healthy Japanese participants

Study 21774 investigated the safety and tolerability and PK after single and multiple doses of elinzanetant (40 mg, 80 mg, 120 mg, 160 mg by using 40 mg soft gel capsules, or 120 mg by using 2 × 60 mg soft gel capsules) in healthy Japanese women aged 40-60 years. In the analysis the C–QTc, interval relationship of elinzanetant was investigated on the basis of paired PK and ECG data obtained in a parallel group design study with 5 single dose steps (Part A) and one multiple dose step (Part B) according to protocol 21774.

The study consisted of 2 parts: Part A (Single dose [SD] steps 1 to 4 and 6 and Part B (MD step 5)). In total 62 Japanese healthy female participants (50 in Part A and 12 in Part B) completed the study. In total 961 paired concentration- QTcF measurements were available (649 for Part A and 312 for Part B).

The study data allowed the application of a linear mixed effects model for the C-QTc relationship for both study parts, separately. The resulting model parameters of both parts independently suggest a small statistically non-significant shortening of the cardiac de- and re-polarization duration with increasing elinzanetant plasma concentration. The CI of the models were small and did not cross the 10 ms threshold of regulatory concern for the elinzanetant plasma concentrations studied.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Clinical studies

In some clinical studies different dosing regimens than the clinical dosing regimen of once daily was investigated (studies 21673 and 21674). Only the pharmacokinetic data of clinical studies with a single dose or once daily dosing were assessed.

Physical-chemical properties

An *in vitro* study was performed in Caco2 cells to investigate the permeability. Low and high permeable compounds were included as reference, but no reference compounds classified as moderate permeability drugs were included. Therefore, it cannot be concluded for certain that elinzanetant is a highly permeable compound, but it is most likely a highly permeable compound (BCS Class II compound).

PopPK modelling

The first population pharmacokinetic model (RunM120) was developed to evaluate the effects of formulation, fed status and circadian rhythm on elinzanetant pharmacokinetics. However, it seems the model does not accurately capture the absorption phase of elinzanetant. Therefore, this model is deemed not fit for purpose for evaluating the effects of different formulations or fed status. Since sufficient data from clinical studies are available, the effects of formulation, fed status and circadian rhythm on elinzanetant pharmacokinetics can be investigated using these studies. The second PopPK model was deemed fit for purpose to simulate the exposure in healthy volunteers and VMS patients.

PBPK modelling

The impact of this discrepancy on the results of the DDI simulations with the PBPK is considered to be of limited impact, because the fraction absorbed stays the same for the DDI simulations with itraconazole, erythromycin and cimetidine.

Exposure-response modelling

In the exposure-efficacy models covariates were only tested for the placebo effect during model development. No covariate was tested for the implemented drug effect parameters. The included data is limited to once daily 120 mg elinzanetant doses in the Phase 3 studies, with estimated $C_{trough,ss}$ between 3-1723 µg/L and limited samples in the lower range. Thus, extrapolation of the data should be interpreted carefully. The definition of hot flashes severity differed between baseline and post-treatment. The definition of hot flashes severity at baseline does not consider the number of 'mild' hot flashes. Therefore, the interpretation of the immediate effect in the model is hampered. Furthermore, 5% of data was defined at weighted residuals outliers and was discarded to reduce the residual unexplained variability. Therefore, the Applicant considered the modelling outcome of hot flashes severity as exploratory. Hot flashes frequency and severity convey similar information with subtle differences (non-weighted vs. weighted frequency of hot flashes) these outcomes are highly correlated, which is shown by the Applicant. Furthermore, the exposure-dependent effect on severity could also be described by fixing the value of EC_{50} to the estimated value for frequency and the same dataset was used to model both outcomes.

In the exposure-safety model, an approximately 3-fold increased risk for adverse events of special interest (somnolence, fatigue, and dizziness) in the elinzanetant treatment group compared to the placebo group was observed. However, no trend with elinzanetant exposure ($C_{max,ss}$ and $C_{trough,ss}$) could be detected. Due to the data that is limited to exposure values with 120 mg once daily elinzanetant doses, it remains unclear if lower exposure to elinzanetant may result in lower rates for adverse events. The exposure-safety model is less well informed with data of doses other than 120 mg and lower number of separated AESIs, no certain conclusions can be drawn.

Pharmacokinetics in patients with vasomotor symptoms

The NCA data from study 21681 shows a trend towards a lower exposure in VMS patients compared to healthy volunteers. The difference in results between the NCA data from clinical study 21681 and the PopPK model are not well understood. The high intra-study and inter-study variability, which was also evident in the Phase 1 studies in healthy volunteers alone, might hamper the comparison between the clinical studies. Also, it is worth noting that in study 21681 the hard gel capsule formulation was used and not the final soft gel capsule formulation, which might have a delayed absorption compared to the soft gel formulation. In case of the NCA data derived from study 21681, this might result in apparently lower exposure in VMS patients when the AUC_{0-24} is compared with that in healthy volunteers treated with the soft gel capsule. It would be more appropriate to compare the AUC_{0-t} and AUC_{0-inf} in this case, which was not calculated in study 21681. Therefore, the NCA comparison of PK in healthy volunteers and VMS patients may not be reliable.

According to the simulated PopPK data, VMS patients have higher exposure compared to healthy volunteers after single dose and at steady state. The (biological) reason for differences in elinzanetant exposure between healthy volunteers and VMS patients is not known. The results of the simulations for a single dose of 120 mg elinzanetant show that the exposure to elinzanetant is 1.4-fold, 1.3-fold and 1.9-fold higher in VMS patients in terms of AUC_{0-24}, C_{max} and C_{trough}, respectively. The results of the simulations for multiple doses of 120 mg daily elinzanetant show that the exposure to elinzanetant is 1.7-fold, 1.4-fold and 2.3-fold higher in VMS patients in terms of AUC_{0-24}, C_{max} and C_{trough}, respectively. It seems that the results of the simulations with the model, based on PK data for a large number of subjects, are more reliable than directly comparing the NCA data between studies. Therefore, the worst-case situation that VMS patients may have a higher elinzanetant exposure compared to healthy volunteers is agreed.

The absolute oral bioavailability is affected by the first-pass metabolism in the intestine and liver and the absorption.

Special populations

Renal impairment. The unbound exposure to elinzanetant is ~2-fold higher in subjects with moderate and severe renal impairment compared to subjects with normal renal function. It is known that severe renal impairment also influences the hepatic function with increasing hepatic function. Thus, the difference observed in exposure between moderate and severe renal impairment may be due to differences in hepatic function. In the clinical studies in patients, the observed exposure data in mild (N=402) and moderate (N=23) renal impairment patients were similar to the observed exposure data in patients with normal renal function (N=586). It is agreed that mild renal impairment does not affect the PK. The plasma concentration data in moderate renal impairment is very limited. No dose adjustment is needed in subjects with mild renal impairment. A dose reduction of 2-fold is proposed based on the observed increase in exposure in moderate and severe renal impairment, the higher exposure in VMS patients and the therapeutic window. Therefore, a dose of 60 mg was accepted for patients with moderate and severe renal impairment.

Hepatic impairment. No dose modification is recommended for individuals with mild hepatic impairment. The use of elinzanetant in patients with moderate and severe hepatic impairment remains not recommended. A dose reduction of 3-fold is proposed based on the observed increase in exposure in moderate hepatic impairment, the higher exposure in VMS patients and the therapeutic window. Therefore, a dose of 40 mg is proposed for patients with moderate hepatic impairment. However, no suitable dose is available. Therefore, the Applicant is encouraged to develop a dose suitable to treat patients with moderate hepatic impairment. Regarding severe hepatic impairment, it is agreed that due to the lack of data no dose recommendation can be given and that therefore elinzanetant is not recommended to be used in patients with severe hepatic impairment.

Ethnic factors. The exposure in healthy Chinese women following daily dosing with 120 mg elinzanetant once in the evening is higher than that of Caucasian of Japanese women. However, this does not lead to an exposure outside the therapeutic window in patients. Therefore, no dose adjustment is needed based on ethnic origin.

Body weight and BMI. The exposure increased with increasing body weight or BMI. As predicted, patients treated with 120 mg elinzanetant with a body weight up to 308 kg or BMI of 87 kg/m^2 still have plasma concentrations below the upper limit of the therapeutic window. No lower boundary for body weight could be calculated and this was agreed. Therefore, the recommended dose does not need to be adapted based on body weight or BMI.

Drug-drug interactions

Victim. Strong CYP3A4 inhibitors such as itraconazole are not recommended as the exposure range clearly exceeds the upper boundary of the therapeutic window and no dose is available to give a dose recommendation that leads to an exposure within the therapeutic window. For moderate CYP3A4 inhibitors, the simulated exposure increase exceeds the therapeutic window (post estimate and CI intervals) and the dose should be reduced to 60 mg. No dose adjustment/recommendation is required for weak CYP3A4 inhibitors because the complete exposure range as determined by PBPK modelling is within the therapeutic window. No dose increase is needed if elinzanetant is given concomitantly with strong and moderate inducers via PXR as clinically relevant efficacy of elinzanetant, i.e. reduction of 2 HF/day, is predicted to be achieved at that exposure level.

Perpetrator. A single dose DDI study with tamoxifen was conducted. However, since the elimination half-lives of tamoxifen and its active metabolites are long (4 to 11 days), the effect of elinzanetant on the steady state PK of tamoxifen and its metabolites is more relevant than after a single dose of tamoxifen. In study OASIS-4, sparse blood samples were collected and concentrations of tamoxifen and its metabolites (N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen) were investigated. The number of patients for which tamoxifen blood samples were available was sufficient (71 patients in the placebo group and 149 patients in the treatment group). Based on the steady state plasma concentrations of tamoxifen and its metabolites (N-desmethyltamoxifen, 4-hydroxytamoxifen and endoxifen), no clinical DDI effect was observed when given concomitantly with elinzanetant. Based on clinical data, no effect on creatinine clearance was observed in a clinical study at supratherapeutic dosages of 600 mg. Overall, this indicates that the observed *in vitro* interaction potential towards MATE1 is clinically not relevant.

Pharmacodynamics

Mode of action

The rationale presented to antagonize NK-3 is acknowledged. The rationale to antagonize NK-1 is that NK-1 receptors may additionally have a role in peripheral vasodilatation. Further, it is hypothesized that beyond reduced estrogen receptor signalling and night-time awakening due to VMS additional biological mechanisms may contribute to sleep disturbances during the menopausal period. In this respect, improvements in wakefulness after sleep onset (WASO) in primary insomnia had been shown for a NK-1 specific receptor antagonist, though not for sleep disturbances associated with menopause.

Primary pharmacology

Two PET studies 21673, 21674 in healthy males were performed to evaluate receptor occupancy for NK-1, both after single dose and multiple doses, with the NK-1 radiotracer [11C]GR-205171. There is a strong relationship between elinzanetant plasma concentration and receptor occupancy of NK-1, PET imaging confirmed that elinzanetant achieves 95% NK-1 receptor occupancy at plasma concentrations of ~19 µg/L, correlating well with its clinical efficacy. There is no ligand for NK-3, but based on *in vitro* data, a 5-10 fold lower receptor binding affinity is expected. Based on preclinical data, 95% receptor occupancy (EC_{95}) is required for the maximum effect. The target plasma concentration for EC_{95} is 95-190 µg/ml (C_{trough}).

There was a dose-dependent decrease in (total and free) testosterone with dose up to 200 mg in the studies with male participants, which normalized during follow-up.

- In healthy women of reproductive age, there was a dose-dependent reduction in LH and estradiol (average across the menstrual cycle). There was no relevant effect observed in FSH. Progesterone reduced in the 80 and 120 mg group and resulted in an increased length by 7 days of the median menstrual cycle in the 120 mg group.
- In postmenopausal women with VMS, there was a dose dependent reduction in LH compared to placebo. Dose related reductions in oestradiol concentrations were noted, but the changes were small. For FSH and testosterone, the differences were small between baseline and Day 15 for all treatment group, including placebo. The effects observed in postmenopausal women are far less pronounced than seen in healthy women of reproductive age.

Secondary pharmacology

Cognitive function, driving ability, alcohol interaction, occurrence of somnolence, cardiac safety

An extensive amount of secondary pharmacodynamic studies was performed, showing no effects on cognitive function, minor transient effects on driving performance after the first two days of intake, and no additional effect of alcohol (blood alcohol concentration 0.05%) together with elinzanetant 200 mg in comparison with alcohol alone. In a supratherapeutic dose of 480 mg, somnolence and dizziness of mild to moderate intensity were reported as adverse events by 22.2% of participants after administration, however in none of the lower or higher dose groups.

The driving ability study 22653 was performed to evaluate potential driving impairment. This study used validated instruments, widely recognized in regulatory submissions evaluating drug-impaired driving (*Kay GG et al., 2018*). Their validity was reconfirmed in this study by use of zopiclone as positive control. The stricter instructions applied in the SWITCH-1 and OASIS 1-3 studies were a precautionary measure, as somnolence and fatigue were noted as potential adverse events in earlier clinical studies, but their relevance on driving ability was not fully investigated yet. The driving ability study was conducted after the SWITCH-1 and concurrently with the OASIS 1-3 studies, and indicated no clinically relevant effects on driving performance, even after twice the therapeutic dose (elinzanetant 240 mg) and therefore strict instructions regarding avoidance of driving were deemed unjustified for the SmPC. Regarding the validity of testing at 9 hours after bedtime dosing, highly time-granular assessments using the Karolinska Sleepiness Scale (KSS) over 24 hours following supratherapeutic doses of 240 to 600 mg were performed. In comparison to a time-identical baseline profile from the day prior to dosing, elinzanetant was not associated with significant acute or residual changes in sleepiness at any timepoint, including at t_{max} (1.5 - 2.5 hours post-dose). As terminal elimination half-life is 35-40 hours, plasma concentrations at 9 hours post-dose provide still clinically relevant exposure, i.e. at a level where full NK1/3 receptor occupancy is expected, in particular with doses 5-times the intended dose. As to onset of somnolence and fatigue, these were generally not associated with peak plasma concentrations of elinzanetant, often reported several hours or even days after the first dose in phase 2-3 studies. Therefore, the Applicant considers driving ability findings obtained in the morning after dosing as valid for all time points before and after the 9-hour post-dose. Based on these arguments, it is concluded that the Applicant has sufficiently substantiated the currently included instructions when driving or using machinery in the SmPC. However, it is noted that the initial instructions included in section 4.7 have been extended with an additional text, "*Elinzanetant has no or negligible influence on the ability to drive and use machines. However, women should be advised to be careful when driving or using machines if they experience fatigue, dizziness or somnolence during treatment with Lynkuet (see section 4.8)*", which is not acceptable, see SmPC assessment.

Based on the non-clinical data and the phase 1 TQT like study (using a positive control in the second part of the study), the study drug does not suggest a pro-arrhythmic effect based on the assessment of non-clinical and clinical study data. In the TQT like study using supra-therapeutic doses, both time-matched QT effect as well as the plasma concentration effect curve did not show signs of QT prolongation with absence of any slope effect and highest upper Confidence Intervals below the level of regulatory concern (10 ms). Absence of effect was confirmed in a Japanese study. Further, this medicinal class has thus far not been associated with a pro-arrhythmic concern. Overall, the results are reassuring.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology of elinzanetant was assessed in healthy volunteers and in female patients with vasomotor symptoms.

The clinical pharmacodynamics was extensively investigated concerning mode of action, primary pharmacology in healthy male volunteers, female volunteers of reproductive age and postmenopausal women and secondary pharmacology, including an alcohol interaction study, a driving performance study, effects on cognitive function, and a TQT study.

The clinical pharmacology was adequately studied by the applicant.

2.6.5. Clinical efficacy

The clinical development programme for elinzanetant in the treatment of VMS associated with menopause or caused by treatment with adjuvant endocrine therapy consists of 2 phase 2 dose-finding studies and 4 phase 3 studies.

An overview of the Phase 2 and Phase 3 clinical development program is provided in Table 11.

Table 11 Overview of Phase 2/3 clinical studies with elinzanetant relevant to efficacy evaluation

Study identifier Study no. *(Report no.)* *location*	**Study period (FPFV, LPLV) No. of participants**	**Design Control type**	**Study & control drugs, dose (participants treated / completed [d]) Route of administration, duration**	**Population main inclusion criteria**
Phase 2 studies				
RELENT-1 [a] **21681** ***(R-13554)*** *USA* **PK/PD**	01 AUG 2016 to 28 Mar 2017 Total screened: 316 Total treated: 76 Total completed: 74	Multi-center, double-blind, randomized, placebo-controlled, multiple ascending dose design	Elinzanetant 50 mg (15 / 15) Elinzanetant 100 mg (15 / 14) Elinzanetant 150 mg (15 / 15) Elinzanetant 300 mg (13 / 13) Placebo (18 / 17) Oral, once daily, 14 days	Post-menopausal women, 40 to 65 years of age with moderate to severe HF
SWITCH-1 **21686 /** **814-PM-02** ***(R-13559)*** *Canada, UK, USA* Efficac/Safety/PK	20 NOV 2018 to 21 NOV 2019 Total screened: 760 Total treated: 199 Total completed: 185	Multi-center, multi-country, double-blind, randomized, placebo-controlled, dose-range finding study	Elinzanetant 40 mg (31 / 29) Elinzanetant 80 mg (17 / 14) Elinzanetant 120 mg (52 / 51) Elinzanetant 160 mg (52 / 43) Placebo (47 / 43) Oral, once daily, 12 weeks	Post-menopausal women, 40 to 65 years of age with moderate to severe HF

Study identifier **Study no.** ***(Report no.)*** ***location***	**Study period (FPFV, LPLV)** **No. of participants**	**Design** **Control type**	**Study & control drugs, dose (participants treated / completed [d])** **Route of administration, duration**	**Population main inclusion criteria**
Treatment of moderate to severe VMS associated with menopause				
Phase 3 – Pivotal studies				
OASIS 1 **21651** *(PH-42782)* *Europe, Israel, USA*	27 AUG 2021 to 27 NOV 2023 Total screened: 1535 Total treated: 393 Total completed: 309	Multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, intervention study	Elinzanetant 120 mg 26 weeks (198 [b] / 156) Placebo (12 weeks), followed by elinzanetant 120 mg (14 weeks) (195 [b] / 159) Oral, once daily	• Post-menopausal women, 40 to 65 years of age with moderate to severe HF. • At least 50 moderate or severe HF (including night-time HF) over the last 7 days that the HFDD was completed
OASIS 2 **21652** *(PH-42780)* *Canada, Europe, USA*	29 OCT 2021 to 10 OCT 2023 Total screened: 1483 Total treated: 400 Total completed: 324	Multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, intervention study	Elinzanetant 120 mg 26 weeks (200 [c] / 160) Placebo (12 weeks), followed by elinzanetant 120 mg (14 weeks) (200 [c] / 170) Oral, once daily	• Post-menopausal women, 40 to 65 years of age with moderate to severe HF • At least 50 moderate or severe HF (including night-time HF) over the last 7 days that the HFDD was completed
Phase 3 – 52-week efficacy and safety study				
OASIS 3 **21810** *(PH-42784)* *Canada, Europe, USA*	27 AUG 2021 to 12 FEB 2024 Total screened: 1524 Total treated: 627 Total completed: 453	Multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, intervention study	Elinzanetant 120 mg (313 / 226) Placebo (315 / 232) Oral, once daily, 52 weeks	Post-menopausal women, 40 to 65 years of age with moderate to severe HF

Study identifier Study no. *(Report no.)* *location*	Study period (FPFV, LPLV) No. of participants	Design Control type	Study & control drugs, dose (participants treated / completed [d]) Route of administration, duration	Population main inclusion criteria
Treatment of moderate to severe VMS caused by AET				
Phase 3 – Pivotal study				
OASIS 4 **21656** **B003761** *Canada, Europe, Israel, Kazakhstan*	14 OCT 2022 to 30 APR 2024 (Part A) / 14 NOV 2024 (Part B) Total screened: 758 Total treated: 473 Total completed: (Part A + B) EZN: 262 PLC/EZN: 133	Double-blind, randomized, placebo-controlled multicenter study over 52 weeks and optionally for an additional 2 years in women with, or at high risk for developing hormone-receptor positive breast cancer	Part A: Elinzanetant 120mg: 315 / 271 26 weeks Placebo (12 weeks), followed by elinzanetant 120 mg (14 weeks): 158 / 139 Part B: Elinzanetant 120 mg (26 weeks) EZN: 315 / 262 PLC/EZN: 158 / 133 Part C: Elinzanetant 120 mg (2 years) Oral, once daily	• Women aged 18 to 70 years with, or at high risk for developing hormone-receptor positive breast cancer and experiencing VMS caused by AET • At least 35 moderate to severe HF (including night-time HF) over the last 7 days that the HFDD was completed.

OD = once daily, trt = treatment

a RELENT-1 is classified as Phase 1b/2a clinical study and therefore appears as Phase 2 study in the dossier.

b OASIS 1: 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.

c OASIS 2: 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

d OASIS 1-2: "completed" refers to those who completed the 26-week treatment phase.
OASIS 3: "completed" refers to those who completed the 52-week treatment phase.
OASIS 4: "completed" refers to 52 weeks of treatment (Part A + B of the ongoing study)

2.6.5.1. Dose response studies

RELENT-1 (Study 21681)

RELENT-1 was a phase 1b/2a study, patient received 50, 100, 150 or 300 mg in a hard capsule formulation for 14 days, to evaluate average Daily Frequency of Moderate and Severe Hot Flushes. A dose-ordered response to treatment was not clearly apparent in this study, although it was evident that the two higher doses (150 mg and 300 mg) were more effective than the two lower doses (50 mg and 100 mg). This absence of a clear dose-ordered response was most likely due to the small size of the study and the variability in exposure associated with the non-optimized hard gel capsule formulation used in the study. The high PK variability and lower exposures (on a mg equivalent basis) achieved with the hard gel capsule formulation precluded its continued development, resulting in the change to the optimized soft gel capsule formulation for continued development and commercialization.

However, the exposures achieved in RELENT-1 provided guidance for the range of doses to be used in the Phase 2b study SWITCH-1. In particular, the 150 mg dose was fully effective and resulted in exposures at steady state that were consistent with full receptor occupancy throughout a 24-hour dose interval.

Table 4–1: Summary of efficacy findings with the 150 mg NT-814 dose in the RELENT-1 study

Mean Daily Frequency		Moderate & Severe Hot Flashes		Night-Time Awakening Secondary to Hot Flashes	
		Placebo (N=18)	NT-814 150 mg (N=15)	Placebo (N=18)	NT-814 150 mg (N=15)
Baseline	Mean (SE)	10.4 (3.87)	10.2 (2.98)	4.51 (2.377)	4.72 (2.209)
Week 2	Mean (SE)	6.6 (4.41)	1.6 (1.68)	3.27 (3.36)	1.06 (0.942)
	LS mean change from Week -1	-4.36	-9.28	-1.46	-3.71
	LS mean change vs placebo	N/A	-4.92	N/A	-2.25
	p-value vs placebo	N/A	0.0002	N/A	0.0003

LS = least squares, N/A= not applicable, SE = standard error

These data were used, together with comparative exposure data from relative bioavailability study (R-13555 (21677)) between 25 mg soft gel and 50 mg hard gel capsule and repeat dose escalating study (R-13551 (21678)) with 40 mg soft gel capsule (814-1-02) to set the range of doses evaluated in the SWITCH-1 study.

SWITCH-1 (Study 21686)

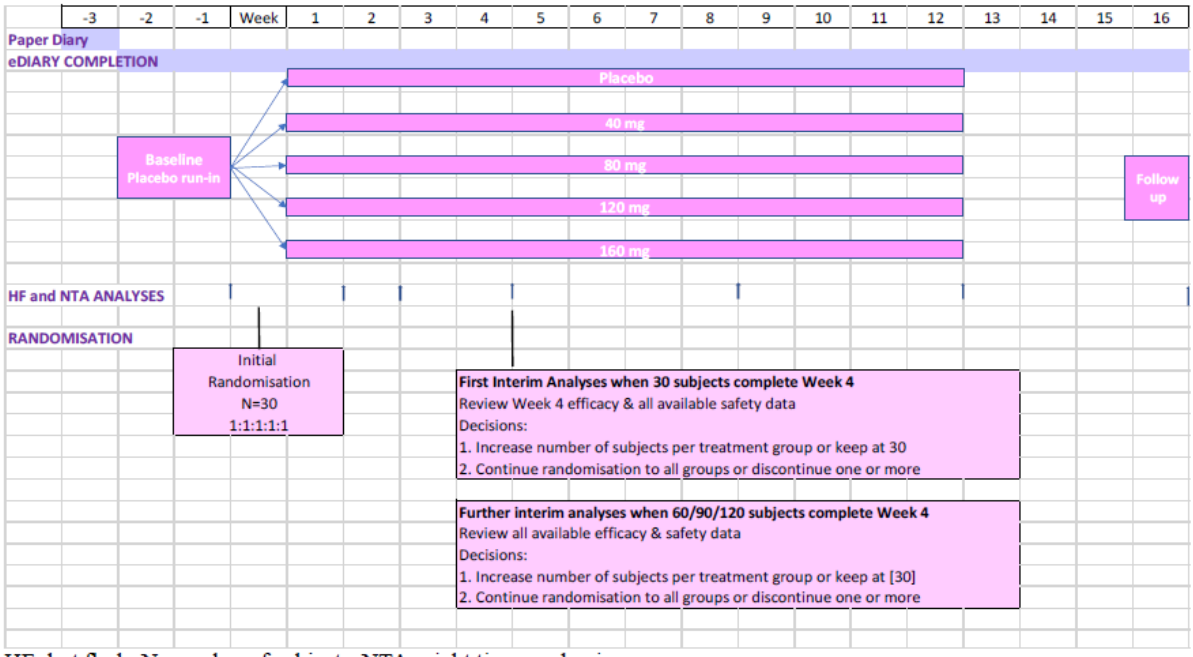
Study design

Phase 2b, multi-centre, multi-country, double-blind, randomised, placebo-controlled, dose-range finding study of NT-814 in post-menopausal women over 12 weeks in participants with at least 7 moderate to severe HF per day.

A total of 165 post-menopausal women were planned to be enrolled using an adaptive design that allowed both the total number of subjects recruited and/or the number of subjects randomised to each treatment group to be modified on the basis of emerging safety and efficacy. The duration of the study was approximately 19 weeks, including a 3-week formal screening and baseline period, 12 weeks of double-blind treatment and a final follow-up visit 4 weeks at end of the treatment.

The study participants were postmenopausal women, aged 40 and 65 years, with spontaneous amenorrhea for at least 12 months or 6 months with FSH >40 IU/L and oestradiol <30 pg/mL, or having had bilateral oophorectomy (at least 6 weeks postsurgical, with or without hysterectomy), with at least 7 moderate to severe HF per day.

Figure 6 Study design SWITCH-1



HF=hot flash; N=number of subjects; NTA=night time awakening.

To overcome the limitations of the hard gel formulation used in the RELENT-1 study, an optimised lipidic soft gel formulation of NT-814 was developed. Based on the results of a relative bioavailability study (Study 814-1-01/ 21677), conducted to compare the exposures achieved with the new soft gel capsule formulation, , it was expected that doses of the soft gel formulation in the range of 40 mg to 160 mg would achieve similar exposures to those associated with efficacy in the RELENT-1 study (100 mg to 300 mg daily of the hard gel capsule formulation).

The primary objective was to evaluate the efficacy of once daily doses of 40 mg, 80 mg, 120 mg and 160 mg NT-814, compared with placebo, in reducing the frequency and severity of hot flashes. The co-primary endpoints were mean change from baseline in mean daily frequency and severity of moderate to severe hot flashes from baseline to Week 4 and Week 12. The primary analysis was based on the intention to treat (randomised treatment) analysis set.

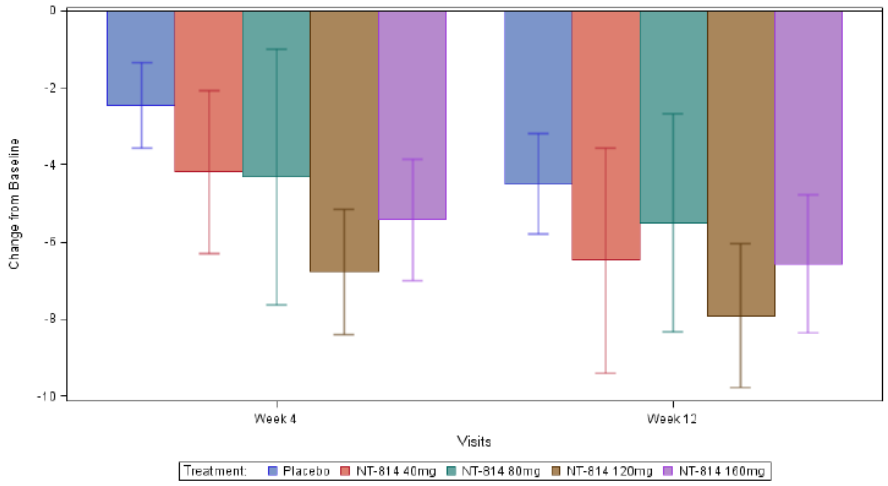
Results SWITCH 1

Efficacy

The **co-primary endpoints** were mean change from baseline in mean daily frequency and severity of moderate and severe HF at Weeks 4 and 12.

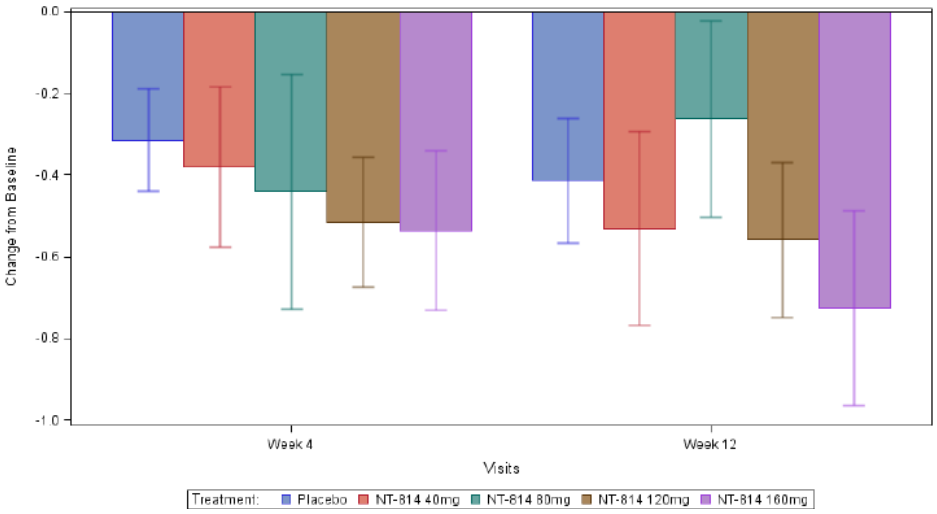
In the FAS, the mean daily *frequency of moderate and severe HF* decreased at both Weeks 4 and 12 in all treatment groups, including placebo. However, larger reductions were observed in all NT-814 groups compared to placebo, with the largest mean [SD] reductions observed in the 120 mg NT-814 dose group at both Week 4 (-6.76 [5.85] versus -2.45 [3.65] for placebo) and Week 12 (-7.91 [6.66] versus -4.49 [4.29] for placebo). The difference between NT-814 and placebo for mean reduction in mean daily frequency of moderate and severe hot flashes from baseline was statistically significant for the 120 mg and 160 mg NT-814 groups at Week 4 (difference in LS mean [SE]: -3.93 [1.02], and - 2.63 [1.03] respectively) and for the 120 mg group at Week 12 (difference in LS mean [SE]: -2.95 [1.15]).

Figure 7 *SWITCH-1: Change from Baseline in Mean Daily Frequency of Moderate and Severe Hot Flashes at Weeks 4 and 12 by Treatment Group (Full Analysis Set)*



In the FAS, the *mean weekly severity of moderate and severe hot flashes* decreased at both Week 4 and Week 12 in all treatment groups, including placebo, see Figure below. However, larger reductions were generally observed in the NT-814 groups compared to placebo, with the largest mean [SD] reductions in the 160 mg NT-814 dose groups at both Week 4 (-0.54 [0.67] versus -0.31 [0.41] for placebo) and Week 12 (-0.73 [0.78] versus -0.41 [0.50] for placebo). The difference between NT-814 and placebo for mean reduction in mean weekly severity of moderate and severe hot flashes from baseline was statistically significant for the 160 mg group at Week 12 (difference in LS mean [SE]: -0.27 [0.13]).

Figure 8 SWITCH-1: Change from Baseline in Mean Weekly Severity of Moderate and Severe Hot Flashes at Weeks 4 and 12 by Treatment Group (Full Analysis Set)



Consistent with the reductions in mean hot flash frequency observed in the NT-814 groups, the **secondary efficacy analysis** showed significantly more subjects that had at least a 50% reduction in hot flash frequency in the 120 mg and 160 mg NT-814 groups compared to placebo at Weeks 4 and 12

Similarly, at least twice the number of subjects had at least a 80% reduction in hot flash frequency in the 120 mg and 160 mg NT-814 groups compared to placebo at Weeks 4 and 12, with the number of subjects significantly greatest for the 160 mg group at Week 12.

Clinically relevant improvements were observed in measures of quality of life (MenQoL-I and HFRDIS), sleep quality (PSQI and ISI) and mood (BDI-II).

At Week 16, after the end of treatment, efficacy parameters began to return towards baseline values. This was most apparent in the NT-814 groups, suggesting that there was a noticeable increase in symptoms for subjects who had been receiving active treatment.

Safety

In the elinzanetant arms, the most frequently reported TEAEs by PT were headache (15 [9.9%]), somnolence (12 [7.9%]), and diarrhoea (10 [6.6%]). Somnolence, fatigue, and dizziness were reported more frequently in the 160 mg arm compared to the lower dose arms or placebo. Somnolence, fatigue and headache were also the most frequently reported TEAEs classified as drug-related in the elinzanetant arms. The only severe TEAE reported in more than one woman was migraine (2 in the 120 mg arm). There were more women in the 160 mg arm (5) who discontinued the study treatment due to TEAEs compared to the lower doses (2 in the 80 mg arm) or placebo (1). A total of 5 serious TEAEs, 2 in the placebo arm (PTs infective exacerbation of chronic obstructive airway disease and sepsis) and 3 in the elinzanetant arms (PTs tooth abscess, migraine and nephrolithiasis) were reported in 5 women, of which only one event (sepsis, placebo arm) was considered related to study drug by the investigator. Two women in the elinzanetant arms (40 mg and 120 mg) experienced mild postmenopausal bleeding (AESI considered unrelated to study drug. TEAEs leading to study discontinuation in the elinzanetant arms included single reports of the following PTs: headache, somnolence, bradycardia, abdominal distension, dyspepsia, fatigue, electrocardiogram QT prolonged, anxiety, depression, liver function test increased and erythema multiforme. Further investigation of the case of QT prolongation revealed that the measurement of QT interval resulting in an assessment of clinical significance was incorrect and there was no prolongation of the QTc interval compared to baseline. Concerning the case of liver function test increase, the data indicate that the subject was non-compliant with the treatment regimen and the event was unrelated to NT-814.

2.6.5.2. Main studies

'Treatment of VMS associated with menopause':

Two replicate design pivotal phase 3 studies were submitted: OASIS 1 (study 21651) and OASIS 2 (study 21652).

OASIS 3 was a placebo-controlled 52-weeks Phase 3 long-term safety study for the treatment of moderate to severe VMS associated with menopause. This study was discussed in the chapter 'supportive studies, section 2.6.5.5'.

'Treatment of VMS caused by adjuvant endocrine therapy':

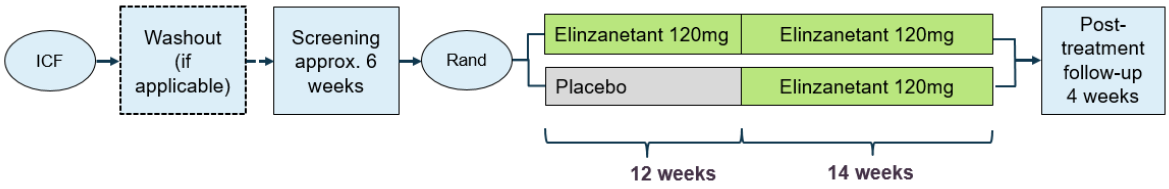
One (ongoing) pivotal phase 3 study OASIS 4 was submitted (study number 21656).

2.6.5.2.1. Treatment of VMS associated with menopause': OASIS 1 and OASIS 2

- ***Methods***

OASIS 1 and 2 are multi-centre, multi-country, double-blind, randomized, parallel-group, placebo-controlled, interventional studies with an initial placebo-controlled period of 12 weeks, followed by an extension phase of 14 weeks. Postmenopausal women, 40 to 65 years of age, with at least 50 moderate to severe HFs (including night-time HFs) associated with menopause per week at baseline and seeking treatment for this condition were treated orally once daily with elinzanetant or matching placebo for 12 weeks, followed by elinzanetant for 14 weeks. Both studies are identical except for a pre-specified assessment of sleep quality in a subgroup using actigraphy in OASIS 1.

Figure 9 Study Schema



- ***Study Participants***

The **main inclusion criteria** were

1. Females aged 40 to 65 years, inclusive, at signing of informed consent.
2. Postmenopausal, defined as:
   a. at least 12 months of spontaneous amenorrhea prior to signing of informed consent, or
   b. at least 6 months of spontaneous amenorrhea prior to signing of informed consent with serum FSH levels > 40 mIU/mL **and** a serum estradiol concentration of < 30 pg/mL, or
   c. at least 6 months after hysterectomy at signing of informed consent with serum FSH levels > 40 mIU/mL **and** a serum estradiol concentration of < 30 pg/mL, or
   d. surgical bilateral oophorectomy with or without hysterectomy at least 6 weeks prior to signing of informed consent.
3. Moderate to severe HF associated with the menopause and seeking treatment for this condition.
4. Negative urine pregnancy test at screening.
5. In good general health
6. Normal or clinically insignificant cervical cytology not requiring further follow-up:
   a. A cervical cytology sample has to be obtained during screening, or

b. A documented normal result has to be available from cervical cytology conducted within 12 months prior to signing of informed consent.

c. HPV testing in participants with ASCUS will be used as an adjunctive test automatically. Participants with ASCUS can be included if they are negative for high-risk HPV strains.

d. HPV testing in participants with "absence of endocervical/transformation zone component" will be used as an adjunctive test automatically. Participants can be included if they are negative for high-risk HPV strains.

7. BMI between 18 and 38 kg/m^2 at screening
8. Participant has a screening mammogram performed, unless she is able to provide a written normal mammogram result obtained no more than 6 months prior to the start of screening.
9. Participant has completed HFDD for at least 11 days during the two weeks preceding baseline visit, and participant has recorded at least 50 moderate or severe HF (including night-time HF) over the last 7 days that the HFDD was completed (assessed at the Baseline Visit).

The **main exclusion criteria** were

1. Any clinically significant prior or ongoing history of arrhythmias, heart block and QT prolongation either determined through clinical history or on ECG evaluation.
2. Any clinically significant abnormal laboratory test result(s) measured during screening (single re-test allowed, except for tests listed in inclusion criteria 2 and exclusion criteria 10).
3. Any active ongoing condition that could cause difficulty in interpreting VMS such as: infection that could cause pyrexia, pheochromocytoma, carcinoid syndrome.
4. Current or history (except complete remission for 5 years or more) of any malignancy (except basal and squamous cell skin tumours). Women receiving adjuvant endocrine therapy (e.g. tamoxifen, aromatase inhibitors, GnRH analogues) cannot be enrolled in this study.
5. Uncontrolled or treatment-resistant hypertension. Women with mild hypertension can be included in the study if they are medically cleared prior to study participation.
6. Untreated hyperthyroidism or hypothyroidism.
7. Any unexplained post-menopausal uterine bleeding.
8. Clinically relevant abnormal findings on mammogram.
9. Renal impairment greater than moderate (i.e. estimated glomerular filtration rate <30 mL/min/1.73 m^2) at screening
10. Abnormal liver parameters (AST, ALT or AP > 2xULN, or TBL or INR>ULN), diagnosis of hepatitis B or C infection.
11. Disordered proliferative endometrium, endometrial hyperplasia, polyp, or endometrial cancer diagnosed based on endometrial biopsy during screening
12. Any other history, condition, therapy, or uncontrolled intercurrent illness which could in the opinion of the investigator affect compliance with study requirements.
13. Unwillingness to wash-out use of any of the prohibited concomitant medications

- ***Treatments***

Participants received either 120 mg (two soft gel capsules of 60 mg) of elinzanetant, or matching placebo orally once daily. Study treatment in both treatment arms was to be taken once daily before going to bed, with or without food.

- ***Objectives***

Primary objectives

- To evaluate the efficacy of elinzanetant for the treatment of VMS associated with the menopause.

Secondary objectives

- To evaluate the onset of efficacy of elinzanetant for the treatment of VMS associated with the menopause
- To evaluate the efficacy of elinzanetant in women treated for relief of VMS associated with the menopause on:
  - Sleep quality
  - Menopause-related quality of life
  - Depressive symptoms
- To evaluate the safety of elinzanetant for the treatment of VMS associated with the menopause

Other pre-specified objectives

- To evaluate variability in exposure in relation to the efficacy and safety for elinzanetant
- To further investigate EZN (e.g., mode-of-action-related effects, safety) and to further investigate patho-mechanisms deemed relevant to VMS and associated health problems
- Assessment of sleep quality measured via actigraphy (optional/sub-study)

- ***Outcomes/endpoints***

Primary endpoints

- Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD)
- Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD)

Key secondary endpoints

- Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD)

- Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD)
- Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12
- Mean change in frequency of moderate to severe HF from baseline to Week 1 (assessed by HFDD)
- Mean change in MENQOL total score from baseline to Week 12

Secondary endpoints

- Mean change in frequency of moderate to severe HF from baseline over time (assessed by HFDD)
- Mean change in BDI-II total score from baseline to Week 12
- Mean change in BDI-II total score from baseline to Week 26

Exploratory endpoints

- Proportion of participants with at least 50% reduction in frequency of HF at Week 4
- Proportion of participants with at least 50% reduction in frequency of HF at Week 12
- Time to treatment response
- Mean change in frequency of mild, moderate, and severe HF from baseline over time (assessed by HFDD)
- Absolute values and changes in the ISI total score over time
- Absolute values of the PGI-C individual item scores over time
- Absolute values and change in PGI-S individual item scores over time
- Absolute values and change in EQ-5D-5L single-dimensions and health state VAS score over time.
- Absolute values and changes in the BDI-II total score over time
- Mean change in MENQOL domain and single item scores from baseline over time
- Mean change in frequency of night-time awakening from baseline over time (assessed by HFDD)
- Mean change in proportion of days with participants rating of "quite a bit" or "very much" sleep disturbances experienced due to HF from baseline over time (assessed by HFDD)
- Number of participants with TEAEs
- Mean change in Sleepiness Scale at Week 1, Week 4, and Week 12 compared to baseline
- Systemic exposure of EZN in plasma via sparse PK sampling
- Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)
- Exploratory analysis of nightly sleep monitoring device data (EZN vs. placebo e.g., total sleep time, sleep efficiency, number of awakenings and their duration) predose compared with data at defined timepoints during treatment

- ***Estimands***

Estimand for primary objective

The main estimand assessed the effect of assigned treatment, i.e., elinzanetant 120 mg compared to placebo including all treatment interruptions, premature discontinuation of randomized treatment, and intake of prohibited concomitant medications having impact on efficacy (treatment policy strategy) in postmenopausal women aged 40–65 years with moderate to severe VMS (further defined by inclusion and exclusion criteria) on change from baseline to Week 4 and Week 12 as defined for the primary endpoints. The mean difference between the treatment arms was used as summary measure.

Table 12 OASIS 1 and 2 - estimands for primary objective

Study Population	Post menopause women aged 40-65 with VMS as described by the inclusion/exclusion criteria detailed in the protocol.	
Treatment condition(s)	120 mg elinzanetant, placebo	
Endpoint (variable)	Efficacy was assessed based on 2 primary endpoints: • Change in frequency of moderate to severe HFs from baseline to Week 4 • Change in frequency of moderate to severe HFs from baseline to Week 12	
Population level summary	• Mean change in frequency of moderate to severe HFs from baseline to Week 4. • Mean change in frequency of moderate to severe HFs from baseline to Week 12. Treatment comparison was based on differences in treatment arm means for each endpoint.	
Intercurrent events (ICEs) and strategy to handle them – *all treatment policy*		
ICE[a]	**Reason for ICE**	**Data handling method**
Temporary Treatment interruption[b]	AEs (treatment related/unrelated)	Utilise the collected data after ICE.
	COVID-19 and administrative reasons	Utilise the collected data after ICE.
Permanent discontinuation of randomized treatment	AEs (treatment related/unrelated) or lack of efficacy	
	• For participants who remained untreated/on background therapy.	Utilise the collected data after ICE.
	• For participants who initiate alternative VMS treatment	Utilise the collected data after ICE.
	Other treatment-unrelated reasons, including COVID-19	Utilise the collected data after ICE.
Intake of prohibited concomitant medication having impact on efficacy	All reasons	Utilise the collected data after ICE.

AE = Adverse event, COVID-19 = Coronavirus disease of 2019, ICE = Intercurrent event, VMS = Vasomotor symptoms
a ICEs were reviewed at the Blinded Review Meeting prior to the study unblinding
b Definition of temporary treatment interruption:
Week 1 = Treatment taken on <5/7 days during week 1.
Week 4 = Treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either week 3 or 4.
Week 8 = Treatment taken <80% during weeks 1-8 (day 1 – 56) OR treatment taken on <5/7 days during either week 7 or 8.
Week 12 = Treatment taken <80% during weeks 1-12 OR treatment taken on <5/7 days during either week 11 or 12.

Estimands for secondary objective

The key secondary endpoints were handled using similar attributes than primary endpoints except for the variables and population summary that are listed below:

Variable:

- Change in severity of moderate to severe HF from baseline to Week 4.
- Change in severity of moderate to severe HF from baseline to Week 12.
- Change in frequency of moderate to severe HF from baseline to Week 1.
- Change in PROMIS SD SF 8b total T-score from baseline to Week 12.
- Change in MENQOL total score from baseline to Week 12.

Population level summary:

- Mean change in severity of moderate to severe HF from baseline to Week 4.
- Mean change in severity of moderate to severe HF from baseline to Week 12.
- Mean change in frequency of moderate to severe HF from baseline to Week 1.
- Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12.
- Mean change in MENQOL total score from baseline to Week 12.

Table 13 Estimands for secondary objective of OASIS 1 and 2

Study Population	Post menopause women aged 40-65 with VMS as described by the inclusion/exclusion criteria detailed in the protocol.	
Treatment condition(s)	120 mg elinzanetant, Placebo	
Endpoint (variable)	Efficacy was further assessed based on 5 key secondary endpoints: • Change in severity of moderate to severe HF from baseline to Week 4. • Change in severity of moderate to severe HF from baseline to Week 12. • Change in frequency of moderate to severe HF from baseline to Week 1. • Change in PROMIS SD SF 8b total T-score from baseline to Week 12. • Change in MENQOL total score from baseline to Week 12.	
Population level summary	• Mean change in severity of moderate to severe HF from baseline to Week 4. • Mean change in severity of moderate to severe HF from baseline to Week 12. • Mean change in frequency of moderate to severe HF from baseline to Week 1. • Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12. • Mean change in MENQOL total score from baseline to Week 12. Treatment comparison was based on differences in treatment arm means for each endpoint.	
Intercurrent events (ICEs) and strategy to handle them – *all treatment policy*		
ICE[a]	**Reason for ICE**	**Data handling method**
Temporary Treatment interruption[b]	AEs (treatment related/unrelated)	Utilise the collected data after ICE.
	COVID-19 and administrative reasons	Utilise the collected data after ICE.
Permanent discontinuation of randomized treatment	AEs (treatment related/unrelated) or lack of efficacy	
	• For participants who remained untreated/on background therapy.	Utilise the collected data after ICE.
	• For participants who initiate alternative VMS treatment	Utilise the collected data after ICE.
	Other treatment-unrelated reasons, including COVID-19	Utilise the collected data after ICE.
Intake of prohibited concomitant medication having impact on efficacy	All reasons	Utilise the collected data after ICE.

AE = Adverse event, COVID-19 = Coronavirus disease of 2019, ICE = Intercurrent event, VMS = Vasomotor symptoms

a) ICEs were reviewed at the Blinded Review Meeting prior to the study unblinding

b) Definition of temporary treatment interruption:
Week 1 = Treatment taken on <5/7 days during week 1.
Week 4 = Treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either week 3 or 4.
Week 8 = Treatment taken <80% during weeks 1-8 OR treatment taken on <5/7 days during either week 7 or 8.
Week 12 = Treatment taken <80% during weeks 1-12 OR treatment taken on <5/7 days during either week 11 or 12.

- ***Sample size***

A total of 370 participants (185 per arm) were to be randomized in a 1:1 ratio to both arms. Assuming a drop-out rate of 10 % in the first 3 months, this would result in approximately 332 evaluable participants (166 per arm), who completed 12 weeks of treatment. The drop-out rate in months 4-6 was also expected to be 10 %, which would result in approximately 298 participants (149 per arm), who completed 6 months of treatment. A formal sample size estimation was performed for the efficacy analyses. The sample size was determined to power the study on the primary and key secondary endpoints at a minimum of 90%. The sample size has been determined via simulation.

For each endpoint, the distribution of the effect for the placebo and treatment arms were built. For endpoints 1, 2, 3, 4 & 6, Bayer used the data from placebo arm in SWITCH-1 study (to build a distribution for the effect of placebo in the study. The placebo arm distribution then was shifted by the estimated treatment effect (from SWITCH-1) to represent the distribution of effects for the treatment arm. For endpoints 5 & 7, there is limited data available in this population and therefore, a standard normal distribution (mean=0, std=1) was assumed for the placebo arm effect. A treatment effect of 0.4 is selected based on clinical team input. Assumed treatment effect and characteristics of the placebo distributions are presented in table 14.

Table 14 Assumed treatment effect and characteristics of the placebo distributions

Endpoint	Treatment effect Treatment vs. placebo	Distribution of the placebo arm	Distribution parameters
1 – CFB HF Freq W4	-3.5	Normal	Mean=-2.29, SD=3.632
2 – CFB HF Freq W12	-2	Normal	Mean=-4.43, SD=4.29
3 – CFB HF Sev W4	-0.22	Mixture normal (Two normal distributions weighted equally at 0.5)	Mean1=-0.543, SD1=0.562, Mean2=-0.105, SD2=0.123
4 – CFB HF Sev W12	-0.26	Mixture normal (Two normal distributions weighted equally at 0.5)	Mean1=-0.897, SD1=0.733, Mean2=-0.128, SD2=0.185
5 – CFB PROMIS SD SF 8b W12	-0.4	Standard Normal	Mean=0, SD=1
6 – CFB HF Freq W1	-2.36	Generalised normal	Psi= 0.43, Kappa=0.628, Alpha=2.277
7 – CFB MENQOL W12	-0.4	Standard Normal	Mean=0, SD=1

- ***Randomisation and Blinding (masking)***

Participants who met all eligibility criteria were centrally assigned to randomized study intervention using IxRS. Participants were randomly assigned 1:1 ratio to both arms. Investigators remained blinded to each participant's assigned study intervention throughout the course of the study. The randomization was stratified by region: North America and rest of the world.

- ***Statistical methods***

The following analysis sets were defined:

Table 15 Definition of the analysis sets of OASIS 1 and 2

Analysis Set	Description
Enrolled	All participants who signed the informed consent form.
Full Analysis Set (FAS)	All randomized participants.
Safety Analysis Set (SAF)	All participants who received at least one dose of study intervention.

Efficacy analyses were based on the FAS and participants were analyzed according to the randomized intervention. Safety analyses were performed on the SAF and participants were analyzed according to the intervention received.

The mean daily frequency of moderate to severe HF at baseline was calculated by aggregating all available days during the 14 days (at least 11 days needed to be available per inclusion criteria) prior to start of treatment to a mean daily frequency as (total number of moderate to severe HF during the 14 days prior to start of treatment) / (total number of available days with data).

The mean daily severity during baseline was calculated for the available days during the 14 days (at least 11 days needed to be available per inclusion criteria) as

> *[(2 x number of moderate HF) + (3 x number of severe HF)] / (total number of moderate to severe hot flashes on that day).*

The mean daily severity during treatment was calculated for the available days as

> *[(1 x number of mild HF) + (2 x number of moderate HF) + (3 x number of severe HF)] / (total number of mild, moderate and severe hot flashes on that day)*.

When no HF were reported for a particular day, the mean severity for that day was set to 0. To obtain the severity of HF during a particular week under treatment, the weekly data was aggregated by averaging the mean daily severity of HF of the available days during that week. In case data is missing for more than 2 days within a week, the value for that particular week was set to missing.

For each of the primary efficacy endpoints, a mixed models repeated measures analysis of covariance (MMRM) was used with treatment arm, week and region (North America vs rest of the world) as factors, with baseline measurement as a covariate, as well as an interaction of treatment by week and an interaction of baseline measurement by week. An unstructured covariance structure was used to model the within-patient errors. A treatment policy strategy was applied to handle all of the specified ICEs in the primary estimand. According to this strategy, all collected data are utilized in the analysis irrespective of occurrence of the ICEs.

Two sensitivity analyses were conducted for the primary estimand to evaluate robustness of the results. The first assessed the normality assumption in the primary analysis and was evaluated by graphical tools (i.e., qqplot and plot of residuals against predicted values). This was assessed based on the observed data before multiple imputation was applied. In the case of extreme violations of the normality assumption, a non-parametric rank ANCOVA was carried out as a sensitivity analysis and the Hodges-Lehmann estimate was calculated as an estimate of the treatment effect. A tipping point analysis was applied as a second sensitivity analysis to assess the sensitivity of the main analysis results to modelling of the missing data that occurred in presence of ICEs. This was done by applying an unfavourable additive shift (i.e. delta) to the values imputed by the MI model for the primary analysis in the elinzanetant arm. For the endpoint related to the frequency of HF, the adjustments were applied with delta values of 1, 2, 3, 4, etc. in each successive tipping point iteration until a tipping point was attained.

The key secondary endpoints were analyzed analogous to the main analysis of primary endpoints.

Exploratory subgroup analyses using descriptive statistics were provided for the primary and key secondary endpoints for the following subgroups, region (North America vs. rest of the world), race, ethnicity, BMI (<18.5, 18.5 to <25, 25 to <30, ≥ 30 kg/m2) and smoking history (Never, Former, Current; derived from habitual cigarette smoking, any other tobacco/nicotine from CRF).

A multiplicity adjustment strategy was defined in these trials using the graphical method (*Bretz et al. 2009*).. The multiplicity adjustment strategy controls the overall Type I error rate at a one-sided $\alpha = 0.025$ level under any joint distribution of the test statistics corresponding to the null hypotheses.

No interim analysis was performed for these studies.

- ***Results***

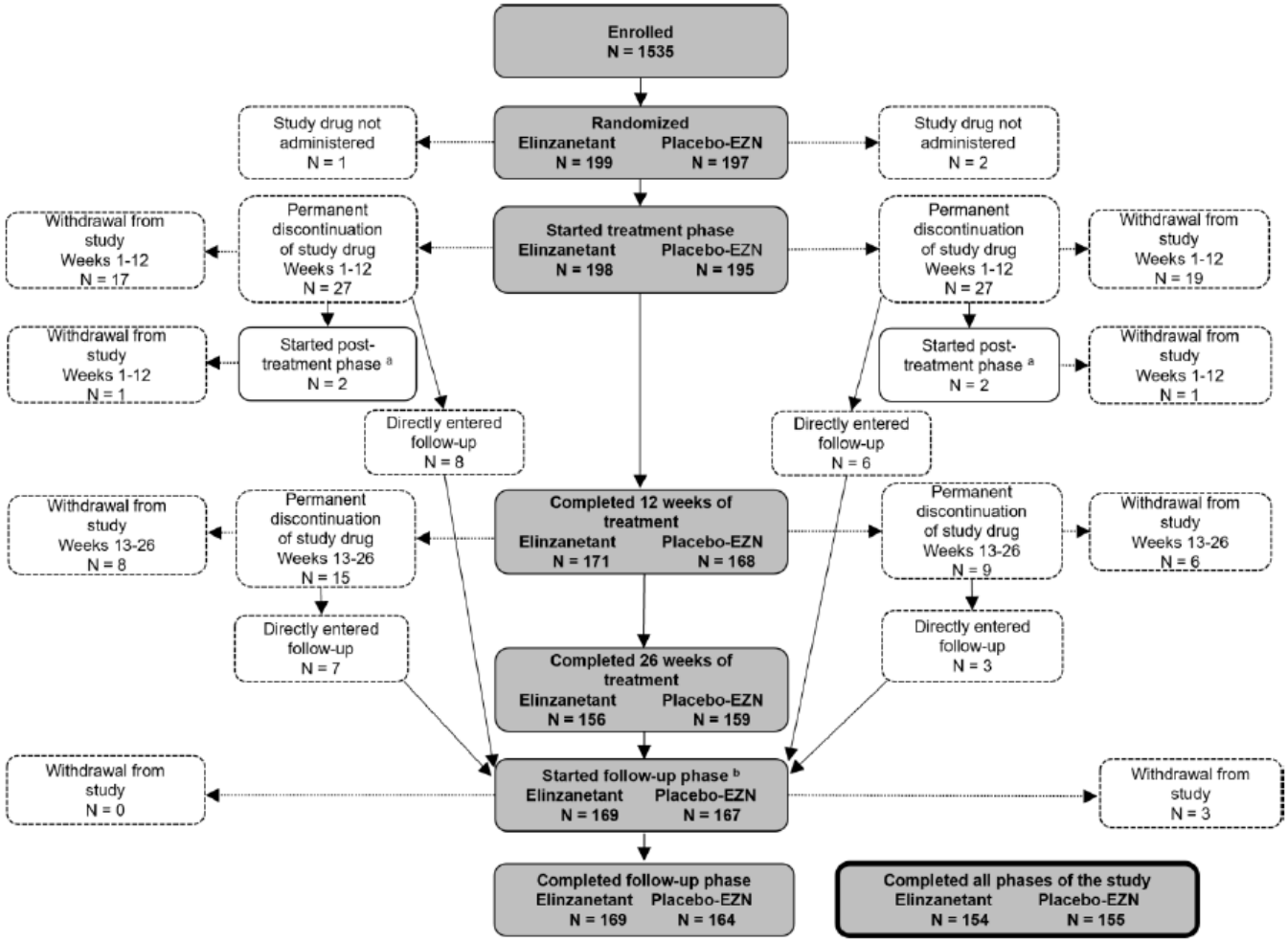
  - **Participant flow**

<u>OASIS 1</u>

Out of the 1535 screened participants, 396 were randomized and 309 completed the study. Not meeting the eligibility criteria was the most common reason for screening failure (1087 [70.8%]). 61 participants (14.6% in the elinzanetant arm and 16.2% in the placebo- arm) did not complete the study and 26 participants (8.0% in the elinzanetant arm and 5.1% in the placebo arm) discontinued the study treatment but remained in the study and completed post-treatment phase or follow-up.

The most common reason for discontinuation of the study drug was adverse event (AE), with similar proportions of women in the two treatment arms (10.1% in the elinzanetant arm and 9.6% in the placebo arm). Other common reasons were subject decision (4.0% in the elinzanetant arm and 2.5% in the placebo arm) and lost to follow-up (3.5% in the elinzanetant arm and 2.0% in the placebo arm). Details on the participant disposition are also included in figure 10.

Figure 10 Participant flow



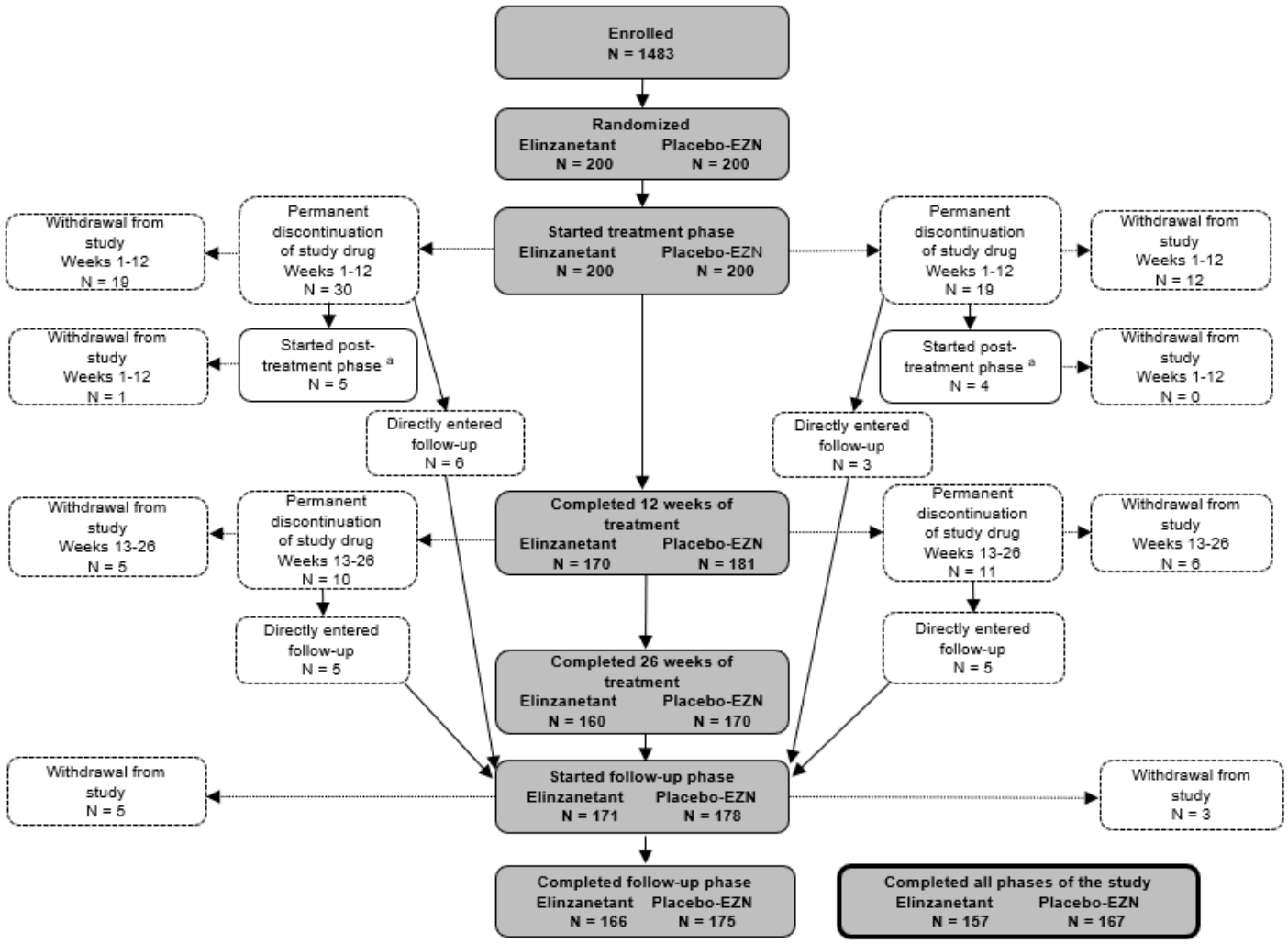
a. If a participant discontinued from study drug before Week 12 but agreed to stay in the study (i.e., in a post-treatment phase), the next scheduled in-person visit covered the assessments expected to be performed during the follow-up visit, and therefore no follow-up visit was needed after the end-of-treatment visit.

b. In addition, 2 participants in the elinzanetant 120 mg arm and 1 participant in the placebo-elinzanetant 120 mg arm completed 26 weeks of treatment but did not come back for follow-up.

OASIS 2

Out of the 1483 screened participants, 400 were randomized and 324 completed the study. Not meeting the eligibility criteria was the most common reason for screening failure (1044 [70.4%]). 51 participants (15.0% in the elinzanetant arm and 10.5% in the placebo- arm) did not complete the study and 25 participants (6.5% in the elinzanetant arm and 6.0% in the placebo arm) discontinued the study treatment but remained in the study and completed post-treatment phase or follow-up. The most common reason for discontinuation of the study drug was subject decision (6.5% in elinzanetant arm and 6.0% in placebo-arm). Other common reasons were AE (8.5% in the elinzanetant and 2.5% in the placebo), lack of efficacy (1.5% in the elinzanetant arm and 1.0% in the placebo arm) and noncompliance with study drug (0.5% in the elinzanetant arm and 2.0% placebo arm).

Figure 11 OASIS 2 participant flow



a. If a participant discontinued from study drug before Week 12 but agreed to stay in the study (i.e., in a post-treatment phase), the next scheduled in-person visit covered the assessments expected to be performed during the follow-up visit, and therefore no follow-up visit was needed after the end-of-treatment visit.

- **Recruitment**

Study period OASIS 1: 27 Aug 2021 (signed informed consent) to 27 Nov 2023 (last participant last visit)

Study period OASIS 2: 29 Oct 2021 (signed informed consent) to 10 Oct 2023 (last participant last visit)

- **Conduct of the study**

All changes in the conduct of the study were implemented by two protocol amendments.

About 61.9% of all participants in OASIS 1 and 49.3% in OASIS 2 had important protocol deviations and the frequency was similar in both treatment arms. There were no major differences in the types of important protocol deviations between the treatment arms. The most common important deviations were procedure deviations in the elinzanetant arm and placebo-elinzanetant arm.

3 intercurrent events (ICEs) were defined for the period of up to Week 12: permanent discontinuation of randomized treatment, temporary treatment interruption and intake of prohibited concomitant medication having impact on efficacy. Overall, the occurrence of ICEs was low.

In OASIS 1 and 2, the most common ICE was permanent discontinuation of randomized treatment: 23 (11.6%) and 25 (12.5%) participants in the elinzanetant arm and 27 (13.7%) and 18 (9.0%) participants in placebo arm.

Compliance with study procedures was documented in different ways. This included daily documentation of study drug intake in the eDiary by the participant, documentation of distributed and returned study medication (pill count) by site personnel, and calculation of missing data for eDiary-based PROs as part of the statistical analysis. Median treatment compliance was over 95% in both treatment arms in OASIS 1 and 2 studies. In both studies, most women achieved a high compliance in Weeks 1-12 (88.0% to 93.9%) and Weeks 13-26 (86.4% to 92.4%) based on the eCRF in both treatment arms. Compliance results were similar whether evaluated from the eCRF or the eDiary data.

- **Baseline data**

Demographics and baseline characteristics

In OASIS 1 and 2, treatment arms were generally well balanced regarding demographic and other baseline characteristics. Most participants were White or Black/African American. The age ranged from 40 to 65 years. The mean BMI was approximately 28 kg/m^2, and most participants had never smoked.

Table 16 OASIS 1 and 2 - demographics (FAS)

	OASIS 1		OASIS 2	
	Elinzanetant 120 mg N=199 (100%)	Placebo - Elinzanetant 120 mg N=197 (100%)	Elinzanetant 120 mg N=200 (100%)	Placebo - Elinzanetant 120 mg N=200 (100%)
Sex				
Female	199 (100.0%)	197 (100.0%)	200 (100.0%)	200 (100.0%)
Race				
White	151 (75.9%)	154 (78.2%)	163 (81.5%)	172 (86.0%)
Black or African American	38 (19.1%)	38 (19.3%)	35 (17.5%)	25 (12.5%)
Asian	2 (1.0%)	1 (0.5%)	0	1 (0.5%)
American Indian or Alaska Native	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Multiple	3 (1.5%)	0	0	1 (0.5%)
Not reported	4 (2.0%)	3 (1.5%)	1 (0.5%)	0
Ethnicity				
Not Hispanic or Latino	180 (90.5%)	179 (90.9%)	186 (93.0%)	175 (87.5%)
Hispanic or Latino	17 (8.5%)	14 (7.1%)	13 (6.5%)	24 (12.0%)
Not reported	2 (1.0%)	4 (2.0%)	1 (0.5%)	1 (0.5%)
Age (years)				
Mean (SD)	54.6 (4.9)	54.5 (4.9)	54.8 (5.0)	54.4 (4.5)

	OASIS 1		OASIS 2	
	Elinzanetant 120 mg N=199 (100%)	Placebo - Elinzanetant 120 mg N=197 (100%)	Elinzanetant 120 mg N=200 (100%)	Placebo - Elinzanetant 120 mg N=200 (100%)
Median	54.0	55.0	55.0	54.0
Min, Max	41, 65	40, 65	40, 65	42, 64
Body Mass Index (kg/m²)				
Mean (SD)	27.78 (4.84)	27.65 (4.52)	27.78 (4.81)	27.95 (4.74)
Median	27.40	27.20	27.00	27.35
Min, Max	18.3, 39.0	18.3, 37.7	17.8, 38.5	18.2, 38.0
Smoking History				
Never	150 (75.4%)	115 (58.4%)	117 (58.5%)	135 (67.5%)
Former	26 (13.1%)	33 (16.8%)	41 (20.5%)	33 (16.5%)
Current	23 (11.6%)	49 (24.9%)	42 (21.0%)	32 (16.0%)

Placebo - Elinzanetant 120 mg = Placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks.
BMI = Body mass index, SD = Standard Deviation

Postmenopausal status

Table 17 Number and percentage of participants by subgroup according to post-menopausal status

Postmenopausal, defined as…	OASIS 1 (21651) N = 396	OASIS 2 (21652) N = 400
Number of subjects with bilateral oophorectomy ≥ 6 weeks prior screening visit	40 (10.1%)	24 (6.0%)
Number of subjects with hysterectomy ≥ 6 months before screening visit & FSH > 40 IU/L and estradiol concentration of <30 pg/mL	107 (27.0%)	100 (25.0%)
Number of subjects with 6 to 12 months of amenorrhea prior screening visit & FSH > 40 IU/L and estradiol concentration of <30 pg/mL	15 (3.8%)	12 (3.0%)
Number of subjects with amenorrhea ≥ 12 months prior screening visit	231 (58.3%)	263 (65.8%)
Other	3 (0.8%)	1 (0.3%)

Medical history

The reported medical and surgical history in OASIS 1 and OASIS 2 studies were similar, and the treatment arms were well balanced across the studies. Most common medical history findings in OASIS 1 and 2 were hypertension, hysterectomy and uterine leiomyoma in both treatment arms. Approximately a third of the participants were hysterectomized[1] and more than 20% had undergone oophorectomy[2]. Prior hormone therapy use was reported by more than 30% (32.8% in the elinzanetant group and 30% in the placebo group, combined for OASIS 1 and 2).

[1] Based on medical history, PTs considered for hysterectomy were hysterectomy, hysterosalpingectomy, hysterosalpingo-oophorectomy and radical hysterectomy.
[2] Based on medical history, PTs considered for oophorectomy were hysterectosalpingo-oophorectomy, oophorectomy, oophorectomy bilateral, salpingo-oophorectomy bilateral, salpingo-oophorectomy unilateral.

Table 18 OASIS 1 and 2 - Medical history: Most frequent PTs in each treatment arm - number (%) of women

	OASIS 1		OASIS 2	
Preferred term MedDRA version 26.0	**Elinzanetant 120 mg N=199 (100%)**	**Placebo - Elinzanetant 120 mg N=194 (100%)**	**Elinzanetant 120 mg N=201 (100%)**	**Placebo - Elinzanetant 120 mg N=199 (100%)**
Number (%) of women with at least one medical history finding	**189 (95.0%)**	**186 (95.9%)**	**189 (94.0%)**	**189 (95.0%)**
Hysterectomy	67 (33.7%)	59 (30.4%)	65 (32.3%)	62 (31.2%)
Hypertension	51 (25.6%)	51 (26.3%)	64 (31.8%)	59 (29.6%)
Uterine leiomyoma	47 (23.6%)	48 (24.7%)	41 (20.4%)	50 (25.1%)
Obesity	27 (13.6%)	20 (10.3%)	35 (17.4%)	38 (19.1%)
Seasonal allergy	28 (14.1%)	29 (14.9%)	25 (12.4%)	22 (11.1%)
Osteoarthritis	22 (11.1%)	15 (7.7%)		
Cholecystectomy	21 (10.6%)	12 (6.2%)		
Heavy Menstrual bleeding	20 (10.1%)	11 (5.7%)		
Hypothyroidism	19 (9.5%)	21 (10.8%)	24 (11.9%)	22 (11.1%)
Migraine	16 (8.0%)	21 (10.8%)	22 (10.9%)	17 (8.5%)
Caesarean section	20 (10.1%)	24 (12.4%)	19 (9.5%)	20 (10.1%)
Hysterectosalpingo-oophorectomy	16 (8.0%)	18 (9.3%)		
Gastrooesophageal reflux disease			18 (9.0%)	19 (9.5%)
Depression	21 (10.6%)	18 (9.3%)	18 (9.0%)	16 (8.0%)
Female sterilisation			18 (9.0%)	11 (5.5%)
Ovarian cyst			15 (7.5%)	17 (8.5%)
Drug Hypersensitivity	14 (7.0%)	28 (14.4%)		

Table 19 Reproductive and menstrual history (full analysis set)

	Elinzanetant 120mg N=399 (100%)	Placebo - Elinzanetant 120mg N=397 (100%)	Total N=796 (100%)
Duration of being amenorrheic (years)			
n	397	396	793
Mean (SD)	7.34 (6.45)	6.90 (6.21)	7.12 (6.33)
Median	6.00	5.00	5.00
Min, Max	0.0, 30.0	0.1, 32.0	0.0, 32.0
Hysterectomy[a]			
No	246 (61.7%)	241 (60.7%)	487 (61.2%)
Yes	153 (38.3%)	156 (39.3%)	309 (38.8%)
Oophorectomy[b]			
No	324 (81.2%)	308 (77.6%)	632 (79.4%)
Yes	75 (18.8%)	89 (22.4%)	164 (20.6%)

Placebo - Elinzanetant 120mg = Placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks.
a Based on Medical History. PTs considered for hysterectomy are: Hysterectomy, Hysterosalpingectomy, Hysterosalpingo-oophorectomy and Radical hysterectomy
b Based on Medical History. PTs considered for oophorectomy are: Hysterosalpingo-oophorectomy, Oophorectomy, Oophorectomy bilateral, Salpingo-oophorectomy, Salpingo-oophorectomy bilateral, Salpingo-oophorectomy unilateral
SD = Standard Deviation.
Bayer: /var/swan/root/bhc/3427080/ia/stat/main001/prod/analysis/pgms/t_adrp_ise_rpmens_hist.sas 08APR2024 20:48
End of table

➢ Numbers analysed

Efficacy analyses are based on the FAS and participants were analyzed according to the randomized intervention. Safety analyses are based on the SAF and participants were analyzed according to the intervention they received. Based on the drug accountability and source documents at the study site, 1 participant who was assigned to the placebo- arm took elinzanetant for the first 16 days at the start of the treatment. Therefore, she is assigned to the elinzanetant arm in the SAF.

Table 20 Number of participants in the analysis sets of OASIS 1 and 2

Analysis set	Elinzanetant 120 mg arm	Placebo-elinzanetant 120 mg arm
OASIS 1		
FAS	199	197
SAF	199	194
OASIS 2		
FAS	200	200
SAF	201	199

➢ Outcomes and estimation

Primary endpoints

In both studies at Weeks 4 and 12, the decrease in mean daily moderate to severe HF frequency was statistically significantly greater for elinzanetant compared to the decrease for placebo.

A clinically meaningful difference (defined by the FDA, adopted by the Applicant, as a reduction in of at least 2 moderate to severe HFs above that demonstrated with placebo per day (14 per week)), in frequency between elinzanetant and placebo was identified in both studies at Week 4 and Week 12. In OASIS 1, the difference between elinzanetant 120 mg and placebo in the change from baseline of the frequency of moderate to severe HFs (LS-Means [95% CI]), was -3.29 [-4.47, -2.10] at Week 4 and -3.22 [-4.81, -1.63] at Week 12. In OASIS 2, the difference between elinzanetant 120 mg and placebo in the change from baseline of the frequency of moderate to severe HFs (LS-Means [95% CI]), was -3.04 [-4.40, -1.68] at Week 4 and -3.24 [-4.60, -1.88] at Week 12.

In summary, in two independent, pivotal Phase 3 efficacy studies, OASIS 1 and OASIS 2, superiority of elinzanetant compared to placebo was demonstrated for the primary endpoints mean change in frequency of moderate to severe HFs from baseline to Week 4 and Week 12.

Table 21 OASIS 1 and 2 - Mean change in frequency of moderate to severe HFs from baseline to Weeks 1[a], 4 and 12 (FAS)

	OASIS 1		OASIS 2	
	Elinzanetant 120 mg (N= 199)	**Placebo (N= 197)**	**Elinzanetant 120 mg (N= 200)**	**Placebo (N= 200)**
Value at Baseline				
n	199	197	199	200
Mean (SD)	13.38 (6.57)	14.26 (13.94)	14.66 (11.08)	16.16 (11.15)
Week 1[a]				
n	196	189	198	197
LS-Means (SE)	-5.13 (0.33)	-2.68 (0.33)	-4.93 (0.39)	-3.28 (0.39)
95% CI for LS-Means	-5.77, -4.49	-3.33, -2.03	-5.69, -4.17	-4.03, -2.52
	Elinzanetant vs placebo		**Elinzanetant vs placebo**	
Difference in LS-Means (SE)	-2.45 (0.46)		-1.66 (0.55)	
95% CI for Difference in LS-Means	-3.36, -1.55		-2.73, -0.58	
p-value (one-sided)	<.0001		0.0013	

	OASIS 1		OASIS 2	
	Elinzanetant 120 mg (N= 199)	**Placebo (N= 197)**	**Elinzanetant 120 mg (N= 200)**	**Placebo (N= 200)**
Week 4				
n	195	188	189	195
LS-Means (SE)	-7.60 (0.43)	-4.31 (0.43)	-8.58 (0.49)	-5.54 (0.49)
95% CI for LS-Means	-8.43, -6.76	-5.16, -3.46	-9.54, -7.62	-6.49, -4.58
	Elinzanetant vs placebo		**Elinzanetant vs placebo**	
Difference in LS-Means (SE)	-3.29 (0.61)		-3.04 (0.69)	
95% CI for Difference in LS-Means	-4.47, -2.10		-4.40, -1.68	
p-value (one-sided)	<.0001		<.0001	
Week 12				
n	179	174	180	184
LS-Means (SE)	-8.66 (0.58)	-5.44 (0.59)	-9.72 (0.50)	-6.48 (0.49)
95% CI for LS-Means	-9.79, -7.53	-6.60, -4.28	-10.70, -8.75	-7.45, -5.52
	Elinzanetant vs placebo		**Elinzanetant vs placebo**	
Difference in LS-Means (SE)	-3.22 (0.81)		-3.24 (0.69)	
95% CI for Difference in LS-Means	-4.81, -1.63		-4.60, -1.88	
p-value (one-sided)	<.0001		<.0001	

a Key secondary endpoint.
n = number of women with observed value for this timepoint and considered in the analysis model.
In case data was not available for more than 2 days within a week, the value for that particular week was set to missing. Multiple imputation was used to impute missing values.
LS-Means = least squares means, SE = standard error, MMRM = mixed model repeated measures, CI = confidence interval

Sensitivity analyses

The assessment of the assumptions for the MMRM modeling via qq-plot (quantile-quantile plot) and scatterplot of residuals against predicted values showed no strong violation in either study. In addition, the results of the non-parametric analysis confirmed the main analysis results for Weeks 4 and 12 for both studies. Tipping point analysis by applying an unfavorable additive shift up to a value of 10 to missing data in the elinzanetant 120 mg arm showed the robustness of the results with respect to missing/imputed data: A tipping point of the main analysis results for Week 4 and Week 12 was not attained in either study.

Supplementary analyses

The two supplementary estimands with alternative strategies for handling observed or missing values that occur in presence of ICEs, demonstrated similar results to the main estimand in both studies.

Key secondary endpoints:

1. **Severity of moderate to severe HFs – change from baseline to Weeks 4 (by HFDD)**
2. **Severity of moderate to severe HFs – change from baseline to Weeks 12 (by HFDD)**

In the HFDD, the severity of HFs was categorized as: 1 = mild, 2 = moderate, and 3 = severe; therefore, a decrease in severity indicates an improvement.

In both studies, the decrease in severity of moderate to severe HFs on elinzanetant from baseline to Week 4 and Week 12 was statistically significantly greater compared to the decrease on placebo.

A decrease in the HF severity of at least -0.53 at Week 4 and -0.62 at Week 12 has been identified as a within-group meaningful change based on triangulation of results from anchor-based methods using data from OASIS 2. In this regard, in OASIS 1, elinzanetant 120 mg but not placebo resulted in a clinically meaningful improvement in HF severity, as measured by the HFDD from baseline to Week 4 and to Week 12.

In OASIS 2, both elinzanetant and placebo treatment resulted in a clinically meaningful improvement in HF severity from baseline to Week 4 and to Week 12.

Table 22 OASIS 1 and 2 - Mean change in severity of moderate to severe HFs from baseline to Weeks 4 and 12 (FAS)

	OASIS 1		OASIS 2	
	Elinzanetant 120 mg (N= 199)	**Placebo (N= 197)**	**Elinzanetant 120 mg (N= 200)**	**Placebo (N= 200)**
Value at Baseline				
N	199	197	199	200
Mean (SD)	2.56 (0.22)	2.53 (0.23)	2.53 (0.24)	2.54 (0.24)
Week 4				
N	195	188	189	195
LS-Means (SE)	-0.73 (0.04)	-0.40 (0.04)	-0.75 (0.04)	-0.53 (0.04)
95% CI for LS-Means	-0.81, -0.66	-0.47, -0.32	-0.84, -0.66	-0.62, -0.45
	Elinzanetant vs placebo		**Elinzanetant vs placebo**	
Difference in LS-Means (SE)	-0.33 (0.06)		-0.22 (0.06)	
95% CI for Difference in LS-Means	-0.44, -0.23		-0.34, -0.09	
p-value (one-sided)	<.0001		0.0003	
Week 12				
N	179	174	180	184
LS-Means (SE)	-0.92 (0.05)	-0.52 (0.05)	-0.91 (0.06)	-0.62 (0.05)
95% CI for LS-Means	-1.02, -0.82	-0.63, -0.42	-1.01, -0.80	-0.72, -0.51
	Elinzanetant vs placebo		**Elinzanetant vs placebo**	
Difference in LS-Means (SE)	-0.40 (0.07)		-0.29 (0.08)	
95% CI for Difference in LS-Means	-0.54, -0.25		-0.44, -0.14	
p-value (one-sided)	<.0001		<.0001	

n = number of women with observed value for this timepoint and considered in the analysis model.
In case data was not available for more than 2 days within a week, the value for that particular week was set to missing
Multiple imputation is used to impute missing values.
LS-Means = least squares means, SE = standard error, MMRM = mixed model repeated measures, CI = confidence interval

3. Sleep disturbances - change from baseline to week 12 (by PROMIS SD SF 8b)

A decrease in the PROMIS SD SF 8b scores (i.e., single item, total raw, and total T-score) indicates an improvement in sleep disturbances.

At baseline, mean PROMIS SD SF 8b total T-scores were similar across both treatments (T-score ~60). In both studies, at Week 12, the mean change in the PROMIS SD SF 8b total T-score from baseline showed statistically significant improvement in sleep disturbances from baseline in favour of elinzanetant compared to placebo.

A decrease in the mean PROMIS SD SF 8b total T-score of at least -7.19 at Week 12 has been identified as a within-group meaningful change based on triangulation of results from anchor-based methods using data from OASIS 2. In this regard, in both studies elinzanetant but not placebo resulted in a clinically meaningful improvement in sleep disturbances, as measured by the PROMIS SD SF 8b total T-score from baseline to Week 12 (see table below).

Table 23 OASIS 1 and 2 - PROMIS SD SF 8b total T-score change from baseline to Week 12 (FAS)

	OASIS 1		OASIS 2	
	Elinzanetant 120 mg (N= 199)	**Placebo (N= 197)**	**Elinzanetant 120 mg (N= 200)**	**Placebo (N= 200)**
Week 12				
N	181	173	179	182
LS-Means (SE)	-10.41 (0.60)	-4.83 (0.62)	-10.28 (0.54)	-5.97 (0.53)
95% CI for LS-Means	-11.58, -9.24	-6.05, -3.62	-11.35, -9.22	-7.00, -4.94
	Elinzanetant vs placebo		**Elinzanetant vs placebo**	
Difference in LS-Means (SE)	-5.58 (0.82)		-4.32 (0.74)	
95% CI for Difference in LS-Means	-7.18, -3.98		-5.77, -2.86	
p-value (one-sided)	<.0001		<.0001	

n = number of women with observed value for this timepoint and considered in the analysis model.
Multiple imputation is used to impute missing values.
LS-Means = least squares means, SE = standard error, MMRM = mixed model repeated measures, CI = confidence interval

4. Frequency of moderate to severe HFs – change from baseline to Week 1 (assessed by HFDD)

At Week 1, in both OASIS 1 and 2 studies, on average the mean daily frequency of moderate to severe HFs was lower than at baseline on both treatment arms, and lower on elinzanetant compared to placebo. The decrease in frequency of moderate to severe HFs on elinzanetant from baseline to Week 1 was statistically significantly greater compared to the decrease on placebo in both OASIS 1 and 2 studies indicating an early onset of effect. The difference in LS-Means [95% CI] was -2.45 [-3.36, -1.55]) for OASIS 1 and -1.66 [-2.73, -0.58]) for OASIS 2.

5. Menopause-related quality of life – change from baseline to week 12 (assessed by MENQOL)

A decrease in MENQOL total score indicates an improvement in menopause-related quality of life.

In both studies, the mean MENQOL total scores were similar across both treatments at baseline (MENQOL ~4.5). At Week 12, the change from baseline (LS-Means [SE]) in the MENQOL total score was greater on elinzanetant than on placebo, and the decrease was statistically significantly greater on elinzanetant compared to the decrease on placebo.

A decrease in the mean MENQOL total score of at least -0.87 at Week 12 has been identified as a within-group meaningful change based on triangulation of results from anchor-based methods using data from OASIS 2. In this regard, both elinzanetant and placebo resulted in a clinically meaningful improvement in menopause-related quality of life from baseline to Week 12 in both OASIS 1 and 2 studies (see table below).

Table 24 OASIS 1 and 2 - MENQOL total score change from baseline at Week 12 (FAS)

	OASIS 1		OASIS 2	
	Elinzanetant 120 mg (N= 199)	**Placebo (N= 197)**	**Elinzanetant 120 mg (N= 200)**	**Placebo (N= 200)**
Week 12				
N	178	173	175	180
LS-Means (SE)	-1.36 (0.08)	-0.94 (0.08)	-1.29 (0.09)	-1.00 (0.08)
95% CI for LS-Means	-1.52, -1.20	-1.10, -0.78	-1.46, -1.12	-1.16, -0.83
	Elinzanetant vs placebo		**Elinzanetant vs placebo**	
Difference in LS-Means (SE)	-0.42 (0.11)		-0.30 (0.12)	
95% CI for Difference in LS-Means	-0.64, -0.20		-0.53, -0.07	
p-value (one-sided)	<.0001		0.0059	

n = number of women with observed value for this timepoint and considered in the analysis model.
Multiple imputation is used to impute missing values.
LS-Means = least squares means, SE = standard error, MMRM = mixed model repeated measures, CI = confidence interval

Pre-defined and ad-hoc important subgroup analyses

Subgroup analyses by region, race, ethnicity, BMI, and smoking status on frequency and severity of HFs, PROMIS SD SF 8b total T-score, and MENQOL total score were performed. For all endpoints and timepoints, consistent treatment effects were observed across various subgroups and no subgroup with an effect outside the expected range for variability was detected.

Concerning OASIS 1, a numerically larger mean (SD) decrease in the daily frequency of moderate to severe HFs from baseline to Week 12 was observed in elinzanetant treated participants outside the US (i.e., "rest of the world"; -9.13 [6.67] per day), in participants who had never smoked (-9.04 [6.92] per day), and in participants with BMI ≥30 kg/m^2 (-9.00 [7.13] per day) compared to the overall change from baseline to Week 12 (elinzanetant: -8.74 [6.70]).

In both OASIS 1 and 2 studies, numerically higher baseline values for the frequency of moderate to severe HFs for both elinzanetant and placebo groups were observed in Black and African American women (N=73 for elinzanetant group and N=63 for placebo group). For Black and African American women in the elinzanetant group slightly higher changes from baseline compared to the overall results were observed.

In the Hispanic and Latino subgroup in OASIS 1 and 2 studies, the placebo group had numerically higher baseline values for the frequency of moderate to severe HFs, and the Hispanic and Latino subgroup showed a slightly lower response compared to the overall results. As this subgroup is small (N=30 for elinzanetant group and N=38 for placebo group), no conclusions can be drawn from these results.

For other endpoints, similar baseline values were observed across the two treatment arms.

Other secondary endpoints

Frequency of moderate to severe HFs – change from baseline over time

In both studies, the numerical change in the frequency of moderate to severe HFs was more pronounced on elinzanetant during the first 12 weeks of treatment compared to placebo. After Week 12, the women who had received elinzanetant since the beginning showed a continued effect with a trend toward further improvement until Week 26.

Those women who had received placebo until Week 12 showed more pronounced numerical improvement after the treatment switch to elinzanetant, and a trend toward further improvement until Week 26 based on descriptive statistics. During the 4-week follow-up period, the daily frequency of moderate to severe HFs increased numerically but stayed at a lower level compared to baseline in both treatment arms (see the table below).

Table 25 OASIS 1 and 2 - Mean change in frequency of moderate to severe HFs from baseline to Week 26 (FAS)

	Elinzanetant 120 mg			Placebo		
OASIS 1	**(N=199)**			**(N=197)**		
Value at visit	**n**	**Mean (SD)**	**Median**	**n**	**Mean (SD)**	**Median**
Baseline	199	13.38 (6.57)	11.71	197	14.26 (13.94)	10.85
Week 26	114	3.21 (4.18)	1.36	110	4.94 (20.17)	1.79
Change from baseline						
Week 26	114	-10.11 (6.41)	-8.45	110	-10.10 (8.75)	-8.36
OASIS 2	**(N=200)**			**(N=200)**		
Value at visit	**n**	**Mean (SD)**	**Median**	**n**	**Mean (SD)**	**Median**
Baseline	199	14.66 (11.08)	11.43	200	16.16 (11.15)	12.46
Week 26	108	3.31 (4.91)	1.43	120	4.78 (7.86)	2.07
Change from baseline						
Week 26	108	-11.76 (11.38)	-9.48	120	-12.76 (12.28)	-9.14

HFs = hot flashes, SD = standard deviation

Depressive symptoms – BDI – II total score

Lower BDI-II total scores indicate less severe depressive symptoms.

Descriptive analysis of the BDI-II total score showed numerically comparable mean BDI-II total scores across both treatment arms at baseline, 87.1% and 89.1% of the participants on elinzanetant and 90.4% and 87.5% on placebo had no depression or suffered from minimal depression in OASIS 1 and OASIS 2, respectively. Very few participants had moderate or severe depression. In OASIS 1, 8 and 3 participants on elinzanetant, and 1 and 3 participants on placebo, respectively. And in OASIS 2, both 3 on elinzanetant and 9 and 3 on placebo.

At Week 12 and Week 26, the mean BDI-II total score remained numerically stable from baseline on both treatments, based on descriptive statistics.

Exploratory endpoints

Proportion of participants with at least 50% reduction in HF at week 4 and 12 and time to treatment response

The proportion of participants having at least a reduction of 50% in mean daily frequency of moderate to severe HF in OASIS 1 and 2, per treatment group can be found in Table 26

Table 26 Proportion of subjects with at least a reduction of 50% in mean daily frequency of moderate to severe hot flashes by treatment group (full analysis set)

Time		OASIS 1		OASIS 2	
		Elinzanetant (N=199)	Placebo - Elinzanetant (N=197)	Elinzanetant (N=200)	Placebo - Elinzanetant (N=200)
Week 4	N	191 (100.0%)	185 (100.0%)	185 (100.0%)	192 (100.0%)
	Yes	120 (62.8%)	54 (29.2%)	115 (62.2%)	62 (32.3%)
	No	71 (37.2%)	131 (70.8%)	70 (37.8%)	130 (67.7%)
Week 12	N	175 (100.0%)	169 (100.0%)	174 (100.0%)	180 (100.0%)
	Yes	125 (71.4%)	71 (42.0%)	130 (74.7%)	87 (48.3%)
	No	50 (28.6%)	98 (58.0%)	44 (25.3%)	93 (51.7%)
Week 26	N	114 (100.0%)	110 (100.0%)	108 (100.0%)	120 (100.0%)
	Yes	93 (81.6%)	93 (84.5%)	88 (81.5%)	104 (86.7%)
	No	21 (18.4%)	17 (15.5%)	20 (18.5%)	16 (13.3%)

The median time to treatment response in the first 12 weeks, in participants with the event (i.e. treatment response) in OASIS 1 was 2 weeks in the elinzanetant group and 8 weeks in the placebo group. In OASIS 2 this was respectively 3 and 8 weeks.

2.6.5.2.2. Treatment of moderate to severe vasomotor symptoms (VMS) caused by AET: OASIS 4

- ***Methods***

OASIS 4 is a pivotal Phase 3 study to assess the efficacy and safety of elinzanetant for the treatment of moderate to severe VMS caused by AET. A multicentre, multi-country, double-blind, randomized, parallel-group, placebo-controlled, interventional study design was used. Women of 18 to 70 years of age with, or at high risk for developing, hormone-receptor positive breast cancer were included. The women participating in the study were required to have a background treatment of

- tamoxifen with or without the use of gonadotropin-releasing hormone (GnRH) analogues, or
- aromatase inhibitors with or without the use of GnRH analogues

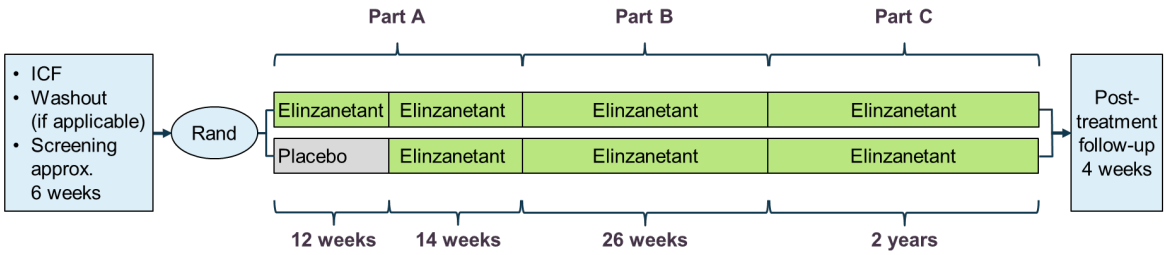
for at least 6 weeks prior to baseline and with moderate to severe HFs caused by AET and seeking treatment for this condition. The study is conducted in Austria, Belgium, Canada, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Kazakhstan, Poland, Portugal, Romania, Spain and United Kingdom

Part A: Women were treated with elinzanetant for 26 weeks, or with placebo for 12 weeks followed by elinzanetant for 14 weeks.

Part B: all participants will be treated with elinzanetant for an additional 26 weeks.

Part C: OASIS 4 was subsequently extended for additional 2 years (Part C) to provide study participants the voluntary option to continue the treatment with elinzanetant and the product be available for regular prescription. During Part C only AEs will be collected.

Figure 12 OASIS 4 – study schema



ICF = informed consent form

Approximately 810 participants were to be screened to achieve 405 participants randomly assigned to study intervention in a 2:1 ratio, resulting in estimated 365 participants evaluable for the primary efficacy analysis (243 and 122 evaluable participants in respectively the elinzanetant and placebo arm) after 12 weeks. The randomization was to be stratified by women with breast cancer or high-risk for developing breast cancer and by type of treatment for the pre-existing condition at baseline (participants on tamoxifen and participants on aromatase inhibitors).

- ***Study Participants***

The **main criteria for inclusion** were:

- Females aged 18 to 70 years, inclusive, at signing of informed consent.
- Women experiencing VMS caused by adjuvant endocrine therapy that they are expected to use for the duration of the study

  a) Tamoxifen with or without the use of GnRH analogues or

  b) Aromatase inhibitors with or without the use of GnRH analogues

  The participant should be on stable adjuvant endocrine therapy at least 6 weeks prior to baseline.

  Switching or dose modification of adjuvant endocrine therapy is only allowed after Visit T6.
- Women must have a personal history of hormone-receptor positive breast cancer or a high risk for developing breast cancer
- Negative urine pregnancy test at Screening and at Baseline if participant has not been confirmed post-menopausal or WONCBP.
- Normal or clinically insignificant cervical cytology
- BMI between 18 and 38 kg/m^2 at screening.
- Participant has completed HFDD for at least 11 days during the two weeks preceding baseline visit, and participant has recorded at least 35 moderate to severe HF (including night-time HF) over the last 7 days that the HFDD was completed (assessed at the Baseline Visit).
- Contraceptive use by women (except for post-menopausal women or WONCBP) should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

The **main exclusion criteria** were:

- Initial diagnosis of metastatic hormone-receptor positive breast cancer (stage IV) or recurrence under adjuvant endocrine therapy of hormone-receptor positive breast cancer.
- Current or history (except complete remission for 5 years or more prior to signing informed consent) of any malignancy, except for hormone-receptor positive breast cancer (Stage 0-III), basal and squamous cell skin tumours.
- 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).
- Planned surgery, chemotherapy, radiotherapy, or immunotherapy within the duration of the study (reconstructive breast surgery allowed after week 12).
- Current pregnancy or less than 3 months since delivery, abortion or stop of lactation prior to signing informed consent.
- History of arrhythmias, heart block and QT prolongation either determined through clinical history or on ECG evaluation.
- Clinically significant abnormal laboratory test result(s).
- Any active ongoing condition that could cause difficulty in interpreting VMS such as: infection that could cause pyrexia, pheochromocytoma, carcinoid syndrome.
- Untreated hyperthyroidism or hypothyroidism.
- Mammogram with clinically relevant malignant or suspicious findings that will require surgery, radiotherapy or chemotherapy as per local guideline.
- Any unexplained vaginal bleeding.
- Renal impairment greater than moderate (i.e. estimated glomerular filtration rate < 30 mL/min/1.73m^2) at screening.
- Abnormal liver parameters (AST, ALT or AP > 2xULN, or TBL or INR>ULN), diagnosis of hepatitis B or C infection.
- Disordered proliferative endometrium, endometrial hyperplasia, polyp, or endometrial cancer diagnosed based on endometrial biopsy during screening.
- Current arterial or venous vascular event (e.g. MI, TIA, stroke, DVT), i.e. within the last 6 months prior to signing informed consent.
- Any other history, condition, therapy, or intercurrent illness which could in the opinion of the investigator affect compliance with study requirements.
- Women with an ovarian cyst/cyst that need further diagnostic procedures to exclude the possibility of malignancy during screening.

- ***Treatments***

Participants will receive either 120 mg (two soft gel capsules of 60 mg) of elinzanetant, or matching placebo orally once daily. Study treatment in both treatment arms was to be taken once daily before going to bed, with or without food.

- ***Objectives***

Primary objective

- To evaluate the efficacy of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer

Secondary objectives

- To evaluate the onset of efficacy of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer
- To evaluate the efficacy of elinzanetant in women with, or at high risk for developing hormone-receptor positive breast cancer on:
  - sleep quality
  - menopause related quality of life
- To evaluate the safety of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer

Other objectives

- To evaluate variability in exposure in relation to the efficacy and safety for elinzanetant
- To further investigate elinzanetant (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to VMS caused by adjuvant endocrine therapy and associated health problems

- ***Outcomes/endpoints***

Primary endpoints

- Mean change in frequency of moderate to severe HF from baseline to Week 4 (by HFDD)
- Mean change in frequency of moderate to severe HF from baseline to Week 12 (by HFDD)

Key secondary endpoints

- Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12
- Mean change in MENQOL total score from baseline to Week 12

Secondary endpoints:

- Mean change in frequency of moderate to severe HF from baseline to Week 1 (by HFDD)
- Mean change in frequency of moderate to severe HF from baseline over time (by HFDD)
- Mean change in severity of moderate to severe HF from baseline to Week 4 (by HFDD)
- Mean change in severity of moderate to severe HF from baseline to Week 12 (by HFDD)

Exploratory efficacy endpoints:

- Proportion of participants with at least 50% reduction in frequency of moderate to severe HF at Week 4
- Proportion of participants with at least 50% reduction in frequency of moderate to severe HF at Week 12
- Time to treatment response
- Mean change in frequency of mild, moderate, and severe HF from baseline over time (by HFDD)
- Absolute values and changes from baseline in the PROMIS SD SF 8b total T- and total raw scores over time
- Absolute values and changes from baseline in MENQOL total, domain and single item scores over time
- Absolute values and changes from baseline in the ISI total score over time
- Absolute values and changes from baseline in EQ-5D-5L single dimensions and health state VAS score over time
- Absolute values and changes from baseline in SF-36 v2.0 Acute domain, physical component summary (PCS) and mental component summary (MCS) scores over time
- Absolute values and changes from baseline in the BDI-II total score over time
- Mean change in frequency of nighttime awakening from baseline over time (assessed by HFDD)
- Mean change in proportion of days with participants rating of "quite a bit" or "very much" sleep disturbances experienced due to HF from baseline over time (by HFDD)

- ***Estimands***

Estimands for the primary objective

The main estimand assessed the effect of assigned treatment, i.e., elinzanetant 120 mg compared to placebo including all treatment interruptions, premature discontinuation of randomized treatment, and intake of prohibited concomitant medications having impact on efficacy and interruptions/discontinuations in intake of AET (treatment policy strategy) in women aged 18-70 years with moderate to severe VMS caused by AET (further defined by inclusion and exclusion criteria) on change from baseline to Week 4 and Week 12 as defined for the primary endpoints. The mean difference between the treatment arms was used as summary measure.

Table 26 OASIS 4 - Estimands for primary objective

Study Population	Women aged 18-70 with VMS caused by adjuvant endocrine therapy, as described by the inclusion/exclusion criteria detailed in the protocol.	
Treatment condition(s)	120 mg elinzanetant, placebo	
Endpoint (variable)	Efficacy was assessed based on 2 primary endpoints: • Change in frequency of moderate to severe HFs from baseline to Week 4 • Change in frequency of moderate to severe HFs from baseline to Week 12	
Population level summary	• Mean change in frequency of moderate to severe HFs from baseline to Week 4. • Mean change in frequency of moderate to severe HFs from baseline to Week 12. Treatment comparison was based on differences in treatment arm means for each endpoint.	
Intercurrent events (ICEs) and strategy to handle them – *all treatment policy*		
ICE [a]	**Reason for ICE**	**Data handling method**
Temporary Treatment interruption [b]	AEs (treatment related/unrelated) COVID-19 and administrative reasons	Utilise the collected data after ICE. Utilise the collected data after ICE.
Permanent discontinuation of randomized treatment	AEs (treatment related/unrelated) or lack of efficacy • For participants who remained untreated/on background therapy. • For participants who initiate alternative VMS treatment Other treatment-unrelated reasons, including COVID-19	 Utilise the collected data after ICE. Utilise the collected data after ICE. Utilise the collected data after ICE.
Intake of prohibited concomitant medication having impact on efficacy	All reasons	Utilise the collected data after ICE.
Interruption/ discontinuation in intake of adjuvant endocrine therapy [c]	All reasons	Utilise the collected data after ICE.

AE = Adverse event, COVID-19 = Coronavirus disease of 2019, ICE = Intercurrent event, VMS = Vasomotor symptoms

a) ICEs will be reviewed at the Blinded Review Meeting prior to the study unblinding

b) Definition of temporary treatment interruption:
Week 1 = Treatment taken on <5/7 days during week 1.
Week 4= Treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either Week 3 or 4.
Week 8 = Treatment taken <80% during weeks 1-8 OR treatment taken on <5/7 days during either week 7 or 8.
Week 12= Treatment taken <80% during weeks 1-12 OR treatment taken on <5/7 days during either Week 11 or 12.

c) Definition of interruption/discontinuation in intake of adjuvant endocrine therapy:
For participants using tamoxifen: reduction of at least 50% of planned daily dosage taken during weeks 3 and 4 OR weeks 11 and 12 compared to baseline.
For participants using aromatase inhibitor: reduction of at least 30% of planned daily dosage taken during weeks 3 and 4 OR weeks 11 and 12 compared to baseline.

Estimands for the secondary objective

The key secondary endpoints were handled using similar attributes than primary endpoint except for the variables and population summary that are:

Variable:

- Change in PROMIS SD SF 8b total T-score from baseline to Week 12
- Change in MENQOL total score from baseline to Week 12

Population level summary:

- Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12
- Mean change in MENQOL total score from baseline to Week 12.

Table 27 Estimands for secondary objective of OASIS 4

Study Population	Women aged 18-70 with VMS caused by adjuvant endocrine therapy, as described by the inclusion/exclusion criteria detailed in the protocol.	
Treatment condition(s)	120 mg elinzanetant, Placebo	
Endpoint (variable)	Efficacy was further assessed based on 2 key secondary endpoints: • Change in PROMIS SD SF 8b total T-score from baseline to Week 12. • Change in MENQOL total score from baseline to Week 12.	
Population level summary	• Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12. • Mean change in MENQOL total score from baseline to Week 12. Treatment comparison was based on differences in treatment arm means for each endpoint.	
Intercurrent events (ICEs) and strategy to handle them – *all treatment policy*		
ICE[a]	**Reason for ICE**	**Data handling method**
Temporary Treatment interruption[b]	AEs (treatment related/unrelated) COVID-19 and administrative reasons	Utilise the collected data after ICE. Utilise the collected data after ICE.
Permanent discontinuation of randomized treatment	AEs (treatment related/unrelated) or lack of efficacy • For participants who remained untreated/on background therapy. • For participants who initiate alternative VMS treatment Other treatment-unrelated reasons, including COVID-19	 Utilise the collected data after ICE. Utilise the collected data after ICE. Utilise the collected data after ICE.
Intake of prohibited concomitant medication having impact on efficacy	All reasons	Utilise the collected data after ICE.
Interruption/ discontinuation in intake of adjuvant endocrine therapy [c]	All reasons	Utilise the collected data after ICE.

AE = Adverse event, COVID-19 = Coronavirus disease of 2019, ICE = Intercurrent event, VMS = Vasomotor symptoms
a) ICEs will be reviewed at the Blinded Review Meeting prior to the study unblinding
b) Definition of temporary treatment interruption:
Week 1 = Treatment taken on <5/7 days during week 1.
Week 4= Treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either week 3 or 4.
Week 8 = Treatment taken <80% during weeks 1-8 OR treatment taken on <5/7 days during either week 7 or 8.
Week 12= Treatment taken <80% during weeks 1-12 OR treatment taken on <5/7 days during either week 11 or 12.
c) Definition of interruption/discontinuation in intake of adjuvant endocrine therapy:
For participants using tamoxifen: reduction of at least 50% of planned daily dosage taken during weeks 3 and 4 OR weeks 11 and 12 compared to baseline
For participants using aromatase inhibitor: reduction of at least 30% of planned daily dosage taken during weeks 3 and 4 OR weeks 11 and 12 compared to baseline

- ***Sample size***

A total of 405 subjects were planned to be randomized in 2:1 ratio to elinzanetant and placebo. The number of participants needed for this study was based on the total number of 1500 participants exposed to elinzanetant at least once and approximately 100 participants for 1 year needed for the safety evaluation per ICH E1 guideline (EMA 1995). Based on the number of participants that are available from previous phase 1 and phase 2 studies, and simultaneously ongoing phase 3 studies, the number of participants needed for the elinzanetant arm in this study was 270, also taking into account the assumed 10% drop-out rate during months 1-3 and 4-6 and overall drop-out rate of 30%.

A formal sample size justification was performed for the primary and key secondary efficacy endpoints using the one-sided two-Sample T-test (equal variance) assuming at least approximate normal distribution and taking into account the drop-out rate of 10% in the first 3 months. Assuming standard deviation of 4.29

based on data on placebo arm from SWITCH-1 study, with N=243 in elinzanetant arm and N=122 in placebo arm, the power for a treatment difference can be seen in the table below.

Table 28 Sample size justification

Endpoint	Standard deviation	Treatment difference Elinzanetant vs. placebo	Power %
Mean change in frequency of moderate to severe HF from baseline to Week 4	3.632	-1.00 -1.50 -2.00	69.67 % 96.01% >99.9 %
Mean change in frequency of moderate to severe HF from baseline to Week 12	4.29	-1.00 -1.50 -2.00	55.38 % 88.16 % 98.71 %
Mean change in PROMIS SD SF 8b total score from baseline to Week 12	1.00	-0.4	94.90 %
Mean change in MENQOL total score from baseline to Week 12	1.00	-0.4	94.90 %

nQuery Version 9.1.0.0 was used for sample size calculation.
HF = Hot Flash, MENQOL=Menopause Specific Quality of Life Scale, PROMIS SD SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b

- ***Randomisation and blinding (masking)***

Participants who met all eligibility criteria of OASIS 4 were randomized in a 2:1 ratio to elinzanetant or placebo. The randomization was stratified by women with a personal history of hormone-receptor positive breast cancer or women at high-risk for developing breast cancer (maximum of 10% of participants for high-risk developing breast cancer) and by type of treatment of pre-existing condition at baseline (at least 40% of participants on tamoxifen and at least 40% of participants on aromatase inhibitors in both population groups, i.e. breast cancer and high-risk for developing breast cancer).

- ***Statistical methods***

The following analysis sets were defined:

Table 29 OASIS 4 - Definition of the analysis sets

Analysis Set	Description
Enrolled	All participants who sign the informed consent form.
Full Analysis Set (FAS)	All randomized participants.
Safety Analysis Set (SAF)	All participants who receive at least one dose of study intervention.

The primary and the key secondary efficacy endpoints were performed using similar methods (sensitivity and supplementary analyses) described for OASIS 1 and OASIS 2.

Efficacy analyses were based on the FAS and participants were analyzed according to the randomized intervention. Safety analyses were performed on the SAF, and participants were analyzed according to the intervention received.

For the evaluation of the frequency of HF, the daily HF assessments were aggregated to a mean daily frequency from the data of a particular week. In case data was missing for more than 2 days within a week, the value for that particular week was set to missing.

For each of the primary efficacy endpoints, a mixed models repeated measures analysis of covariance (MMRM) was used with treatment arm, week and type of treatment of pre-existing condition at baseline (tamoxifen or aromatase inhibitor) as factors, with baseline measurement as a covariate, as well as an interaction of treatment by week and an interaction of baseline measurement by week. An unstructured covariance structure was used to model the within-patient errors. A treatment policy strategy was applied to handle all of the specified ICEs in the primary estimand. According to this strategy, all collected data was utilized in the analysis irrespective of occurrence of the ICEs.

Although all study participants were expected to be followed after ICEs, some missing data occurred. Missing values that occurred while participants continued on their randomized treatment and simply represented missed assessments were assumed missing at random (MAR). Such missing values could be intermittent or monotone and were imputed using a Monte Carlo Markov Chain (MCMC) multiple imputation (MI) method.

Due to study design, it would have been difficult to implement a modelling approach aligned with the treatment policy strategy with the imputation model estimated from participants who discontinued the randomized treatment and provided data. The number of such participants was expected to be too small for estimating a robust imputation model. Therefore, the washout method was used to impute missing data from participants who experience the ICEs (i.e. permanent treatment discontinuation) (*Wang et al. 2023*).

A placebo-effect is expected to be seen with the placebo group while the elinzanetant treatment effect would consist of both the placebo-effect and the effect of elinzanetant. The washout method effectively 'washes out' any pre-ICE treatment effect of elinzanetant in participants with an ICE randomized to elinzanetant, while modelling the mean placebo effect. Missing data in participants randomized to placebo was assumed to be MAR.

For participants randomized to elinzanetant, the imputation model had the dependent variable as the endpoint measurement at week 4 with the baseline measurement and the stratification factor, type of treatment of pre-existing condition, at baseline as independent variables. The multiple imputation model was estimated only based on placebo participants who remained in the study through week 4 and had available data at week 4. Similarly, week 1, 8 and 12 missing values after an ICE were imputed using the same model specification but with endpoint measurement at week 1, 8 or 12, respectively, as the dependent variable.

The key secondary endpoints were analysed analogous to the main analysis of the primary endpoints.

Exploratory subgroup analyses using descriptive statistics were provided for the primary and key secondary endpoints for the following subgroups: type of treatment for the pre-existing condition at baseline (tamoxifen, aromatase inhibitors), race, ethnicity, BMI (<18.5, 18.5 to <25, 25 to <30, >= 30 kg/m2) and smoking history (Never, Former, Current; derived from habitual cigarette smoking and any other tobacco/nicotine from the CRF).

Error probabilities, adjustment for multiplicity and interim analyses

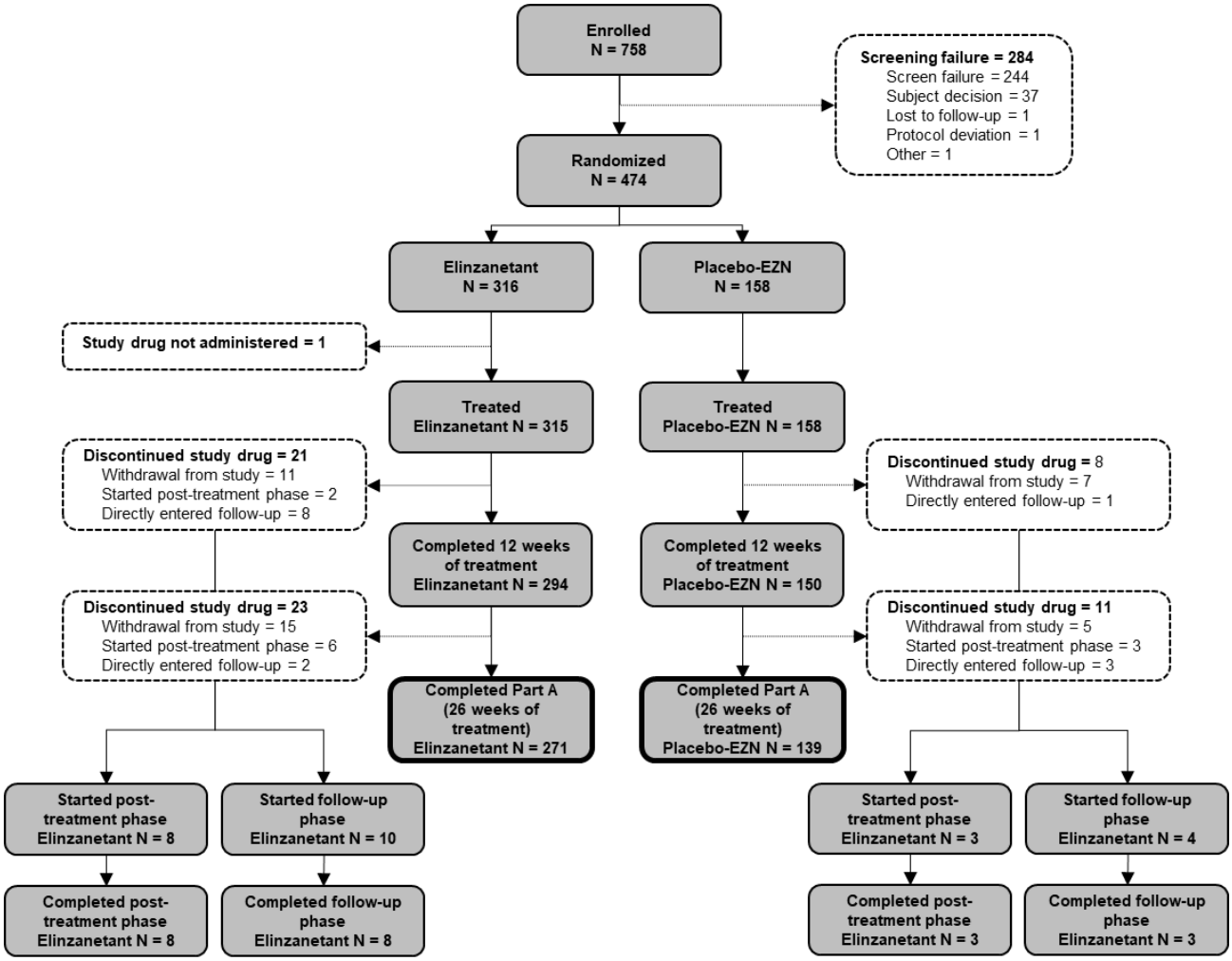
A hierarchical testing procedure was used. It follows a fixed sequence, and it stops as soon as any of tests cannot be rejected at an alpha level of 0.025 and all further tests after failing to reject one null hypothesis in the testing sequence will be considered exploratory. This fixed sequence procedure accounts for the multiplicity created by carrying out multiple tests. Moreover, all other endpoints were summarized descriptively and therefore no multiplicity adjustment was needed.

- ***Results***

  - **Participant flow**

Out of the 758 screened participants, 474 were randomized and 410 completed Part A of the study. Not meeting the eligibility criteria was the most common reason for screening failure (244 [32.2%]). 1 participant did not receive treatment and 63 participants (13.9% in elinzanetant and 12.0% in placebo- arm) did not complete 26 weeks of treatment. 22 of those 63 participants (5.1% in elinzanetant and 3.8% in placebo arm) discontinued the study treatment but remained in the study and completed follow-up or went to post-treatment phase. The most common reasons for not completing Part A of the study were AEs, with similar proportions of participants in both treatment arms (4.4% in the elinzanetant 120 mg arm and 3.8% in the placebo-elinzanetant 120 mg arm) and subject decision (3.5% in the elinzanetant 120 mg arm and 2.5% in the placebo-elinzanetant 120 mg arm).

Figure 13 OASIS 4 - participant flow



EZN = Elinzanetant. If a participant discontinued from study drug but agreed to stay in the study (i.e., in a post-treatment phase), the next scheduled in-person visit covered the assessments expected to be performed during the follow-up visit, and therefore no follow-up visit was needed after the end of treatment visit.

- **Recruitment**

Study period: 14 Oct 2022 to 30 Apr 2024

- **Conduct of the study**

All changes in the conduct of the study were implemented by two protocol amendments.

In total, 28.1% of all participants had important protocol deviations and the frequency was similar in both treatment arms. There were no major differences in the types of important protocol deviations between the treatment arms. The most common important deviations were inclusion/exclusion criteria not met but subject

entered the treatment (10.4% in the elinzanetant 120 mg arm vs. 10.1% in the placebo-elinzanetant 120 mg arm) and procedure deviations (8.9% vs. 11.4%).

Overall, the occurrence of ICEs was low, with 4 intercurrent events (ICEs) defined for the period of up to Week 12: permanent discontinuation of randomized treatment (most frequent, 7%), temporary treatment interruption, intake of prohibited concomitant medication having impact on efficacy, and interruption/discontinuation in intake of adjuvant endocrine therapy having impact on efficacy.

Median treatment compliance with investigational intervention was over 96% in both treatment arms, and similar in FAS and SAF. In the FAS, most participants (95.6% to 98.1%) achieved a high (≥80% to 120%) compliance in Weeks 1-12 and Weeks 13-26 (94.0% to 94.2%) based on the eCRF in both treatment arms. Compliance results were similar whether evaluated from the eCRF or the eDiary data.

- **Baseline data**

Demographics and baseline data

The treatment arms were generally well balanced regarding demographic and other baseline characteristics. There were no relevant differences in age, ethnicity, race, weight, height or BMI in FAS. The mean age was 51.0 years (SD 7.3 years, range from 28 to 70 years), and most of the women were in the age groups 50-59 years (49.6%) and 40-49 years (32.3%). Most women were White (88.2%), and 2.5% were Hispanic or Latino by ethnicity. Most of the women (65.2%) had never smoked.

Tamoxifen was used as an AET by 55.9% of all participants and aromatase inhibitors by 44.1% of all participants; the distribution was similar in the elinzanetant and the placebo-elinzanetant treatment arms, as well as the type of aromatase inhibitor and the concomitant use of GnRH analogues. Mean (SD) duration of AET was 1.92 (1.47) years and was similar between treatment arms. Of 474 women in OASIS 4, 321 (67.7%) were classified as Woman of non-childbearing potential (WONCBP) and 153 (32.3%) were classified as Woman of childbearing potential (WOCBP). Amenorrhea of at least one year was documented in 414 women (87.3% of total study population), including 308 women (65% of total study population) in the WONCBP group and 106 women (22.4% of total study population) in the WOCBP group. The documentation of amenorrhea did not distinguish between natural menopause and amenorrhea due to medical intervention, e.g. anti-hormonal treatment.

In women classified as WOCBP, the use of a highly effective contraceptive method was required as per study protocol. This included use of an intrauterine device without hormonal release (IUD), bilateral tubal occlusion, azoospermic partner, or sexual abstinence.

Table 30 OASIS 4 - Demographics (FAS)

	EZN 120 mg N=316 (100%)	Placebo - EZN 120 mg N=158 (100%)	Total N=474 (100%)
Population type			
Breast-cancer	315 (99.7%)	158 (100.0%)	473 (99.8%)
High-risk for developing breast-cancer	1 (0.3%)	0	1 (0.2%)
Type of treatment for the pre-existing condition			

	EZN 120 mg N=316 (100%)	Placebo - EZN 120 mg N=158 (100%)	Total N=474 (100%)
Tamoxifen	175 (55.4%)	90 (57.0%)	265 (55.9%)
Tamoxifen with GnRH	10 (3.2%)	4 (2.5%)	14 (3.0%)
Tamoxifen without GnRH	165 (52.2%)	86 (54.4%)	251 (53.0%)
Aromatase inhibitors	141 (44.6%)	68 (43.0%)	209 (44.1%)
Aromatase inhibitors with GnRH	6 (1.9%)	3 (1.9%)	9 (1.9%)
Aromatase inhibitors without GnRH	135 (42.7%)	65 (41.1%)	200 (42.2%)
Type of Aromatase inhibitor			
Letrozole	70 (22.2%)	26 (16.5%)	96 (20.3%)
Anastrozole	39 (12.3%)	15 (9.5%)	54 (11.4%)
Exemestane	36 (11.4%)	28 (17.7%)	64 (13.5%)
Duration of adjuvant endocrine therapy (years)			
n	316	158	474
Mean (SD)	1.98 (1.45)	1.82 (1.51)	1.92 (1.47)
Median	1.70	1.50	1.60
Min, Max	0.0, 8.1	0.1, 9.7	0.0, 9.7
Sex			
Female	316 (100.0%)	158 (100.0%)	474 (100.0%)
Race			
White	278 (88.0%)	140 (88.6%)	418 (88.2%)
Black or African American	6 (1.9%)	1 (0.6%)	7 (1.5%)
Asian	1 (0.3%)	1 (0.6%)	2 (0.4%)
American Indian or Alaska Native	2 (0.6%)	1 (0.6%)	3 (0.6%)
Not reported	29 (9.2%)	15 (9.5%)	44 (9.3%)
Ethnicity			
Not Hispanic or Latino	289 (91.5%)	143 (90.5%)	432 (91.1%)
Hispanic or Latino	7 (2.2%)	5 (3.2%)	12 (2.5%)
Not reported	20 (6.3%)	10 (6.3%)	30 (6.3%)
Age (years)			
n	316	158	474
Mean (SD)	50.8 (7.5)	51.5 (6.7)	51.0 (7.3)
Median	51.0	52.0	51.0
Min, Max	28, 70	32, 67	28, 70
Age group I			
< 40 years	23 (7.3%)	7 (4.4%)	30 (6.3%)
40 - 49 years	106 (33.5%)	47 (29.7%)	153 (32.3%)
50 - 59 years	148 (46.8%)	87 (55.1%)	235 (49.6%)
60 - 65 years	28 (8.9%)	14 (8.9%)	42 (8.9%)
> 65 years	11 (3.5%)	3 (1.9%)	14 (3.0%)
Age group II			
18-64 years	303 (95.9%)	153 (96.8%)	456 (96.2%)
>= 65 years	13 (4.1%)	5 (3.2%)	18 (3.8%)
Weight (kg)			

	EZN 120 mg N=316 (100%)	Placebo - EZN 120 mg N=158 (100%)	Total N=474 (100%)
N	316	158	474
Mean (SD)	71.44 (12.56)	72.61 (13.64)	71.83 (12.93)
Median	69.00	71.00	70.00
Min, Max	46.5, 110.0	41.3, 111.0	41.3, 111.0
Height (cm)			
N	316	158	474
Mean (SD)	165.52 (6.49)	164.55 (6.18)	165.20 (6.40)
Median	166.00	165.00	165.40
Min, Max	149.0, 184.0	146.8, 180.0	146.8, 184.0
Body Mass Index (kg/m2)			
N	316	158	474
Mean (SD)	26.11 (4.56)	26.79 (4.65)	26.33 (4.59)
Median	25.40	26.40	25.60
Min, Max	18.1, 38.7	17.2, 40.0	17.2, 40.0
Body Mass Index Group (kg/m²)			
<18.5	2 (0.6%)	2 (1.3%)	4 (0.8%)
18.5 to <25	145 (45.9%)	61 (38.6%)	206 (43.5%)
25 to <30	111 (35.1%)	60 (38.0%)	171 (36.1%)
>=30	58 (18.4%)	35 (22.2%)	93 (19.6%)
Smoking History			
Never	201 (63.6%)	108 (68.4%)	309 (65.2%)
Former	71 (22.5%)	33 (20.9%)	104 (21.9%)
Current	44 (13.9%)	17 (10.8%)	61 (12.9%)
Level of Education			
Missing	2 (0.6%)	1 (0.6%)	3 (0.6%)
College or university education	192 (60.8%)	103 (65.2%)	295 (62.2%)
Professional certification	66 (20.9%)	29 (18.4%)	95 (20.0%)
Attending college	14 (4.4%)	6 (3.8%)	20 (4.2%)
Other	42 (13.3%)	19 (12.0%)	61 (12.9%)

A subject can have more than one type of aromatase inhibitor.
Duration of adjuvant endocrine therapy is calculated from initiation of therapy based on "Prior and Concomitant Medication - Background Therapy" page until baseline visit.

Medical history

All except 1 participant in the elinzanetant arm had a medical history of breast cancer. Breast cancer characteristics were overall similar between treatment arms with some variability in the distribution of histologic cancer types between treatment arms.

The most common medical history findings were hypertension (18.4% vs. 13.9%), arthralgia (13.0% vs. 13.3%), insomnia (11.4% vs. 9.5%) and depression (10.5% vs. 10.1%) in the elinzanetant arm and the placebo arm, respectively, and were similar between the treatment arms. 12.7% (13.3% and 11.4% for elinzanetant and placebo) of the women had undergone hysterectomy and 12.9% had undergone oophorectomy (14.9.3% and 8.9% for elinzanetant and placebo).

The most common prior procedures were radiotherapy (39.0% vs. 38.0%), breast conserving surgery (33.3% vs. 29.7%) and mastectomy (24.8% vs. 24.1%) in the elinzanetant arm and the placebo-elinzanetant arm, respectively. Prior chemotherapy was more common in the placebo-elinzanetant arm (13.7% vs. 20.3%).

- **Numbers analysed**

Efficacy analyses are based on the FAS, and participants were analyzed according to the randomized intervention.

Safety analyses are based on the SAF, and participants were analyzed according to the intervention they received. 1 participant in the elinzanetant 120 mg arm never took study drug and was excluded from the SAF. Number of participants in the analysis sets:

FAS: 316 participants in elinzanetant arm; 158 participants in the placebo-elinzanetant arm.

SAF: 315 participants in elinzanetant arm; 158 participants in the placebo-elinzanetant arm.

- **Outcomes and estimation**

Primary efficacy endpoints

Frequency of moderate to severe hot flashes – change from baseline to Weeks 4 and 12 (assessed by HFDD)

The decrease of mean daily frequency of moderate to severe HFs from baseline to both Week 4 and to Week 12 was significantly greater on elinzanetant compared to the decrease on placebo. A clinically meaningful difference in frequency between elinzanetant and placebo was identified at both Week 4 and Week 12. The difference between elinzanetant 120 mg and placebo in the change from baseline of the frequency of moderate to severe HFs (LS-Means [95% CI]), was – 3.48 [- 4.35, - 2.61] at Week 4 and -3.38 [- 4.21, - 2.54] at Week 12.

Table 31 OASIS 4 - Mean change in frequency of moderate to severe HFs from baseline to Weeks 4 and 12 (FAS)

		Elinzanetant 120 mg (N=316)			Placebo (N=158)	
Value at visit	n	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	316	11.41 (6.89)	9.86	157	11.52 (6.43)	9.71
Week 4	306	4.95 (4.60)	3.71	152	8.47 (7.00)	7.14
Week 12	292	3.64 (4.27)	2.14	148	7.42 (5.60)	6.71
Change from baseline	n	LS-Mean (SE)	95% CI	n	LS-Mean (SE)	95% CI
Week 4	307	-6.47 (0.26)	-6.98, -5.96	153	-2.99 (0.36)	-3.70, -2.28
Week 12	297	-7.53 (0.25)	-8.02, -7.05	148	-4.16 (0.35)	-4.84, -3.47
MMRM analysis, elinzanetant 120 mg vs placebo						
Week 4	Difference in LS-means (SE)		-3.48 (0.44)			
	95% CI for difference in LS-means		-4.35, -2.61			
	p-value (one-sided)		<.0001			
Week 12	Difference in LS-means (SE)		-3.38 (0.43)			
	95% CI for difference in LS-means		-4.21, -2.54			
	p-value (one-sided)		<.0001			

CI = confidence interval, HFs = hot flashes, LS-means = least squares means, MMRM = mixed model repeated measures, SD = standard deviation, SE = standard error

Key secondary endpoints

1. Sleep disturbances - change from baseline to week 12 (by PROMIS SD SF 8b)

A decrease in the PROMIS SD SF 8b scores (i.e., single item, total raw, and total T-score) indicates an improvement in sleep disturbances. At baseline, mean PROMIS SD SF 8b total T-scores were similar across both treatments. At Week 12, mean change in the PROMIS SD SF 8b total T-score from baseline showed statistically significant improvement in sleep disturbances from baseline in favour of elinzanetant compared to placebo.
A decrease in the mean PROMIS SD SF 8b total T-score of at least -7.19 at Week 12 has been identified as a within-group meaningful change based on triangulation of results from anchor-based methods using data from OASIS-2. In this regard, elinzanetant 120 mg but not placebo resulted in a clinically meaningful improvement in sleep disturbances, as measured by the PROMIS SD SF 8b total T-score from baseline to Week 12 (see table below).

Table 32 OASIS 4 - PROMIS SD SF 8b total T-score change from baseline to Week 12

		Elinzanetant 120 mg (N=316)			Placebo (N=158)	
Value at visit	n	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	313	60.60 (6.33)	60.40	155	60.74 (6.80)	60.40
Week 12	291	50.09 (7.54)	50.10	149	56.63 (7.23)	56.30
Change from baseline	n	LS-Mean (SE)	95% CI	n	LS-Mean (SE)	95% CI
Week 12	300	-10.06 (0.41)	-10.85, -9.26	149	-3.94 (0.57)	-5.06, -2.82
MMRM analysis, elinzanetant 120 mg vs placebo						
Week 12	Difference in LS-means (SE)	-6.12 (0.70)				
	95% CI for difference in LS-means	-7.49, -4.75				
	p-value (one-sided)	<.0001				

CI = confidence interval, LS-means = least squares means, MMRM = mixed model repeated measures, PROMIS SD SF 8b = Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, SD = standard deviation, SE = standard error

2. Menopause-related quality of life – change from baseline to week 12 (by MENQOL)

A decrease in the MENQOL total score indicates improvement in menopause-related quality of life.

Mean MENQOL total scores were similar across both treatments at baseline. At Week 12, the change from baseline (LS-Means [SE]) in the MENQOL total score was greater on elinzanetant than on placebo, and the decrease was statistically significantly greater on elinzanetant compared to the decrease on placebo. A decrease in the mean MENQOL total score of at least -0.87 at Week 12 has been identified as a within-group meaningful change based on triangulation of results from anchor-based methods using data from OASIS-2. In this regard, elinzanetant 120 mg but not placebo resulted in a clinically meaningful improvement in menopause-related quality of life from baseline to Week 12.

Table 33 OASIS 4 - MENQOL total score change from baseline to Week 12 (FAS)

		Elinzanetant 120 mg (N=316)			Placebo (N=158)	
Value at visit	**n**	**Mean (SD)**	**Median**	**n**	**Mean (SD)**	**Median**
Baseline	311	4.82 (1.17)	4.83	155	4.77 (1.25)	4.84
Week 12	288	3.56 (1.23)	3.44	146	4.24 (1.28)	4.25
Change from baseline	**n**	**LS-Mean (SE)**	**95% CI**	**n**	**LS-Mean (SE)**	**95% CI**
Week 12	297	-1.23 (0.06)	-1.34, -1.11	146	-0.55 (0.08)	-0.71, -0.38
MMRM analysis, elinzanetant 120 mg vs placebo						
Week 12	Difference in LS-means (SE)		-0.68 (0.10)			
	95% CI for difference in LS-means		-0.88, -0.48			
	p-value (one-sided)		<.0001			

CI = confidence interval, LS-means = least squares means, MENQOL= Menopause Specific Quality of Life Scale, MMRM = mixed model repeated measures, SD = standard deviation, SE = standard error

Pre-defined and ad hoc important subgroup analyses

For all primary and key secondary endpoints and timepoints, consistent treatment effects were observed across subgroups (region, race, ethnicity, BMI, smoking history and type of underlying AET) and no subgroup with an effect outside of the expected range for variability was detected.

Efficacy outcomes by type of AET at baseline were determined, descriptive analysis of subgroups showed that at Week 12, there was a more pronounced decrease in frequency of HFs in the placebo arm of the aromatase inhibitor subgroup compared to the tamoxifen subgroup (mean (SD) were respectively -5.84 (7.07) and -3.01 (4.90)), while the decrease in the elinzanetant arm was comparable in both subgroups (mean (SD) were respectively for the aromatase inhibitor subgroup and the tamoxifen group -7.39 (4.72) and -8.07 (7.15)). Consequently, the difference between elinzanetant and placebo at this time point was more pronounced in the tamoxifen subgroup. Additionally requested test result showed no statistically significant difference in the treatment effect (LS-means (95% CI): -1.67 (-3.36, 0.01)) for change in frequency of HF from baseline to week 12, between women receiving aromatase inhibitors and those receiving tamoxifen, although a trend was visible showing a lesser effect with aromatase inhibitors, see table below.

Table 34 Change from baseline at week 12 in mean daily frequency of moderate to severe hot flashes - MMRM analysis - by treatment group and background therapy (full analysis set) - OASIS 4 (21656)

Background therapy	Statistics	EZN 120 mg (N=316)	Placebo - EZN 120 mg (N=158)	EZN 120 mg vs. Placebo
Aromatase inhibitor	n	135	62	
	LS-Means (SE)	-7.46 (0.37)	-5.03 (0.53)	
	95% CI for LS-Means	-8.17, -6.74	-6.07, -3.99	
	Difference in LS-Means (SE)			-2.43 (0.64)
	95% CI for Difference in LS-Means			-3.69, -1.17
	p-value (two-sided)*			0.0002

Background therapy	Statistics	EZN 120 mg (N=316)	Placebo - EZN 120 mg (N=158)	EZN 120 mg vs. Placebo
Tamoxifen	n	162	86	
	LS-Means (SE)	-7.58 (0.34)	-3.48 (0.46)	
	95% CI for LS-Means	-8.24, -6.92	-4.37, -2.58	
	Difference in LS-Means (SE)			-4.10 (0.57)
	95% CI for Difference in LS-Means			-5.21, -2.99
	p-value (two-sided)*			<.0001
Tamoxifen vs. Aromatase inhibitor	Difference in LS-Means (SE)	-0.12 (0.50)	1.55 (0.70)	-1.67 (0.86)
	95% CI for Difference in LS-Means	-1.09, 0.85	0.18, 2.92	-3.36, 0.01
	p-value (two-sided)*	0.8065	0.0266	0.0515

* Nominal p-value
Placebo - Elinzanetant 120mg = Placebo for 12 weeks, followed by elinzanetant 120 mg for 40 weeks.
n = number of subjects with observed value for this timepoint and considered in the analysis model.
In case data was missing for more than 2 days within a week, the value for that particular week was set to missing
Multiple imputation is used to impute missing values.
LS-Means = Least Squares Means, SE = Standard Error, MMRM = Mixed Model Repeated Measures, CI = Confidence Interval

Other secondary endpoints

1. Severity of moderate to severe HFs – change from baseline to Weeks 4 and 12 (by HFDD)

At baseline, the mean (SD) daily severity of moderate to severe HFs was 2.49 (0.24) in the elinzanetant 120 mg arm and 2.49 (0.22) in the placebo arm.

At Week 4, the mean (SD) daily severity of moderate to severe HFs was numerically lower than at baseline on both treatments and numerically lower on elinzanetant 120 mg compared to placebo: the value was 1.76 (0.64) on elinzanetant 120 mg and 2.06 (0.49) on placebo. The change from baseline was -0.73 (0.60) and -0.43 (0.43) for elinzanetant and placebo, respectively.

At Week 12, the mean (SD) daily severity of moderate to severe HFs was numerically lower than at baseline on both treatments and numerically lower on elinzanetant 120 mg compared to placebo: the value was 1.52 (0.75) on elinzanetant 120 mg and 1.96 (0.64) on placebo. The change from baseline was -0.98 (0.72) and -0.53 (0.60) for elinzanetant and placebo, respectively.

2. Frequency of moderate to severe HFs – change from baseline to Week 1 (by HFDD)

A decrease in the mean frequency of moderate to severe HFs was already seen at Week 1 in both treatment arms. The decrease in frequency (mean [SD]) of moderate to severe HFs was numerically greater on elinzanetant 120 mg compared to the decrease on placebo (-4.04 [5.11] vs. -1.76 [3.83]).

3. Frequency of moderate to severe HFs – change from baseline over time (by HFDD)

Descriptive analysis of mean change in frequency of moderate to severe HFs over time showed a baseline frequency (mean [SD]) of moderate to severe HFs of 11.41 (6.89) per day on elinzanetant 120 mg and 11.52 (6.43) per day on placebo. The numerical change in the frequency of moderate to severe HFs was more pronounced on elinzanetant 120 mg during the first 12 weeks of treatment compared to placebo. After

Week 12, when the participants initially randomized to placebo had switched to elinzanetant 120 mg, a continued effect of elinzanetant 120 mg was seen until Week 26. The numerical decrease was comparable to that observed in the elinzanetant 120 mg arm at Week 26 and was maintained until Week 50.

Exploratory analysis - Proportion of participants with at least 50% reduction in frequency of moderate to severe HF at Week 4 and 12

Descriptive results showed a numerically larger proportion of participants with treatment response on elinzanetant, in week 4 and 12. At week 26, when all participants had been treated with elinzanetant, treatment response was equal between the two groups.

Table 35 Proportion of subjects with at least a reduction of 50% in mean daily frequency of moderate to severe hot flashes by treatment group (full analysis set)

Time		Elinzanetant 120mg (N=316)	Placebo - Elinzanetant 120mg (N=158)
Week 4	n	306 (100.0%)	152 (100.0%)
	missing	0	1 (0.7%)
	Yes	187 (61.1%)	41 (27.0%)
	No	119 (38.9%)	110 (72.4%)
Week 12	n	292 (100.0%)	148 (100.0%)
	missing	0	1 (0.7%)
	Yes	217 (74.3%)	53 (35.8%)
	No	75 (25.7%)	94 (63.5%)
Week 26	n	98 (100.0%)	55 (100.0%)
	missing	0	0
	Yes	88 (89.8%)	50 (90.9%)
	No	10 (10.2%)	5 (9.1%)

Placebo - Elinzanetant 120mg = Placebo for 12 weeks, followed by elinzanetant 120 mg for 40 weeks
Bayer: /var/swan/root/bhc/3427080/21656/stat/main02/prod/analysis/pgms/t_8_2_3_1_hfss_hf_s.sas 19JUN2024 14:02
End of table

2.6.5.2.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36 Summary of main efficacy trials

Pivotal OASIS 1

Title	**A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women**		
Study identifier	**OASIS-1** (**O**verall **A**ssessment of efficacy and **S**afety of elinzanetant **I**n patients with vasomotor **S**ymptoms); Protocol no.: 21651; Report no.: PH-42782, Eudra CT: 2020-004908-33; ClinicalTrials.gov: NCT05042362		
Design	Phase 3, multi-center, multi-country, randomized, placebo-controlled, double-blind intervention study, in postmenopausal women with moderate to severe vasomotor symptoms Duration of run-in phase: 6 weeks (screening) Duration of main phase: 26 weeks (treatment) Duration of extension phase: 4 weeks (follow-up)		
Hypothesis	The hypotheses for the primary and key secondary efficacy endpoints are defined as: **H1**- H_{01}: $\mu_{1P} \leq \mu_{1V}$ versus H_{11}: $\mu_{1P} > \mu_{1V}$ where μ_{1P} and μ_{1V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at Week 4. **H2**- H_{02}: $\mu_{2P} \leq \mu_{2V}$ versus H_{12}: $\mu_{2P} > \mu_{2V}$ where μ_{2P} and μ_{2V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at Week 12. **H3**- H_{03}: $\mu_{3P} \leq \mu_{3V}$ versus H_{13}: $\mu_{3P} > \mu_{3V}$ where μ_{3P} and μ_{3V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF severity at Week 4. **H4**- H_{04}: $\mu_{4P} \leq \mu_{4V}$ versus H_{14}: $\mu_{4P} > \mu_{4V}$ where μ_{4P} and μ_{4V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF severity at Week 12. **H5**- H_{05}: $\mu_{5P} \leq \mu_{5V}$ versus H_{15}: $\mu_{5P} > \mu_{5V}$ where μ_{5P} and μ_{5V} stand for the mean change from baseline in the placebo (P) and verum (V) group in PROMIS SD SF 8b at Week 12. **H6**- H_{06}: $\mu_{6P} \leq \mu_{6V}$ versus H_{16}: $\mu_{6P} > \mu_{6V}$ where μ_{6P} and μ_{6V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at Week 1. **H7**- H_{07}: $\mu_{7P} \leq \mu_{7V}$ versus H_{17}: $\mu_{7P} > \mu_{7V}$ where μ_{7P} and μ_{7V} stand for the mean change from baseline in the placebo (P) and verum (V) group in MENQOL at Week 12.		
Treatment groups	EZN 120 mg: Elinzanetant 120 mg for 26 weeks	Overall treatment duration, mean (SD): 22.6 (6.6) weeks Weeks 1-12, treatment duration, mean (SD): 11.6 (2.3) weeks Number randomized (FAS): 199	
	Placebo: Placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks	Overall treatment duration, mean (SD): 22.5 (7.2) weeks Weeks 1-12, treatment duration, mean (SD): 11.4 (2.8) weeks Number randomized (FAS): 197	
Endpoints and definitions	**Primary Endpoint (All regions)**	HF freq: BL to W4	Mean change in frequency of moderate to severe HFs from baseline (BL) to Week 4
	Primary Endpoint (All regions)	HF freq: BL to W12	Mean change in frequency of moderate to severe HFs from baseline to Week 12
	Primary Endpoint (US) / Key Secondary Endpoint (other regions)	HF severity: BL to W4	Mean change in severity of moderate to severe HFs from baseline to Week 4
	Primary Endpoint (US) / Key Secondary Endpoint (other regions)	HF severity: BL to W12	Mean change in severity of moderate to severe HFs from baseline to Week 12
	Key Secondary Endpoint (All regions)	PROMIS SD SF 8b T-score BL to W12	Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12
	Key Secondary Endpoint (All regions)	HF freq: BL to W1	Mean change in frequency of moderate to severe HFs from baseline to Week 1
	Key Secondary Endpoint (All regions)	MENQOL total score: BL to W12	Mean change in MENQOL total score from baseline to Week 12

Pivotal OASIS 1 continued

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Results and Analysis

Analysis description	**Primary Analysis** Estimated treatment effect includes all treatment interruptions, premature discontinuation, and prohibited concomitant medications (treatment policy). Endpoints were analyzed using mixed models with repeated measures (MMRM) on the change from baseline. Baseline, treatment, region, and week, as well as the interaction term between baseline and week and interaction term between treatment and week were included as covariables in the model. Treatment comparisons are based on differences in treatment group means for each endpoint.
Analysis population and time point description	Full analysis set (FAS): all randomized participants analyzed according to their randomized treatment Time points: Baseline, Week 1, Week 4, and Week 12 as defined for the particular endpoint

Descriptive statistics and estimate variability	**Treatment group**	**EZN 120 mg**	**Placebo**
	Number of subjects	**199**	**197**
	HF freq: BL to W4		
	mean	-7.48	-4.37
	standard deviation	5.80	6.73
	HF freq: BL to W12		
	mean	-8.74	-5.53
	standard deviation	6.70	10.16
	HF severity: BL to W4		
	mean	-0.73	-0.39
	standard deviation	0.64	0.43
	HF severity: BL to W12		
	mean	-0.95	-0.55
	standard deviation	0.78	0.60
	PROMIS SD SF 8b T-score: BL to W12		
	mean	-10.8	-5.0
	standard deviation	9.6	6.9
	HF freq: BL to W1		
	mean	-5.00	-2.72
	standard deviation	5.05	4.99
	MENQOL total score: BL to W12		
	mean	-1.41	-0.96
	standard deviation	1.30	1.11

Pivotal OASIS 1 continued

Effect estimate per comparison	**Primary endpoint (All regions)** HF freq: BL to W4	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in Least Squares (LS) means	-3.29
		95% confidence interval	-4.47, -2.10
		p-value (one-sided, MMRM)	<.0001
	Primary endpoint (All regions) HF freq: BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-3.22
		95% confidence interval	-4.81, -1.63
		p-value (one-sided, MMRM)	<.0001
	Primary endpoint (US) / Key Secondary (other regions) HF severity: BL to W4	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-0.33
		95% confidence interval	-0.44, -0.23
		p-value (one-sided, MMRM)	<.0001
	Primary endpoint (US) / Key Secondary (other regions) HF severity: BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-0.40
		95% confidence interval	-0.54, -0.25
		p-value (one-sided, MMRM)	<.0001
	Key Secondary endpoint PROMIS SD SF 8b T-score BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-5.58
		95% confidence interval	-7.18, -3.98
		p-value (one-sided, MMRM)	<.0001
	Key Secondary endpoint HF freq: BL to W1	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-2.45
		95% confidence interval	-3.36, -1.55
		p-value (one-sided, MMRM)	<.0001
	Key Secondary endpoint MENQOL total score: BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-0.42
		95% confidence interval	-0.64, -0.20
		p-value (one-sided, MMRM)	<.0001
Notes	Primary reason for withdrawal from study during placebo-controlled phase (Weeks 1-12): EZN 120 mg: Adverse event 7 participants (3.5%) Placebo: Adverse event 7 participants (3.6%)		

Pivotal OASIS 2

Title	**A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women**		
Study identifier	**OASIS-2** (**O**verall **A**ssessment of efficacy and **S**afety of elinzanetant **I**n patients with vasomotor **S**ymptoms) Protocol no.: 21652; Report no.: PH-42780; Eudra CT: 2020-004855-34, ClinicalTrials.gov: NCT05099159		
Design	Phase 3, multi-center, multi-country, randomized, placebo-controlled, double-blind intervention study, in postmenopausal women with moderate to severe vasomotor symptoms Duration of run-in phase: 6 weeks (screening) Duration of main phase: 26 weeks (treatment) Duration of extension phase: 4 weeks (follow-up)		
Hypothesis	The hypotheses for the primary and key secondary efficacy endpoints are defined as: **H1-** $H_{01}: \mu_{1P} \leq \mu_{1V}$ versus $H_{11}: \mu_{1P} > \mu_{1V}$ where μ_{1P} and μ_{1V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at Week 4. **H2-** $H_{02}: \mu_{2P} \leq \mu_{2V}$ versus $H_{12}: \mu_{2P} > \mu_{2V}$ where μ_{2P} and μ_{2V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at Week 12. **H3-** $H_{03}: \mu_{3P} \leq \mu_{3V}$ versus $H_{13}: \mu_{3P} > \mu_{3V}$ where μ_{3P} and μ_{3V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF severity at Week 4. **H4-** $H_{04}: \mu_{4P} \leq \mu_{4V}$ versus $H_{14}: \mu_{4P} > \mu_{4V}$ where μ_{4P} and μ_{4V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF severity at Week 12. **H5-** $H_{05}: \mu_{5P} \leq \mu_{5V}$ versus $H_{15}: \mu_{5P} > \mu_{5V}$ where μ_{5P} and μ_{5V} stand for the mean change from baseline in the placebo (P) and verum (V) group in PROMIS SD SF 8b at week 12. **H6-** $H_{06}: \mu_{6P} \leq \mu_{6V}$ versus $H_{16}: \mu_{6P} > \mu_{6V}$ where μ_{6P} and μ_{6V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at Week 1. **H7-** $H_{07}: \mu_{7P} \leq \mu_{7V}$ versus $H_{17}: \mu_{7P} > \mu_{7V}$ where μ_{7P} and μ_{7V} stand for the mean change from baseline in the placebo (P) and verum (V) group in MENQOL at Week 12.		
Treatment groups	EZN 120 mg: Elinzanetant 120 mg for 26 weeks	Overall treatment duration, mean (SD):22.4 (7.4) weeks Weeks 1-12, treatment duration, mean (SD): 11.4 (3.0) weeks Number randomized (FAS): 200	
	Placebo: Placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks	Overall treatment duration, mean (SD): 23.1 (6.5) weeks Weeks 1-12, treatment duration, mean (SD): 11.7 (2.6) weeks Number randomized (FAS): 200	
Endpoints and definitions	**Primary Endpoint (All regions)**	HF freq: BL to W4	Mean change in frequency of moderate to severe HFs from baseline (BL) to Week 4 (assessed by Hot Flash Daily Diary, HFDD)
	Primary Endpoint (All regions)	HF freq: BL to W12	Mean change in frequency of moderate to severe HFs from baseline to Week 12
	Primary Endpoint (US) / Key Secondary Endpoint (other regions)	HF severity: BL to W4	Mean change in severity of moderate to severe HFs from baseline to Week 4
	Primary Endpoint (US) / Key Secondary Endpoint (other regions)	HF severity: BL to W12	Mean change in severity of moderate to severe HFs from baseline to Week 12
	Key Secondary Endpoint (All regions)	PROMIS SD SF 8b T-score BL to W12	Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12
	Key Secondary Endpoint (All regions)	HF freq: BL to W1	Mean change in frequency of moderate to severe HFs from baseline to Week 1
	Key Secondary Endpoint (All regions)	MENQOL total score: BL to W12	Mean change in MENQOL total score from baseline to Week 12

Pivotal OASIS 2 continued

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Results and Analysis

Analysis description	**Primary Analysis** Estimated treatment effect includes all treatment interruptions, premature discontinuation, and prohibited medications (treatment policy). Endpoints were analyzed using mixed models with repeated measures (MMRM) on the change from baseline. Baseline, treatment, region, and week, as well as the interaction term between baseline and week and interaction term between treatment and week were included as covariables in the model. Treatment comparisons are based on differences in treatment group means for each endpoint.
Analysis population and time point description	Full analysis set (FAS): all randomized participants analyzed according to their randomized treatment Time points: Baseline, Week 1, Week 4, and Week 12 as defined for the particular endpoint

Descriptive statistics and estimate variability	**Treatment group**	**EZN 120 mg**	**Placebo**
	Number of subjects	**200**	**200**
	HF freq: BL to W4		
	mean	-8.58	-6.07
	standard deviation	9.16	8.91
	HF freq: BL to W12		
	mean	-9.96	-7.24
	standard deviation	10.25	8.49
	HF severity: BL to W4		
	mean	-0.75	-0.53
	standard deviation	0.68	0.55
	HF severity: BL to W12		
	mean	-0.97	-0.65
	standard deviation	0.78	0.67
	PROMIS SD SF 8b T-score: BL to W12		
	mean	-10.6	-5.5
	standard deviation	7.7	6.9
	HF freq: BL to W1		
	mean	-4.66	-3.57
	standard deviation	6.70	6.86
	MENQOL total score: BL to W12		
	mean	-1.34	-0.97
	standard deviation	1.29	1.16

Pivotal OASIS 2 continued

Effect estimate per comparison	**Primary endpoint (All regions)** HF freq: BL to W4	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in Least Squares (LS) means	-3.04
		95% confidence interval	-4.40, -1.68
		p-value (one-sided, MMRM)	<.0001
	Primary endpoint (All regions) HF freq: BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-3.24
		95% confidence interval	-4.60, -1.88
		p-value (one-sided, MMRM)	<.0001
	Primary endpoint (US) / Key Secondary (other regions) HF severity: BL to W4	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-0.22
		95% confidence interval	-0.34, -0.09
		p-value (one-sided, MMRM)	0.0003
	Primary endpoint (US) / Key Secondary (other regions) HF severity: BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-0.29
		95% confidence interval	-0.44, -0.14
		p-value (one-sided, MMRM)	<.0001
	Key Secondary endpoint HF freq: BL to W1	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-1.66
		95% confidence interval	-2.73, -0.58
		p-value (one-sided, MMRM)	.0013
	Key Secondary endpoint PROMIS SD SF 8b T-score BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-4.32
		95% confidence interval	-5.77, -2.86
		p-value (one-sided, MMRM)	<.0001
	Key Secondary endpoint MENQOL total score: BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**
		Difference in LS-means	-0.30
		95% confidence interval	-0.53, -0.07
		p-value (one-sided, MMRM)	0.0059
Notes	Primary reason for withdrawal from study during placebo-controlled phase (Weeks 1-12): EZN 120 mg: Subject decision 7 participants (3.5%) Placebo: Subject decision 5 participants (2.5%)		

Pivotal OASIS 4 (Parts A + B)

Title	**A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms caused by adjuvant endocrine therapy, over 52 weeks and optionally for an additional 2 years in women with, or at high risk for developing hormone-receptor positive breast cancer**		
Study identifier	**OASIS-4** (**O**verall **A**ssessment of efficacy and **S**afety of elinzanetant **I**n patients with vasomotor **S**ymptoms in women with, or at high risk for developing hormone-receptor positive breast cancer); Protocol no.: 21656; Report no.: B003761, EU CT: 2023-508265-33-00 (former Eudra CT: 2022-000095-18)		
Design	Phase 3, multi-center, multi-country, randomized, placebo-controlled, double-blind intervention study, in women with, or at high risk for developing hormone-receptor positive breast cancer Duration of Parts A and B of the study: Duration of run-in phase: 6 weeks (screening) Duration of main phase: 52 weeks (treatment) Duration of extension phase: optional 2 years (part C) followed by / or 4 weeks (follow-up)		
Hypothesis	The hypotheses for the primary and key secondary efficacy endpoints are defined as: **H1**- $H_{01}: \mu_{1P} \leq \mu_{1V}$ versus $H_{11}: \mu_{1P} > \mu_{1V}$ where μ_{1P} and μ_{1V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at Week 4. **H2**- $H_{02}: \mu_{2P} \leq \mu_{2V}$ versus $H_{12}: \mu_{2P} > \mu_{2V}$ where μ_{2P} and μ_{2V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at Week 12. **H3**- $H_{03}: \mu_{3P} \leq \mu_{3V}$ versus $H_{13}: \mu_{3P} > \mu_{3V}$ where μ_{3P} and μ_{3V} stand for the mean change from baseline in the placebo (P) and verum (V) group in PROMIS SD SF 8b at Week 12. **H4**- $H_{04}: \mu_{4P} \leq \mu_{4V}$ versus $H_{14}: \mu_{4P} > \mu_{4V}$ where μ_{4P} and μ_{4V} stand for the mean change from baseline in the placebo (P) and verum (V) group in MENQOL at Week 12.		
Treatment groups	EZN 120 mg: Elinzanetant 120 mg for 52 weeks	Overall treatment duration, mean (SD): 45.1 (13.8) weeks Weeks 1-12, treatment duration, mean (SD): 11.9 (2.2) weeks Weeks 13-26, treatment duration, mean (SD): 12.7 (2.1) weeks Weeks 27-52, treatment duration, mean (SD): 24.9 (2.8) weeks Number randomized (FAS): 316	
	Placebo: Placebo for 12 weeks, followed by elinzanetant 120 mg for 40 weeks	Overall treatment duration, mean (SD): 45.8 (13.1) weeks Weeks 1-12, treatment duration, mean (SD): 12.0 (2.1) weeks Weeks 13-26, treatment duration, mean (SD): 12.6 (2.4) weeks Weeks 27-52, treatment duration, mean (SD): 24.9 (2.8) weeks Number randomized (FAS): 158	
Endpoints and definitions	**Primary Endpoint**	HF freq: BL to W4	Mean change in frequency of moderate to severe HFs from baseline (BL) to Week 4
	Primary Endpoint	HF freq: BL to W12	Mean change in frequency of moderate to severe HFs from baseline to Week 12
	Key Secondary Endpoint	PROMIS SD SF 8b T-score BL to W12	Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12
	Key Secondary Endpoint	MENQOL total score: BL to W12	Mean change in MENQOL total score from baseline to Week 12
Database lock	**09 DEC 2024 (Parts A + B)**		

Results and Analysis

Analysis description	**Primary Analysis** Estimated treatment effect includes all treatment interruptions, premature discontinuation, and prohibited concomitant medications (treatment policy). Endpoints were analyzed using mixed models with repeated measures (MMRM) on the change from baseline at various weeks including weeks 1, 4, 8 and 12. Baseline, treatment, week, type of treatment of pre-existing condition at baseline (stratification factor for randomization) as well as the interaction term between baseline and week and interaction term between treatment and week were included as covariables in the model. Treatment comparisons are based on differences in treatment group means for each endpoint.			
Analysis population and time point description	Full analysis set (FAS): all randomized participants analyzed according to their randomized treatment Time points: Baseline, Week 4, and Week 12 as defined for the particular endpoint			
Descriptive statistics and estimate variability	**Treatment group**		**EZN 120 mg**	**Placebo**
	Number of subjects		**316**	**158**
	HF freq: BL to W4			
		mean	-6.51	-3.04
		standard deviation	6.13	5.04
	HF freq: BL to W12			
		mean	-7.76	-4.20
		standard deviation	6.17	6.06
	PROMIS SD SF 8b T-score: BL to W12			
		mean	-10.55	-4.06
		standard deviation	8.20	7.35
	MENQOL total score: BL to W12			
		mean	-1.30	-0.53
		standard deviation	1.11	1.15
Effect estimate per comparison	**Primary endpoint** HF freq: BL to W4	**Comparison groups**	**EZN 120 mg vs placebo**	
		Difference in Least Squares (LS) means	-3.48	
		95% confidence interval	-4.35, -2.61	
		p-value (one-sided, MMRM)	<.0001	
	Primary endpoint HF freq: BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**	
		Difference in LS-means	-3.38	
		95% confidence interval	-4.21, -2.54	
		p-value (one-sided, MMRM)	<.0001	
	Key Secondary endpoint PROMIS SD SF 8b T-score BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**	
		Difference in LS-means	-6.12	
		95% confidence interval	-7.49, -4.75	
		p-value (one-sided, MMRM)	<.0001	
	Key Secondary endpoint MENQOL total score: BL to W12	**Comparison groups**	**EZN 120 mg vs placebo**	
		Difference in LS-means	-0.68	
		95% confidence interval	-0.88, -0.48	
		p-value (one-sided, MMRM)	<.0001	

Notes	Primary reason for withdrawal from study during placebo-controlled phase (Weeks 1-12): EZN 120 mg: Adverse event - 7 participants (2.2%) Placebo: Adverse event, non-compliance with study drug, subject decision - 2 participants each (1.3%)

2.6.5.3. Clinical studies in special populations

Please refer to section *Clinical pharmacokinetics.*

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

A pooled presentation across the pivotal studies, OASIS 1 and 2, for the treatment of moderate to severe VMS associated with menopause has been performed and is considered supportive.

Primary efficacy endpoints (pool across OASIS 1 and 2): Frequency of moderate to severe HFs – change from baseline to Weeks 4 and 12 (assessed by HFDD)

A pooled analysis across OASIS 1 and 2 confirmed the results of the individual studies of a clinically meaningful reduction at both Week 4 and Week 12.

Table 37 Pooled OASIS 1 and 2 - MMRM analysis, Mean change in frequency of moderate to severe HFs from baseline to Weeks 1, 4 and 12, elinzanetant 120 mg vs placebo (FAS)

		Pooled OASIS 1 and 2
Week 1 [a]	Difference in LS-Means (SE) 95% CI for Difference in LS-Means p-value (one-sided)[b]	-2.03 (0.37) -2.75, -1.31 <0.0001
Week 4	Difference in LS-Means (SE) 95% CI for Difference in LS-Means p-value (one-sided)[b]	-3.11 (0.48) -4.06, -2.16 <0.0001
Week 12	Difference in LS-Means (SE) 95% CI for Difference in LS-Means p-value (one-sided)[b]	-3.19 (0.54) -4.26, -2.13 <0.0001

a) Key secondary endpoint.

CI = confidence interval, HFs = hot flashes, LS-Means = least squares means, MMRM = mixed model repeated measures, SD = standard deviation, SE = standard error

b) p-values are nominal.

Key secondary endpoints (pool across OASIS 1 and 2): Severity of moderate to severe HFs – change from baseline to Weeks 4 and 12 (assessed by HFDD)

In the HFDD, the severity of HFs was categorized as: 1 = mild, 2 = moderate, and 3 = severe; therefore, a decrease in the HF severity score indicates an improvement.

A decrease in the HF severity of at least -0.53 at Week 4 and -0.62 at Week 12 has been identified as a within-group meaningful change based on triangulation of results from anchor-based methods using data from OASIS 2. When applying these thresholds to the pooled data, elinzanetant 120 mg but not placebo resulted in a clinically meaningful improvement in HF severity, as measured by the HFDD from baseline to Week 4 and to Week 12.

Table 38 Pooled OASIS 1 and 2: MMRM analysis, Mean change in Severity of moderate to severe HFs from baseline to Weeks 4 and 12, elinzanetant 120 mg vs placebo (FAS)

		Pooled OASIS 1 and 2
Week 4	Difference in LS-Means (SE) 95% CI for Difference in LS-Means p-value (one-sided)[a]	-0.27 (0.04) -0.36, -0.19 <0.0001
Week 12	Difference in LS-Means (SE) 95% CI for Difference in LS-Means p-value (one-sided)[a]	-0.34 (0.05) -0.45, -0.24 <0.0001

a) p-values are nominal. CI = confidence interval, HFs = hot flashes, LS-Means = least squares means, MMRM = mixed model repeated measures, SD = standard deviation, SE = standard error

Key secondary endpoint: Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12

A decrease in the PROMIS SD SF 8b scores (i.e., single item, total raw, and total T-score) indicates an improvement in sleep disturbances.

Table 39 Pooled OASIS 1 and 2 - MMRM analysis, PROMIS SD SF 8b total T-score change from baseline to Week 12, elinzanetant 120 mg vs placebo (FAS)

		Pooled OASIS 1 and 2
Week 12	Difference in LS-Means (SE) 95% CI for Difference in LS-Means p-value (one-sided)[a]	-4.94 (0.55) -6.02, -3.85 <.0001

a) p-value is nominal. CI = confidence interval, LS-Means = least squares means, MMRM = mixed model repeated measures, PROMIS SD 8B = Patient-Reported Outcomes Measurement Information System Sleep Disturbance short-form 8b, SE = standard error

Key secondary endpoint: Menopause-related quality of life – change from baseline to week 12 (assessed by MENQOL)

A decrease in the MENQOL total score indicates an improvement in menopause-related quality of life.

Table 40 Pooled OASIS 1 and 2 - MMRM analysis, Mean change in MENQOL total score from baseline to Week 12, elinzanetant 120 mg vs placebo (FAS)

		Pooled OASIS 1 and 2
Week 12	Difference in LS-Means (SE) 95% CI for Difference in LS-Means p-value (one-sided)[a]	-0.36 (0.08) -0.52, -0.20 <.0001

a) p-value is nominal. CI = confidence interval, LS-Means = least squares means, MENQOL = Menopause-specific quality of life questionnaire, MMRM = mixed model repeated measures, SE = standard error

Secondary efficacy endpoints (pooled OASIS 1 and 2): Frequency of moderate to severe HFs – change from baseline over time (assessed by HFDD)

Table 41 Pooled OASIS 1 and 2 - mean change in frequency of moderate to severe HFs from baseline to Week 26 (FAS)

	Elinzanetant 120 mg			Placebo		
Pooled OASIS 1 and 2	**(N=399)**			**(N=397)**		
Value at visit	**n**	**Mean (SD)**	**Median**	**n**	**Mean (SD)**	**Median**
Baseline	398	14.02 (9.12)	11.57	397	15.22 (12.63)	11.46
Week 26	222	3.26 (4.54)	1.43	230	4.86 (15.03)	2.00
Change from baseline						
Week 26	222	-10.92 (9.19)	-9.32	230	-11.49 (10.80)	-8.75

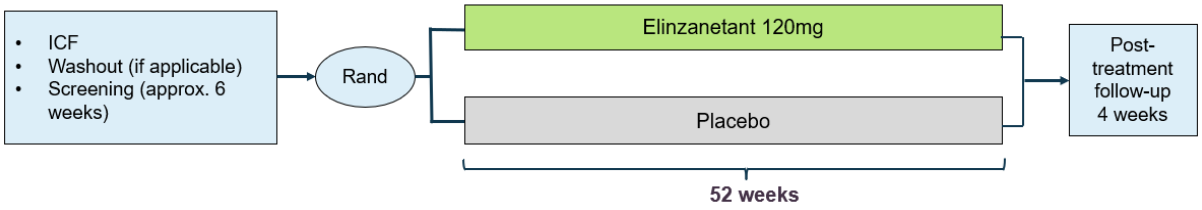
HFs = hot flashes, SD = standard deviation

2.6.5.5. Supportive study - OASIS 3 (Study 21810)

- ***Methods***

OASIS 3 was a randomized, double-blind, placebo-controlled efficacy and safety study with a duration of 52 weeks. Women with moderate to severe HFs associated with menopause (no minimum number of HFs at baseline) and seeking treatment for this condition were included.

Figure 14 OASIS 3 – study schema



- **Study participants**

Inclusion and exclusion criteria were largely identical to the OASIS 1 and 2 studies except that no minimum daily number of moderate to severe HFs was required for inclusion. In OASIS 3, participants had to complete HFDD for at least 11 days during the two weeks preceding baseline visit and was showing eligibility with respect to inclusion criterion "moderate to severe HFs associated with the menopause and seeking treatment for this condition" during this time period.

- **Treatments**

Study treatment in both treatment arms was to be taken once daily before going to bed, with or without food. All participants received either 120 mg of elinzanetant or matching placebo orally once daily for 52 weeks.

- **Objectives**

Primary objective

- To evaluate the efficacy of elinzanetant for the treatment of VMS associated with the menopause.

The main estimand assessed the effect of assigned treatment, i.e., elinzanetant 120 mg compared to placebo including all treatment interruptions, premature discontinuation of randomized treatment, and intake of prohibited concomitant medications having impact on efficacy (treatment policy strategy) in postmenopausal women aged 40–65 years with moderate to severe VMS (further defined by inclusion and exclusion criteria)

on change from baseline to Week 12 as defined for the primary endpoint. The mean difference between the treatment arms was used as summary measure.

Secondary objectives

- To evaluate the efficacy of elinzanetant on sleep disturbances, menopause related quality of life and weight and body composition.

- **Outcomes/endpoints**

Primary endpoint

- Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD)

Secondary endpoints

- Mean change in PROMIS SD SF 8b total T-score from baseline over time
- Mean change in MENQOL total score from baseline over time

- **Sample size**

A total of 600 subjects were planned to be randomized in a 1:1 ratio: 300 subjects in each treatment arm. The number of participants needed for this study was based on the total number of 1500 participants exposed to elinzanetant at least once needed for the safety evaluation per ICH E1 guideline. Based on the number of participants that were available from previous phase 1 and phase 2 studies, and simultaneously ongoing phase 3 studies OASIS 1 and 2, the number of participants needed for the elinzanetant arm in this study was 300, also taking into account the assumed 10% drop-out rate during months 1-3 and 4-6 and overall drop-out rate of 30%.

A formal sample size justification was performed for the primary efficacy endpoint using the one-sided two-Sample T-test (equal variance) assuming at least approximate normal distribution. Assuming standard deviation of 4.29 based on data from the placebo arm of the SWITCH-1 study, the power for a treatment difference of -2.0 in mean daily frequency of HFs or more was calculated to be > 99.9% with N=270 per treatment arm.

- **Randomisation and blinding (masking)**

In OASIS 3, the method used for randomization and blinding was the same as for OASIS 1 and 2.

- **Statistical methods**

The following analysis sets were defined:

Table 42 OASIS 3 - Definition of the analysis sets

Analysis Set	Description
Enrolled	All participants who signed the informed consent form.
Full Analysis Set (FAS)	All randomized participants.
Safety Analysis Set (SAF)	All participants who received at least one dose of study intervention.

Efficacy analyses were based on the FAS and participants were analyzed according to the randomized intervention. Safety analyses were performed on the SAF and participants were analyzed according to the intervention received.

The ***primary efficacy endpoint***, mean change in frequency of moderate to severe HF from baseline to Week 12, was analysed using similar methods (primary, sensitivity and supplementary analyses) described for OASIS 1 and OASIS 2.

Secondary efficacy endpoints, mean change in PROMIS SD SF 8b total T-score from baseline over time and mean change in MENQOL total score from baseline over time, were summarized descriptively.

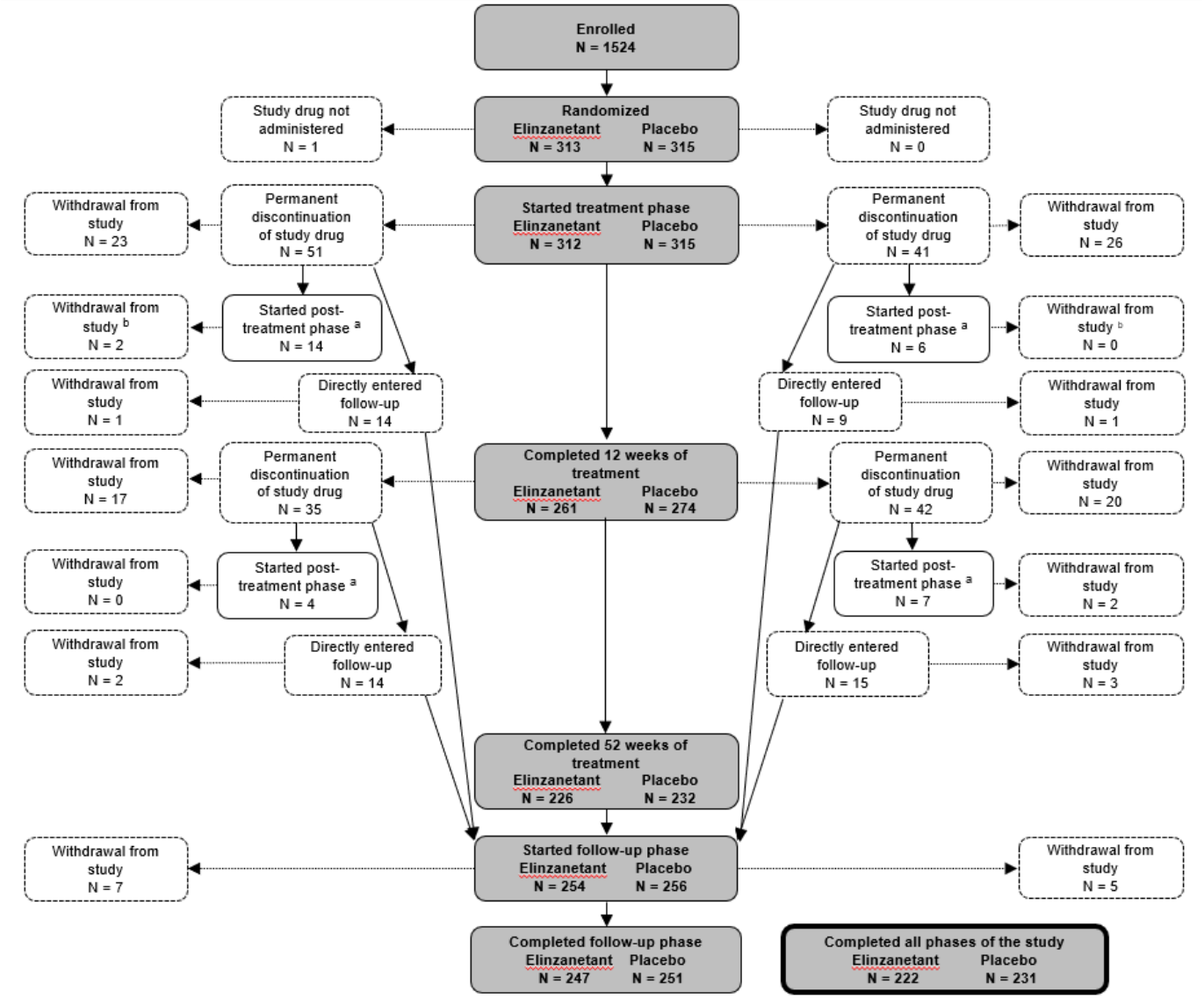
Exploratory subgroup analyses using descriptive statistics were provided for the primary and the secondary endpoints for the following subgroups: region (North America vs. rest of the world), race, ethnicity, BMI (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m2), smoking history (Never, Former, Current; derived from habitual cigarette smoking and any other tobacco/nicotine from the CRF) and moderate to severe HFs at baseline (< 35, ≥ 35).

- **Results**

  - **Participant flow**

Out of the 1524 screened participants, 628 were randomized and 453 completed the study. Not meeting the eligibility criteria was the most common reason for screening failure (828 [54.3%]). 103 participants (16.0% in the elinzanetant 120 mg arm and 16.8% in the placebo arm) did not complete the study and 72 participants (13.1% in the elinzanetant 120 mg arm and 9.8% in the placebo arm) discontinued the study treatment but remained in the study and completed post-treatment phase or follow-up. The most common reason for discontinuation of the study was subject decision in both treatment arms (6.7% in the elinzanetant 120 mg arm and 8.9% in the placebo arm).

Figure 15 OASIS 3 Participant flow



a. If a participant discontinued from study drug but agreed to stay in the study (i.e., in a post-treatment phase), the next scheduled in-person visit covered the assessments expected to be performed during the follow-up visit, and therefore no follow-up visit was needed after the end-of-treatment visit.
b. Withdrawal from study could take place at any point during Weeks 1-52 after the participant had entered the post-treatment phase.

3 intercurrent events (ICEs) were defined for the period of up to Week 12: permanent discontinuation of randomized treatment, temporary treatment interruption, and intake of prohibited concomitant medication having impact on efficacy. Overall, the occurrence of ICEs was low. The most common ICE was permanent discontinuation of randomized treatment, which was reported for 43 (13.7%) participants in the elinzanetant 120 mg arm and for 30 (9.5%) participants in the placebo arm.

- **Baseline data**

Treatment arms were generally well balanced regarding demographic and other baseline characteristics. Most participants were White (78.5%) or Black/African American (15.1%). 10.8% were Hispanic or Latino by ethnicity. The mean (SD) age was 54.7 (4.8) years, ranged from 41 to 65 years, and the mean (SD) BMI was 27.60 (4.69) kg/m2, ranged from 17.7 to 40.8 kg/m2. There was a slightly higher proportion of participants who were current smokers in the elinzanetant 120 mg arm. For a detailed overview of the baseline data and demographics, please refer to the Day 80 clinical AR.

Table 43 Number and percentage of participants by subgroup according to post-menopausal status

Postmenopausal, defined as…	**OASIS 3 (21810) N = 628**
Number of subjects with bilateral oophorectomy ≥ 6 weeks prior screening visit	25 (4.0%)
Number of subjects with hysterectomy ≥ 6 months before screening visit & FSH > 40 IU/L and estradiol concentration of <30 pg/mL	135 (21.5%)
Number of subjects with 6 to 12 months of amenorrhea prior screening visit & & FSH > 40 IU/L and estradiol concentration of <30 pg/mL	14 (2.2%)
Number of subjects with amenorrhea ≥ 12 months prior screening visit	451 (71.8%)
Other	3 (0.5%)

28.1% of the participants in the elinzanetant 120 mg arm and 29.6% in the placebo arm had undergone hysterectomy[3] and 11.5% of participants in the elinzanetant 120 mg arm and 14.6% participants in the placebo arm had undergone oophorectomy[4]. Median duration of amenorrhea was similar in between the treatment arms (4.95 years in the elinzanetant 120 mg arm and 5.00 years in the placebo arm. The most common medical history findings were obesity (28.8% vs. 28.3%), hypertension (27.5% vs. 29.9%), and hysterectomy (22.0% vs. 22.9%) in the elinzanetant 120 mg arm and the placebo arm, respectively, and were similar between the treatment arms except for insomnia, which was more frequent in the elinzanetant 120 mg arm compared to the placebo arm (13.1% vs. 8.6%).

- **Numbers analysed**

Efficacy analyses are based on the FAS and participants were analyzed according to the randomized intervention.

Safety analyses are based on the SAF, and participants were analyzed according to the intervention they received. 1 participant who was assigned to the elinzanetant 120 mg arm received no study drug and was excluded from the SAF. In addition, 1 participant who was assigned to the placebo arm received a kit containing elinzanetant at the Week 8 visit and is therefore assigned to the elinzanetant 120 mg arm in the SAF.

[3] Based on medical history, PTs considered for hysterectomy were hysterectomy, hysterosalpingectomy, hysterosalpingo-oophorectomy, and radical hysterectomy.
[4] Based on medical history, PTs considered for oophorectomy were hysterosalpingo-oophorectomy, oophorectomy,oophorectomy bilateral, salpingo-oophorectomy, salpingo-oophorectomy bilateral, and salpingo-oophorectomy unilateral.

Number of participants in the analysis sets:

FAS: 313 participants in the elinzanetant 120 mg arm, 315 participants in the placebo arm.

SAF: 313 participants in the elinzanetant 120 mg arm 314 participants in the placebo arm.

- **Outcomes and estimations**

Primary efficacy endpoint

- **Frequency of moderate to severe hot flashes – change from baseline to Week 12 (assessed by HFDD)**

In OASIS 3 the decrease of mean daily frequency of moderate to severe HFs from baseline to Week 12 was statistically significantly greater on elinzanetant 120 mg compared to the decrease on placebo. Efficacy was maintained for a treatment duration of 50 weeks.

Table 44 OASIS 3 - Mean change in daily frequency of moderate to severe HFs from baseline to Week 12 (FAS)

	Elinzanetant 120 mg (N=313)			Placebo (N=315)		
Value at visit	n	Mean (SD)	Median	n	Mean (SD)	Median
Baseline	312	6.71 (7.15)	5.04	315	6.81 (6.15)	5.50
Week 12	258	1.59 (2.45)	0.64	278	3.38 (4.17)	2.07
Change from baseline	n	LS Mean (SE)	95% CI	n	LS Mean (SE)	95% CI
Week 12	273	-4.89 (0.18)	-5.25, -4.53	282	-3.34 (0.18)	-3.70, -2.98
MMRM analysis, elinzanetant 120 mg vs placebo						
Difference in LS-Means (SE)			-1.55 (0.25)			
95% CI for difference in LS-Means			-2.04, -1.05			
p-value (one-sided)			<0.0001			

CI = confidence interval, LS-Means = least squares means, MMRM = mixed model repeated measures, SD = standard deviation, SE = standard error

Secondary endpoint: Sleep disturbances - change from baseline over time (assessed by PROMIS SD SF 8b)

In the OASIS 3 study, mean change in PROMIS SD SF 8b total T-score from baseline over time was evaluated as secondary endpoint.

Descriptive analyses showed that the mean PROMIS SD SF 8b total T-scores were similar across both treatment arms at baseline and showed a continuous numerical decrease in both the elinzanetant 120 mg arm and the placebo arm from baseline until Week 24, being more pronounced on elinzanetant 120 mg compared to placebo at all time points. After Week 24, the mean values remained stable in both treatment arms until Week 52.

Table 45 OASIS 3 - Mean change in PROMIS SD SF 8b total T-scores from baseline to Week 1, Week 4, Week 12, Week 24, and Week 52 (FAS)

	Elinzanetant 120 mg (N=313)			Placebo (N=315)		
	N	Mean (SD)	Median	n	Mean (SD)	Median
Value at visit						
Baseline	270	57.4 (6.7)	57.3	274	58.0 (7.6)	58.3
Week 1	301	52.2 (8.0)	52.2	306	56.4 (7.2)	56.3
Week 4	289	49.6 (8.3)	49.0	297	54.2 (7.2)	54.3
Week 12	265	49.5 (8.0)	49.0	277	52.8 (7.6)	53.3
Week 24	204	47.7 (8.7)	47.9	219	52.4 (8.1)	53.3
Week 52	172	48.1 (8.5)	47.9	186	52.3 (7.7)	53.3
Change from baseline						
Week 1	265	-5.2 (7.2)	-4.3	270	-1.6 (5.4)	-1.2
Week 4	249	-7.7 (8.3)	-7.6	263	-3.8 (7.0)	-3.2
Week 12	228	-8.0 (8.0)	-7.6	246	-5.3 (8.0)	-4.6
Week 24	178	-9.8 (9.0)	-8.6	195	-5.9 (7.8)	-5.1
Week 52	151	-9.4 (8.4)	-8.6	159	-5.7 (7.9)	-5.7

FAS = full analysis set, PROMIS SD SF 8b = Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, SD = standard deviation

Secondary endpoint: Menopause-related quality of life – change from baseline over time (assessed by MENQOL)

In the OASIS 3 study, mean change in MENQOL total score from baseline over time was evaluated as secondary endpoint.

Based on descriptive statistics, the mean MENQOL total scores were comparable across both treatment arms at baseline. The mean MENQOL total score showed a numerical decrease in both the elinzanetant 120 mg and the placebo arm at Week 4, Week 12, Week 24, and Week 52 compared to baseline, being more pronounced on elinzanetant 120 mg compared to placebo at all time points.

Table 46 OASIS 3 - Mean change in MENQOL total scores from baseline to Week 1, Week 4, Week 12, Week 24, and Week 52 (FAS)

	Elinzanetant 120 mg (N=313)			Placebo (N=315)		
	n	Mean (SD)	Median	n	Mean (SD)	Median
Value at visit						
Baseline	262	4.10 (1.21)	3.91	264	4.41 (1.37)	4.30
Week 4	278	3.15 (1.32)	2.97	291	3.70 (1.45)	3.60
Week 12	260	3.05 (1.37)	2.89	273	3.44 (1.43)	3.28
Week 24	201	2.76 (1.17)	2.63	213	3.27 (1.43)	3.02
Week 52	172	2.81 (1.34)	2.66	184	3.26 (1.36)	3.05
Change from baseline						
Week 4	235	-0.94 (1.22)	-0.88	250	-0.67 (1.21)	-0.52
Week 12	220	-1.10 (1.25)	-1.04	235	-0.95 (1.32)	-0.84
Week 24	173	-1.25 (1.17)	-1.16	185	-1.15 (1.37)	-0.93
Week 52	147	-1.30 (1.33)	-1.21	154	-1.11 (1.35)	-0.89

FAS = full analysis set, MENQOL= Menopause-Specific Quality of Life Scale, SD = standard deviation

Pre-defined and ad-hoc important subgroup analyses

Subgroup analyses by region, race, ethnicity, BMI, smoking status, and the number of moderate to severe HFs at baseline (< 35, ≥ 35) on the frequency of HFs, PROMIS SD SF 8b total T-score, MENQOL total score and VMS domain subscore were performed. For PROMIS SD SF 8b total T-scores, subgroup analyses by ISI categories were also performed.

For all endpoints and timepoints, homogenous treatment effects were observed across subgroups and no subgroup with an effect outside the expected range for variability was detected. A numerically larger mean (SD) decrease in the daily frequency of moderate to severe HFs from baseline to Week 12 was observed in elinzanetant 120 mg treated participants whose number of moderate to severe HFs at baseline was ≥35 over the last 7 days before start of treatment (-8.12 [8.92] per day) and in elinzanetant 120 mg treated participants who were either former or current smokers (-6.24 [7.47] per day and -7.07 [12.73] per day) compared to the overall change from baseline at Week 12 (elinzanetant 120 mg: -5.40 [7.29]).

A decrease in the PROMIS SD SF 8b total T-scores and the ISI scores indicate an improvement in sleep disturbances/insomnia. Baseline values of sleep disturbances as measured by the PROMIS SD SF 8b total T-score and insomnia as measured by the ISI total score were compared. The more severe the ISI category (no clinically significant insomnia, sub-threshold insomnia, moderately severe clinical insomnia, and severe clinical insomnia) reached at baseline, the greater the mean value for PROMIS SD SF 8b total T-score was at baseline as well.

The more severe the ISI category was at baseline, the greater was the numerical decrease from baseline in PROMIS SD SF 8b total T-score at Week 12 and Week 52 on both treatments, while numerically greater decreases in PROMIS SD SF 8b total T-score were observed on elinzanetant 120 mg compared to placebo.

2.6.6. Discussion on clinical efficacy

Two pivotal replicate design studies were performed (OASIS 1 and 2), and one long-term, placebo-controlled safety study, OASIS 3, to support durability of efficacy of elinzanetant.

There is one single on-going pivotal phase 3 efficacy and safety study, OASIS 4.

Dose-response studies

Two double-blind, placebo-controlled dose-response studies in patients with moderate to severe VMS were performed to support the selection of the 120 mg dose in the phase 3 studies.

In the **RELENT-1**, a phase 1b/2a study, patients received 50, 100, 150 or 300 mg in a hard capsule formulation for 14 days, to evaluate average Daily Frequency of Moderate and Severe Hot Flushes. The 150 mg and 300 mg doses were more effective in reduction of VMS versus placebo compared to the 50 and 100 mg doses after 14 days of treatment. Further, particularly the 150 mg dose resulted in an exposure at steady state consistent with full receptor occupancy throughout a 24-hour dose interval. It is therefore reasonable to take the 150 mg as starting point for further dose selection in the SWITCH-1 study. This hard capsule formulation was not further developed for the commercial market, due to low exposures and excessive within- and between- subject variability. Based on a relative bioavailability study, the 150 mg and 300 mg hard gel formulations of elinzanetant are expected to achieve similar exposures as the 40 mg to 160 mg soft gel formulation.

In the second **dose-response study, SWITCH-1**, an adaptive design phase 2b study, patients received 40 mg, 80 mg, 120 mg, or 160 mg for 12 weeks, using a soft capsule formulation to evaluate mean change from baseline in mean daily frequency and severity of moderate and severe hot flashes from baseline to Week 4 and 12. Adaptive randomization design was used to optimize allocation of women to dose levels that, on the basis of emerging safety and efficacy data, warranted further evaluation.

Of note, as a result of the early closure of the 80 mg dosing arm, the number of patients in this treatment group is considered too small to appropriately assess the efficacy regarding the reduction of HF. Based on the current provided data, it might be argued if the 80 mg dose would have been a suitable option for use in this population. Nevertheless, based on the efficacy and safety data of the 120 mg and 160 mg dosing groups, the choice for the 120 mg dose as the lowest effective and safe dose can be supported. Elinzanetant will be available at 60 mg capsule, which requires administration of 2 tablets to achieve recommended dose of 120 mg, as the current formulation does not allow for the 120 mg dose in one single, reasonably sized capsule.

Treatment of moderate to severe VMS associated with menopause

Design and conduct of *OASIS 1 and 2*

The study designs of OASIS 1 and 2 are identical and therefore discussed simultaneously.

The design of the two pivotal studies OASIS 1 and 2 consisted of a 12-week, randomized, placebo-controlled, double-blind phase to assess the efficacy and safety of elinzanetant in postmenopausal women with moderate to severe vasomotor symptoms (VMS (hot flashes)) followed by a 14-week non-controlled extension treatment period in which former placebo patients received elinzanetant 120 mg (total treatment period of 26 weeks). A placebo-controlled treatment period of 12 weeks (i.e. 3 months) is generally agreed for the evaluation of efficacy in VMS, which is also in line with the *CHMP "Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women" (EMEA/CHMP/021/97 Rev. 1)*.

The **patient population** selected were women aged 40-65 inclusive with at least 50 moderate to severe HF (including night-time) per week at baseline. The minimum frequency of HF at baseline is in concordance with the CHMP guideline mentioned above, e.g. 5 HF per day. The inclusion and exclusion criteria are generally acceptable and reflective of a target population indicated for treatment of VMS associated with menopause, although, based on the in- and exclusion criteria, perimenopausal women will not be included. This is not reflected in the approved indication, but section 5.1 of the SmPC mentions that only postmenopausal women were included in the OASIS studies. This is acceptable, and in line with another recently EU-approved non-hormonal NK-3 receptor antagonist, fezolinetant. The decision to prescribe HRT or another treatment option should be made on an individual basis, weighing the potential benefits and risks of all options, including the woman's personal preference in a shared decision-making process with her treating physician, as recommended in clinical guidelines.

Participants were randomized 1:1 to elinzanetant or placebo, provided in the same dosing schedule. Efficacy of elinzanetant was assessed compared to placebo which is considered acceptable and in line with the study design of another non-hormonal treatment for VMS symptoms associated with menopause. Randomization and blinding procedures are considered acceptable. Elinzanetant 120 mg or placebo were to be taken once daily before going to bed, with or without food. The dose of 120 mg elinzanetant once-daily at bedtime, is in line with the proposed recommendations on dosing in section 4.2 of the proposed SmPC of elinzanetant, and therefore acceptable.

The **primary efficacy analysis** in the pivotal studies consisted of 2 primary endpoints (i.e. change in the frequency of VMS at week 4 and at week 12) for 120 mg elinzanetant vs placebo. These primary endpoints are acceptable and in line with the recommendations in the *CHMP "Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women" (EMEA/CHMP/021/97 Rev. 1)*. Severity at 4 and 12 weeks is included as 2 **key secondary endpoints**, which is acceptable. Other key secondary endpoints included *frequency of HF at week 1*, mean *change in the PROMIS SD SF 8b total T-score from baseline to week 12* in order to assess self-reported sleep disturbance over the past 7 days at week 12, and *change in the MENQOL total score at week 12*. The selection of key secondary endpoints is considered acceptable and supportive for the primary analysis.

Other secondary and exploratory endpoints included further evaluation of HF frequency over time, evaluation of depressive symptoms and several quality-of-life (QoL) assessments, including patient reported outcomes (PROs) on menopause and specific symptoms such as sleep, productivity and HF impact as well as questions on the general health status of participants. Also responder rate (i.e. proportion of patients with at least 50% reduction in HF frequency) was included as exploratory endpoint. The selected other secondary and exploratory endpoints are acceptable and agreed with.

The treatment policy **estimand** is used for the primary and key secondary objectives, which reflects the real-world usage of this medication and is to the disadvantage of the treatment. This is therefore acceptable.

The proposed **sample size** determination and analysis are overall suitable, a total of 370 participants (185 per arm) per study were planned to be randomized. The applicant has used reasonable parameters for the sample size, and, where available, estimations were performed based on the phase 2 trial. The definitions of the analysis populations are standard and acceptable. Regarding the **statistical methods**, the analysis of the primary endpoints was performed with MMRM to detect the change of frequencies at week 4 and 12. This is a standard method, and therefore acceptable. It was pre-defined which days constitute week 4 and 12, and average frequencies were calculated accordingly. All covariates appear to have been taken into account. This analysis approach is appropriate. The multi-test correction via the method by Bretz will preserve the overall type I and is acceptable, and the graphical distribution of the test order is reasonable. The imputation of missing values was performed via MCMC, which is a suitable method to impute non-linear values, and is suitable for this type of data. The subgroup analysis covers the relevant subgroups in this population. Data quality assurance is considered acceptable, the measures taken are adequate.

Efficacy data and additional analyses OASIS 1 and 2

OASIS 1 and 2 – 12-week double-blind, placebo-controlled study period

Regarding the **participant flow,** for OASIS 1, a total of 1535 participants were screened, as a relatively higher number of a total of 1139 (74%) failed screening. Eventually, a total of 396 were randomized, 199 to elinzanetant and 197 to placebo. For OASIS 2, a total of 1483 participants were screened, a total of 1083 (73%) failed screening and 400 (27%) were randomized 1:1 to elinzanetant and placebo.

In OASIS 1, 171 and 168 participants completed the placebo-controlled period of 12 weeks (86%/85%) and respectively 156 and 159 completed 26 weeks of treatment (78%/81%), percentages are considered high. About 10% discontinued due to adverse events in both treatment groups during the treatment period of 26 weeks. Other reasons were subjects' decision and lost to follow up (all between 2% and 4%). For OASIS 2, a total of 170 (85%) and 181 (91%) in the elinzanetant group and placebo/elinzanetant group completed the placebo-controlled 12-week treatment period and 160 participants (80%) in the elinzanetant and 170 (85%) in the placebo/elinzanetant group completed the 26 weeks treatment period. Common reasons for

discontinuation, during the 26-week treatment period, were adverse events (8.5% and 2.5% in the elinzanetant and placebo/elinzanetant group, respectively) and subject decision (6.5% and 6.0 for elinzanetant and placebo respectively). The percentage of important **protocol deviations** is considered high, respectively 62% and 49% for OASIS 1 and 2. Mostly, this consisted of procedure deviations, respectively around 40% and 30%. The reported protocol deviations primarily affected the secondary endpoint PROMIS SD SF 8b and/or MENQOL missing at baseline, which, due to equal distribution, is unlikely to have had an impact in the statistical analysis (no imputation of missing data was performed). Based on eCRF data, treatment compliance up to week 12 was high, with a median of 95% in both studies and treatment groups and was comparable to treatment compliance based on eDiary.

Generally, the recruited patients reflect a postmenopausal population with VMS regarding **demographics and baseline characteristics**. The participants had a median age of 54-55 years. Most participants were white (77% in OASIS 1 and 84% in OASIS 2) and mostly non-Hispanic or Latino. In both treatment arms and in both studies arms, the median body mass index was ~27 kg/m2. In general, the demographics are well balanced between the treatment groups, however the current smoking status did differ slightly among the studies and treatment arms. However, an effect of smoking is not expected, since incubation with an inhibitor of CYP1A2 resulted in <20% inhibition and therefore not considered significant.

Concerning the **medical/gynaecologic history**, the median time of women being amenorrhoeic was 6 years for elinzanetant and 5 years for placebo (OASIS 1 and 2 combined). There is a remarkable high percentage of women with a hysterectomy (38.8%) and oophorectomy (20.6%), equal for both treatment arms. The patient characteristics with regard to postmenopausal state as categorized in the 4 subgroups (i.e. spontaneous amenorrhea for ≥ 12 consecutive months, spontaneous amenorrhea for ≥ 6 months with biochemical criteria of menopause (FSH > 40 IU/L or estradiol concentration of <30 pg/mL), ≥ 6 months after hysterectomy with biochemical criteria of menopause (FSH > 40 IU/L estradiol concentration of <30 pg/mL) or having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit (with or without hysterectomy)) The number of subjects with bilateral oophorectomy ≥ 6 weeks prior screening visit, with hysterectomy ≥ 6 months before screening visit & FSH > 40 IU/L and estradiol concentration of <30 pg/mL, with 6 months ≤ amenorrhea < 12 months prior screening visit, with amenorrhea ≥ 12 months prior screening visit, and Other are more or less comparable between groups. Hormone replacement therapy (HRT) during the study treatment was prohibited. In OASIS 1, 67.3% of the participants in the elinzanetant group and 69.0% in the placebo group reported having never received hormonal treatment for menopausal vasomotor symptoms. In OASIS 2, the respective percentages were 67.0% in the elinzanetant 120 mg group and 71.0% in the placebo group. In OASIS 3, the respective percentages were 71.2% in the elinzanetant 120 mg group and 68.8% in the placebo group.

Regarding the **primary analysis,** the change in the frequency of moderate to severe VMS from baseline to weeks 4 and 12 have been evaluated. Regarding the **first primary endpoint**, treatment with elinzanetant resulted in a higher reduction in the frequency of moderate to severe VMS from baseline to **week 4** compared to placebo:

In OASIS 1, the difference in LS means of elinzanetant vs placebo was statistically significant (LS mean (SE) i.e. -3.29 (0.61; 95% CI: -4.47 to -2.10). The difference in LS means of elinzanetant vs placebo in OASIS 2 was also statistically significant (LS mean (SE) i.e. -3.04 (0.69; 95% CI: -4.40 to -1.68).

Based on these outcomes, it can be concluded that the first primary endpoint on the mean change in the frequency of moderate to severe VMS from baseline to week 4 was met.

Regarding the **second primary endpoint** treatment with elinzanetant resulted also in a higher reduction in the frequency of moderate to severe VMS from baseline to week 12 compared to placebo.

In OASIS 1, the difference in LS means of elinzanetant vs placebo was statistically significant (LS mean (SE) i.e. -3.22 (0.81; 95% CI: -4.81 to -1.63). The difference in LS means of elinzanetant vs placebo in OASIS 2 were also statistically significant (LS mean (SE) i.e. -3.24 (0.69; 95% CI: -4.60 to -1.88).

Therefore, that also the second primary endpoint on the mean change in the frequency of moderate to severe VMS from baseline to week 12 was met.

Based on these data, for both OASIS 1 and 2, it can be concluded that participants treated with elinzanetant had statistically significant reductions in the frequency of moderate to severe VMS from baseline to weeks 4 and 12, relative to placebo.

Of note, the improvement in VMS frequency in participants in both studies and at both timepoints can be interpreted as clinically meaningful (defined as an additional reduction of minimal 2 compared to placebo) as they consistently reduced the number of VMS (hot flushes) with ≥ 3 per day relative to placebo.

Further, **the sensitivity and supplementary analysis** showed the robustness of the primary analysis. The outcomes appear to be robust against missing data, as no major differences were seen if up to 10 hot flush events were added in the elinzanetant arm for the calculation of the frequency. The tipping point analysis for the calculation of the severity showed that the results would only become non-significant if the treatment was considerably weaker. The assumption of normal distribution appears to hold, as tests with non-parametric methods such as ANCOVA did not yield different results. The alternative estimands (usage of the hypothetical estimand for some ICEs such as Covid-19 infection) yielded comparable results to the primary estimand and confirm that the treatment policy estimand did not considerably disadvantage the treatment. All assumptions and outcomes are appropriate.

Regarding the first **2 key secondary endpoints**, a reduction in the change from baseline in mean severity of moderate to severe VMS has been observed in **week 4**, compared to placebo.

The differences in LS means of elinzanetant vs placebo were statistically significant (OASIS 1: LS mean (SE) of -0.33 (0.06); 95% CI: -0.44 to -0.23; OASIS 2: LS mean (SE) of -0.22 (0.06); 95% CI: -0.34 to -0.09).

Similarly, a reduction in the change from baseline in mean severity of moderate to severe VMS has been observed in **week 12**, compared to placebo:

The difference in LS means of elinzanetant vs placebo was statistically significant (OASIS 1: LS mean (SE) of -0.40 (0.07); 95% CI: -0.54 to -0.25; OASIS 2: LS mean (SE) i.e. -0.29 (0.08); 95% CI: -0.44 to -0.14).

Based on these outcomes, of both OASIS 1 and 2, it can be concluded that the key secondary endpoints on the mean change in the severity of moderate to severe VMS from baseline to both week 4 and week 12 was met.

A decrease in the HF severity of at least -0.53 at Week 4 and -0.62 at Week 12 has been identified as a within-group meaningful change based on triangulation of results from anchor-based methods using data from OASIS 2. These values correspond to a change of 1 in the Patient Global Impression of Severity scale (PGI-S) and responding `a little better´ to the Patient Global Impression of Change (PGI-C) patient reported outcomes, which has been identified via participant interviews as meaningful, and are therefore supportive of the overall conclusion. A difference between-groups in reduction of severity of -0.23 and -0.32 for week 4 and 12 respectively, were identified as meaningful changes. For OASIS 1, the between-group meaningful changes were achieved, while not for OASIS 2.

The third **key secondary endpoint,** mean change in the PROMIS SD SF 8b total T-score from baseline to week 12, was selected to assess self-reported sleep disturbance over the past 7 days. The PRO questionnaire includes 8 questions regarding perceptions of sleep. A decrease indicates an improvement in sleep disturbances from baseline. A within-group meaningful change was determined as a T-score change of at least -7.19 at week 12. This difference was only reached in the elinzanetant groups.

The difference in LS means of elinzanetant vs placebo was statistically significant: OASIS 1: -5.58 (0.82; CI 95%: -7.18, -3.98); OASIS 2: -4.32 (0.74; CI 95%: -5.77, -2,86).

The change in sleep disturbances from baseline over time showed already a result after one week of treatment, remaining largely stable over the treatment duration. For participants switching from placebo to elinzanetant after 12 weeks, they catch up with those already on elinzanetant soon after the switch. As expected, the treatment effect did not continue after treatment discontinuation, i.e. after 4 weeks during the follow up values increased but did not reach baseline values (yet).

Sleep disorder was not an inclusion criterion. However, a medical history of sleep disorders was reported in both treatment arms with similar distribution in both elinzanetant arm (21 participants, 10.6%) and placebo-elinzanetant arm (21 participants, 10.8%). The most commonly reported sleep disorder at baseline was insomnia. Comparable number of participants from both study arms reported prior treatment for sleep disorders (9/21 (42.9%) in the elinzanetant arm and 10/21 (47.6%) in the placebo-elinzanetant arm). 28.6% and 38.1% of subjects who reported prior treatment for sleep disorders in the elinzanetant and placebo groups, respectively, continued their sleep disorder treatment during study. Further, several study participants in each arm newly initiated treatment for sleep disorders during the course of the study. The number of patients using concomitant treatment for sleep disorder is low and balanced between treatment groups. A post-hoc analysis excluding participants using concomitant sleep treatment was requested to support the results for this key secondary endpoint. The difference at week 12 in LS-Means (95%-CI), corrected for concomitant treatment for sleep disorders between elinzanetant (n=170) and placebo (n=164) was -5.37 (-7.02, -3.73) in OASIS 1 and the difference between elinzanetant (n=171) and placebo (n=170) was -4.29 (-5.79, -2.80) in OASIS 2. In a sleep sub-study, numerical reduction in the mean wake after sleep onset time and numerical increases of mean sleep efficiency during elinzanetant 120 mg treatment were shown.

The **fourth key secondary endpoint** selected was change from baseline in frequency of moderate to severe HF at week 1.

The difference in LS means of elinzanetant vs placebo was statistically significant in both pivotal studies (OASIS 1 and OASIS 2)

A reduction in frequency in HF was seen as soon as 1 week after treatment start. For both studies this was statistically significant, and for OASIS 1 the clinical meaningful change of 2 HF compared to placebo was already achieved.

The **fifth key secondary endpoint** change in MENQOL total score from baseline to week 12, was selected to assess the presence of menopausal symptoms and the impact of menopause on health-related quality of life over the week. A decrease in the mean MENQOL total score of at least -0.87 at Week 12 was considered meaningful.

Although the difference in both treatment arms was statistically significant, it is noted that also in the placebo group a meaningful change in mean MENQOL total score is observed. Change over time shows the largest effect during the first 4 weeks in the elinzanetant group, which slowly decreases further until a plateau is

reached at 16 weeks. In the (former) placebo group, a comparable decrease to baseline – week 4 in the elinzanetant group is observed. The effect does not maintain after treatment stops after 26 weeks but remains below baseline values.

The results of all five key secondary endpoints support the results of the primary endpoints/ analysis. The subgroup analyses with respect to region, race, ethnicity, BMI, and smoking status, performed for the primary and key secondary analysis, suggested that none of these subgroups had an impact on the primary efficacy results of elinzanetant. In general, results obtained were consistent between groups, and between OASIS 1 and 2.

Other secondary endpoints suggested similar beneficial effects in favour of elinzanetant, in line with the findings in the primary analyses. In both OASIS 1 and OASIS 2, treatment with elinzanetant resulted in a larger decrease from baseline in mean frequency of moderate to severe VMS, compared with placebo as soon as the first measurement point after baseline (week 1), and continued to decrease until week 8, after which the decrease proceeded, although less pronounced.

With respect to the BDI-II total score (i.e. depressive symptoms), most participants had no or only minimal depression and no relevant differences at baseline or changes over time and between treatment arms were observed during week 1-12.

The beneficial effect of elinzanetant was also seen in the **exploratory endpoint,** the proportion of responders, i.e. ≥50% reduction in HF at week 4, week 12. In the elinzanetant group at week 4, 62% were responders, compared to ~30% in the placebo group, and further increased to 71-75% in the elinzanetant group and to 42-48% in the placebo group at 12 weeks. For those patients in the elinzanetant group who reached the responder status during the first 12 weeks, the median time to response was as soon as 3 weeks. It is noted that higher number of subjects initially randomised to placebo and switched to active treatment achieved responder status at Week 26, compared to subjects who were initially randomized to elinzanetant (84.5% vs 81.6%). Several (other) exploratory endpoints were assessed during the study. Specifically, the proportions of subjects with treatment response by 12 weeks was larger for elinzanetant 120 mg, with 79.9% versus 61.4% (OASIS 1) and 78.5% versus 58.5% (OASIS 2) of participants on elinzanetant 120 mg compared to placebo. Additionally, mean changes in the frequency of mild, moderate, and severe hot flashes, insomnia severity index scores, and sleep disturbances showed greater reductions in the elinzanetant group compared to placebo.

OASIS 3 – supportive long-term placebo-controlled efficacy and safety study

Design and conduct OASIS 3

OASIS 3 was a randomized, double-blind, placebo-controlled efficacy and safety study of 52 weeks. The study population, randomization and concomitant/ prohibited drugs are largely equal to OASIS 1 and 2. However, unlike OASIS 1and 2, no minimum daily number of moderate to severe hot flushes was defined. The absence of a minimum number of HF at baseline is not in line with the recommendations in the CHMP "*Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women*"(EMEA/CHMP/021/97 Rev. 1), i.e. a minimum of 5 moderate to severe HF per day. However, since OASIS 3 study is considered primarily a long-term safety, absence of a minimum number of HF is acceptable. Further, it is noted that in the proposed wording of the indication no minimum of VMS is included, neither in the indications for standard HRTs. A duration of 52 weeks of treatment is considered adequate, see safety section.

The **primary efficacy endpoint** was the mean change in daily frequency of moderate to severe HF from baseline to Week 12, while in OASIS 1 and 2 this was a primary endpoint of change at week 4 and week 12. No key secondary endpoints in OASIS3 were selected. The **secondary efficacy endpoints** are mean change in PROMIS SD SF 8b and MENQOL total scores over time. This is generally in line with the key secondary endpoints selected in OASIS 1 and 2. The **exploratory efficacy endpoints** are accepted, although they differ from the other OASIS studies.

Subgroup analyses were planned in line with OASIS 1 and 2. Furthermore, a subgroup analysis was planned for the number of moderate to severe HF at baseline (<35 and ≥35), which is acceptable, since a baseline value of 35 HFs is comparable to OASIS 4 (indication for AET) and can be considered the minimum number of HF following the Guideline on HRT.

Regarding the **statistical methods**, the estimands, treatment policy for all ICEs, and as alternative hypothetical in same cases were similar to OASIS 1 and 2. The calculation of the sample size (i.e. 600 participants, randomized 1:1 to elinzanetant and placebo) also used the same assumptions as for OASIS 1 and 2, with necessary adjustments for the longer duration of this study. This is all acceptable.

Efficacy data and additional analysis OASIS 3

A total of 1524 **participants** were screened, of which 628 were randomized (41%), 313 to elinzanetant and 315 to placebo. A total of 453 participants completed 52 weeks of treatment, 222 (71%) in the elinzanetant group and 231 (73%) in the placebo group. The **baseline demographic characteristics** are mostly well-balanced across study arms and largely comparable to those in OASIS 1 and 2.

At baseline, the mean daily number of moderate to severe HF was 6.7 for elinzanetant and 6.8 for placebo, lower compared to OASIS 1 and 2. However, this was expected, since there was no inclusion criterion concerning a minimum in the frequency of HF per day/week in OASIS 3.

Regarding the **primary efficacy endpoint,** of frequency of moderate to severe VMS from baseline to week 12, the LS mean (SD) from baseline was -4.89 (0.18) for elinzanetant and -3.34 (0.18) for placebo, which difference was statistically significant (LS mean (SE) of -1.55 (0.25) (95% CI: -2.04; -1.05). Therefore, the primary efficacy endpoint was met. Although a statistically significant difference was observed and a considerable decrease in HF frequency was found in the elinzanetant group, the clinically meaningful difference between placebo and active treatment group of an additional 2 HF per day was not reached in this study. Descriptive analysis of the mean change in frequency of moderate to severe HFs over time showed a continuous numerical decrease in both the elinzanetant 120 mg arm and the placebo arm from baseline until Week 24, being more pronounced on elinzanetant 120 mg compared to placebo at all time points. After Week 24, the mean values remained stable in both treatment arms until Week 50. Nevertheless, this difference, based on a relatively low number of HF at baseline compared to OASIS 1 and 2 is supportive for the beneficial effect found in these pivotal studies. The **secondary endpoints** (mean (SD) change in PROMIS SD SF 8b total T-scoreand MENQOL from baseline over time), are in line with the results from OASIS 1 and 2. The **exploratory endpoints**, change in frequency and severity of moderate to severe HF over time in general support the primary analysis.

Treatment of moderate to severe VMS caused by AET

Design and conduct of OASIS 4 (Part A + B)

The one pivotal study in support of the indication of treatment of VMS caused by AET, is a double-blind, randomized, placebo-controlled study of 12 weeks, followed by an extension of 13-52 weeks and optionally

for an additional 2 years. Part A (week 1-26) has been submitted with the initial application, Part B (week 27-52) has been submitted at day 120. The duration of placebo-controlled period of 12 weeks is in line with OASIS 1 and 2. The adequacy of the duration of in total 52 weeks is discussed in the safety section. As to efficacy, it is plausible that VMS caused by adjuvant endocrine therapy is comparable to VMS associated with natural menopause. Therefore, a single placebo-controlled period of 12 weeks is considered acceptable to support the efficacy in this second target population.

Concerning the **study population** of OASIS 4, women needed to be on stable background AET treatment with tamoxifen or aromatase inhibitors (with or without GnRH analogues) for least 6 weeks prior to baseline. This period of 6 weeks is acceptable with regard to tamoxifen, which has a large half-life of 7 days, indicating that steady-state will be reached after about 28-35 days. For one of the aromatase inhibitors, letrozole, steady-state is reached between 2 and 6 weeks. The requirement that women had to be stable on AET for at least 6 weeks before they could be included in the OASIS 4 study was of importance for a reliable assessment of efficacy that the number and intensity of hot flashes women experience under AET prior treatment with elinzanetant 120 mg were stable. Participants should have at least 35 moderate to severe HF (including night-time HF) over the last 7 days before baseline. This is a lower minimum compared to OASIS 1 and 2, in which 50 HF was the minimum. Nevertheless, the requirement from the HRT Guideline (see above) is 5 HF per day, meaning that 35 is at the lower end, but acceptable.

The studied population consisted of women with, or at high risk for developing, hormone receptor positive breast cancer. As hormonal therapy in the adjuvant setting is used only for breast cancer. This was specified in section 4.1 of the SmPC for clarity.

Eligible patients were randomly assigned 2:1 to receive **study treatment** of elinzanetant 120 mg or placebo. The 120 mg dose and once daily dose regimen is also applied in this target population.

The **two primary endpoints** (mean change in frequency of moderate to severe HF from baseline at Week 4 and Week 12) selected are comparable with OASIS 1 and 2. A hierarchical testing approach was applied, involving the two primary efficacy variables, and for the two key secondary variables, see below. The type I error was one sided at $\alpha=0.025$. This implies that mean change in frequency of HF from baseline at week 12 was only assessed if the difference at Week 4 was statistically significant. For a positive study outcome, both tests for primary variables needed to be significant. The **two key secondary endpoints** were mean change in the PRO PROMIS SD SF 8b total T-score (sleep disturbances) and the PRO MENQOL (menopause related quality of life) total score from baseline to week 12, which were also among the 5 key secondary endpoints selected in OASIS 1 and 2. These are included in the hierarchical testing procedure with the two primary endpoints. As both sleep disturbance and quality of life are related complaints accompanied with VMS, it is acknowledged that the inclusion of these endpoints could be supportive for the primary analysis. Severity of moderate to severe HF were included as **other secondary endpoints,** together with HF frequency from baseline to week 1, i.e. the other 3 key secondary endpoints from OASIS 1 and 2 and change frequency over time (also a secondary endpoint in OASIS 1 and 2). **Exploratory endpoints** among others included proportion of patients with at least 50% reduction in frequency of moderate to severe HF at week 4 and week 12 (i.e. responder analysis) and absolute values of sleep disturbances and quality of life. All these endpoints were in general comparable to the other studies. These are acceptable and agreed with.
Regarding the **statistical methods** of the study, the treatment policy estimand used for both the primary and secondary endpoints, to handle intercurrent events, and is the same as applied in OASIS 1 and 2. The randomization was to be stratified in women with hormone receptor positive breast cancer or at high-risk for developing breast cancer, the last group should be at max 10% of the participants. Treatment was also stratified by type of pre-existing treatment, i.e. tamoxifen (for premenopausal women) and aromatase

inhibitors (for postmenopausal women), both at least 40%, holding for both for breast cancer and at high-risk for developing breast cancer.

Efficacy data and additional analyses *OASIS 4*

Regarding **patient disposition**, a total of 758 participants were screened, 474 (62,5%) were randomized, n=316 elinzanetant and n=158 placebo. A total of 410 participants completed part A of the study (12 weeks placebo or elinzanetant, followed by treatment of 14 weeks with Elinzanetant). Part B consisting of an additional 26 weeks of treatment has been submitted at Day 120. Part C is currently on-going. During week 1-26, the number of patients completing part A is considered high 86-88% at 26 weeks. The main reasons for discontinuation in Part A were adverse events (8%) and subject decision (3.6%). Intercurrent events (permanent discontinuation or temporary interruption of study treatment, intake of prohibited concomitant medication having impact on efficacy or interruption/discontinuation in intake of AET), were low and did not significantly differ among both groups. Treatment compliance was based on diaries and confirmatory capsule counts during study visits. Treatment compliance was high with 97% in both groups. No confirmatory blood measurements were taken for treatment compliance.

The percentage of protocol deviations was relatively high, with overall 28.1%. Most common were in- and exclusion criteria that were not met but the subject entered treatment, and procedure deviations.

Generally, treatment arms were comparable regarding **demographic characteristics**, medical history, and prior and concomitant medication. However, it is noted that very limited number of patients above 65 years of age was included in the study, which is reflected in the SmPC. The type of AET was 55.4% and 57% for tamoxifen and 44.6% and 43% for aromatase inhibitors was comparable between elinzanetant and placebo group, respectively, as well as the type of aromatase inhibitor and the concomitant use of GnRH analogues. The median duration of AET treatment prior to study start was between 1.5 and 1.7 years. Although a maximum of 10% of women at high risk for breast cancer was planned to be included in the study, only one participant at risk for developing breast cancer has been included. Hysterectomy and oophorectomy/ ovariectomy was reported both arms in about 13%. 67.7% were women of non-childbearing potential (WONCBP) and 32.3% were women of childbearing potential (WOCBP).

Regarding the **primary analysis**, **2 primary efficacy endpoints** on the frequency of moderate to severe VMS from baseline to weeks 4 and 12 have been evaluated. At Week 4 and 12, the mean decrease in frequency of HF from baseline was statistically significantly greater for elinzanetant 120 mg compared to placebo.

For the **primary endpoint** frequency of moderate to severe HF from baseline to Week 4, the difference in LS means of elinzanetant vs placebo was statistically significant (LS mean (SE)) -3.48 (0.44; 95% CI: -4.35 to -2.61). For the **primary endpoint** frequency of moderate to severe HF from baseline to Week 12, the difference in LS means of elinzanetant vs placebo was statistically significant (LS mean (SE) of -3.38 (0.43; 95% CI: -4.21 to -2.54).

Therefore, both primary endpoints, on the mean change in the frequency of moderate to severe VMS from baseline to week 4 and week 12 were met. These findings were comparable to those in OASIS 1 and 2.

Key secondary endpoints. The results for both key secondary endpoints support the primary endpoints/ analysis. Regarding the mean change in PROMIS SD SF 8b total T-score from baseline to week 12, a greater reduction in LS mean (SE) in sleep disturbances was observed with elinzanetant (-10.06 (0.41)) versus placebo (-3.94 (0.57)) which difference (LS means) was statistically significant (-6.12 (0.70; CI 95%: -7.49, -4.75). The within-group clinically meaningful change (i.e. -7.19), see OASIS 1 and 2 for details, is reached

in the elinzanetant group. The change from baseline over time showed already a result after 1 one week of treatment, remaining largely stable from week 2 until week 12. Regarding the MENQOL total score from baseline to week 12, a greater reduction in LS mean (SE) in impact of VMS symptoms has been observed with elinzanetant (-1.23 (0.06)) versus placebo (-0.55 (0.08)), which difference in LS means was statistically significant (–0.68 (0.10; CI 95%: -0.88, -0.48). The within-group clinically meaningful change (i.e. -0.87) is reached in the elinzanetant group. The change over time shows the largest effect during the first 4 weeks in the elinzanetant group.

The outcomes of the **other secondary endpoints**, and exploratory endpoints are in support of the primary efficacy analysis. With respect to the severity of moderate to severe HFs, descriptive analysis demonstrated the decrease from baseline in the severity of moderate to severe HFs was numerically greater at Week 4 and Week 12 on elinzanetant 120 mg compared to placebo. At Week 4 the value was 1.76 (0.64) on elinzanetant 120 mg and 2.06 (0.49) on placebo. At Week 12, the value was 1.52 (0.75) on elinzanetant 120 mg and 1.96 (0.64) on placebo. The responder rate, which was 74.3% in the elinzanetant arm and 35.8% in the placebo arm at 12 weeks, and largely in line with the findings from OASIS studies 1 and 2.

The subgroup analyses with respect to region, race, ethnicity, BMI, smoking history for the primary and key secondary analysis, suggested that none of these subgroups had a relevant impact on the primary efficacy analysis. In general, results obtained were consistent between groups. However, there was a more pronounced decrease in frequency of HFs in the placebo arm of the aromatase inhibitor subgroup compared to the tamoxifen subgroup, while the decrease in the elinzanetant 120 mg arm was comparable in both subgroups. The elinzanetant vs placebo difference was only -1.55 for the aromatase inhibitors group compared to -5.06 for the tamoxifen group. A test for significance (although not prespecified) was requested. Boxplots for change from baseline in frequency of moderate to severe HF to week 12 by treatment group and adjuvant endocrine therapy are given (including two displays with and without outliers, respectively), and MMRM analysis. The test result showed no statistically significant difference in the treatment effect (LS-means (95% CI): -1.67 (-3.36, 0.01)) for change in frequency of HF from baseline to week 12, between women receiving aromatase inhibitors and those receiving tamoxifen.

2.6.7. Conclusions on the clinical efficacy

Concerning the indication 'VMS associated with menopause':

- Based on efficacy data set (based on OASIS 1, 2 and 3), a statistical significant and clinically relevant beneficial treatment effect of elinzanetant has been demonstrated as compared to placebo in terms of reduction in frequency of VMS at weeks 4 and 12. Also a relevant improvement over placebo in the five key secondary endpoints, i.e. severity of VMS at week 4 and at week 12, frequency at week 1 and the PRO's sleep disturbance and impact of menopause on health-related quality of life, was observed. The primary and key secondary efficacy outcomes were supported with positive trends in favour of elinzanetant in the other secondary endpoints on change in frequency over time and depression scores. Also, the exploratory endpoint, the 50% responder rate, was in favour of elinzanetant. In OASIS 3, efficacy in HF reduction was maintained for a treatment duration of 52 weeks. In conclusion, these study data support the claimed indication.

Concerning the indication 'VMS caused by adjuvant endocrine therapy (AET)':

- Based on the current submitted data of the ongoing OASIS 4, with an efficacy evaluation for up to 12 weeks of treatment, a statistical significant and clinically relevant beneficial treatment effect of elinzanetant has been demonstrated as compared to placebo in terms of frequency of VMS at weeks 4

and 12. Also, a relevant improvement over placebo in the two key secondary endpoints, i.e. the PRO's sleep disturbance and impact of menopause on health-related quality of life, was observed. The primary and key secondary efficacy outcomes were supported with positive trends in favour of elinzanetant in the other secondary endpoints on severity of VMS at week 4 and 12, change in frequency at week 1, change in frequency over time, and 50% responder rate (exploratory endpoint).

2.6.8. Clinical safety

Treatment of moderate to severe VMS associated with menopause

The long-term safety assessment of elinzanetant is primarily based on safety results from the 52-weeks placebo-controlled OASIS 3 study.

Additionally, supportive pooled safety analysis is provided including the following studies:

- Phase 2 study SWITCH-1 (elinzanetant 120 mg and placebo arms only)
- Phase 3 study OASIS 1
- Phase 3 study OASIS 2
- Phase 3 study OASIS 3

Rationale for pooling these studies is the overall similar study population, application of the intended dose and formulation of elinzanetant 120 mg. OASIS 1 and 2 have an initial placebo-controlled phase of 12 weeks, followed by an extension phase of 14 weeks, respectively. The SWITCH-1 study was a placebo-controlled with duration of 12 weeks.

Safety assessments based on the pooled analysis comprised TEAEs, laboratory parameters (including liver monitoring), vital signs, and physical examinations, mammogram, transvaginal ultrasound (TVU), endometrial biopsies, sleepiness scale, suicidal ideation and behaviour measured with Electronic Columbia Suicide Severity Rating Scale (eC-SSRS), and ECGs. Bone mineral density (BMD) was measured in OASIS 3 only.

Treatment of moderate to severe VMS caused by AET

The safety assessment of elinzanetant is based on the safety results from Parts A + B of the OASIS 4 study of 52 weeks duration in women aged 18 to 70 years with, or at high risk for developing hormone-receptor positive breast cancer. Part C of the OASIS 4 study (optional, 2 further years) is currently on-going, during which all women have the option to continue the treatment with elinzanetant 120 mg until the product may be approved and be available for regular prescription.

Safety assessments comprised TEAEs, clinical safety laboratory assessments (including liver monitoring), sleepiness scale, endometrial biopsies, TVU, breast imaging (mammogram/ ultrasound), vital signs, and physical examinations.

2.6.8.1. Patient exposure

Treatment of moderate to severe VMS associated with menopause

OASIS 3 – long-term placebo-controlled study of 52 weeks

In total, 627 women started treatment: 312 with elinzanetant and 315 with placebo. The 52-week treatment period was completed by 226 women (72.2%) in the elinzanetant arm and 232 women (73.7%) in the placebo arm. The most common reason for discontinuation was an AE, with higher proportion of women in the elinzanetant arm (12.5%) vs. placebo arm (4.1%).

Pooled safety analysis (SWITCH-1, OASIS 1, 2 and 3)

Across the 4 studies, 765 women started with elinzanetant and 754 women started with placebo. After 12 weeks, 348 women in OASIS 1 and 2 switched treatment from placebo to receive elinzanetant. Thus, a total of 1113 women from SWITCH-1 and OASIS 1- 3 studies were exposed to at least one dose of elinzanetant 120 mg. Due to different study designs, treatment duration varied across the 4 studies (12 weeks in SWITCH-1, 14 and 26 weeks in OASIS 1 and 2, and 52 weeks in OASIS 3). Of 1113 women exposed to elinzanetant:

- 966 women were treated with elinzanetant 120 mg for at least 12 weeks
- 575 women were treated with elinzanetant 120 mg for at least 23 weeks
- 219 women were treated with elinzanetant 120 mg for at least 50 weeks

Of the 1113 women treated with elinzanetant, 923 completed treatment as per protocol. Among those who discontinued early, an AE was the most frequent reason (7.5%), followed by subject decision (4.6%).

Treatment of moderate to severe VMS caused by AET

A total of 758 women were screened, of whom 474 were randomized in a 2:1 ratio and 473 were treated. 315 women started treatment with elinzanetant 120 mg, and 158 women started with placebo. After 12 weeks, 150 women from the placebo arm switched treatment to elinzanetant 120 mg. Thus, a total of 465 women received at least one dose of elinzanetant 120 mg during Week 1-52.

In total, 395 women completed the 52-week treatment period: 262 women (82.9%) in the elinzanetant 120 mg arm and 133 women (84.2%) in the placebo-elinzanetant 120 mg arm. The most common reasons for discontinuation of the study drug were AEs, with similar proportions of women in the two treatment arms (9.2% in the elinzanetant 120 mg arm and 8.2% in the placebo-elinzanetant 120 mg arm) and subject decision (5.1% in the elinzanetant 120 mg arm and 3.2% in the placebo-elinzanetant 120 mg arm).

Population

The treatment arms were generally well-balanced regarding demographics and other baseline characteristics. There were no relevant differences in age, ethnicity, race, weight, height or BMI. Most women in the SAF were White (88.2%), 1.5% were Black or African American, 0.6% were American Indian or Alaska Native and 0.4% were Asian. 2.5% of the women were of Hispanic or Latino by ethnicity. The overall mean (SD) age was 51.0 (7.3) years, and the overall mean (SD) BMI was 26.34 (4.60) kg/m^2. Majority of women (65.3%) never smoked.

All except for 1 woman (with a high risk for developing breast cancer) in the elinzanetant 120 mg arm had a medical history of breast cancer. Tamoxifen was used as an adjuvant endocrine therapy by 55.8% of all women and aromatase inhibitors by 44.2% of all women; the distribution was similar in the elinzanetant 120 mg and the placebo-elinzanetant 120 mg treatment arms. Mean (SD) duration of adjuvant endocrine therapy was 1.92 (1.46) years and was similar between treatment arms.

Medical history findings were similar between the treatment arms. In total, the most frequent medical history findings were hypertension (16.9%), arthralgia (13.1%), insomnia (10.8%), and depression (10.4%).

2.6.8.2. Adverse events

Treatment-emergent AEs (TEAEs) were defined as those that occurred or worsened on or after the first dose of study drug up to 14 days after the last dose of study drug. In the pooled safety population for the VMS associated with menopause (SWITCH-1, OASIS 1-3), the numbers of women with AEs are provided by treatment arm using MedDRA terms grouped by primary System Organ Class (SOC) and preferred term (PT) for the following types of AEs:

- Pre-treatment AEs and post-treatment AEs (i.e., occurring >14 days after end of study drug)
- TEAEs, Serious TEAEs, Study drug-related TEAEs, Study drug-related serious TEAEs. TEAE leading to discontinuation (including TEAEs assessed by the investigator as related to the study drug), TEAEs with fatal outcome
- AEs of special interest (AESI):
    - potential AESI liver event (any condition triggering close liver observation according to protocol results in true AESIs of liver events),
    - somnolence or fatigue,
    - phototoxicity,
    - postmenopausal uterine bleeding.

Additional analyses include TEAEs with heterogenous treatment effects between studies, risk difference and risk ratio of TEAEs with a relative frequency of at least 2% in any group (up to Week 12 only), and cumulative incidence of time to TEAEs.

Treatment of moderate to severe VMS associated with menopause

OASIS 3 – long-term placebo-controlled study of 52 weeks

Overall frequency of treatment emergent adverse events (TEAE)

As reflected in the table below, the percentage of participants with overall TEAEs [219 (70.0%) vs. 192 (61.1%)], TEAEs that were assessed by the investigator to be related to study intervention [95 (30.4%) vs. 46 (14.6%)], and TEAEs of special interest [53 (16.9%) vs. 35 (11.1%)] were higher in the elinzanetant arm compared to the placebo arm. In most participants, TEAEs were reported as mild or moderate in intensity. Serious TEAEs were reported were low in both treatment arms [13 (4.2%) vs. 6 (1.9%)]. None were assessed by the investigator as related to the study intervention. No deaths were reported. The number of TEAEs leading to permanent discontinuation was higher in the elinzanetant arm compared to the placebo arm [39 (12.5%) vs. 13 (4.1%)], of which 3 participants in the elinzanetant arm had a serious TEAE leading to permanent discontinuation.

Table 47 OASIS 3 - Treatment-emergent adverse events: overall summary (SAF)

	Elinzanetant 120 mg N=313 (100%)	Placebo N=314 (100%)
Number (%) of participants with TEAEs		
Any TEAE	219 (70.0%)	192 (61.1%)
Any study drug-related TEAE	95 (30.4%)	46 (14.6%)
Any TEAE related to procedures required by the protocol	7 (2.2%)	3 (1.0%)
Any TEAE leading to discontinuation of study drug	39 (12.5%)	13 (4.1%)
Any TEAE of special interest	53 (16.9%)	35 (11.1%)
Any serious TEAE	13 (4.2%)	6 (1.9%)

	Elinzanetant 120 mg N=313 (100%)	Placebo N=314 (100%)
Any study drug-related serious TEAE	0	0
Any serious TEAE related to procedures required by the protocol	0	0
Any serious TEAE leading to discontinuation of study drug	3 (1.0%)	0
TEAE with outcome death	0	0

SAF = safety analysis set, TEAE = treatment-emergent adverse event
For TEAEs of special interest, the following AEs are considered: potential AESI liver event (any condition triggering close liver observation according to protocol results in true AESIs of liver events. The frequencies shown in the table are beyond the protocol definition of the AESI.), somnolence or fatigue, phototoxicity, and postmenopausal uterine bleeding.

Most frequently reported TEAEs (5) by primary System Organ Class (SOC)

The primary SOCs with most frequently reported TEAEs in OASIS 3 are presented below.

Table 48 OASIS 3 - TEAEs: 5 most frequent primary SOCs in each treatment arm (SAF)

Primary System Organ Class MedDRA Version 26.1	Elinzanetant 120 mg N=313 (100%)	Placebo N=314 (100%)
Infections and infestations	95 (30.4%)	103 (32.8%)
Nervous system disorders	69 (22.0%)	37 (11.8%)
Gastrointestinal disorders	61 (19.5%)	57 (18.2%)
Musculoskeletal and connective tissue disorders	54 (17.3%)	40 (12.7%)
Investigations	45 (14.4%)	35 (11.1%)

MedDRA = Medical dictionary for regulatory activities, SAF = safety analysis set, SOC = System Organ Class, TEAE = treatment-emergent adverse event

TEAEs reported in ≥5% of patients by preferred Term (PT)

TEAEs reported in ≥5% of the participants by PT are presented below. Headache, fatigue, and somnolence were reported more frequently in the elinzanetant arm compared to the placebo arm, were Headache (9.6% on elinzanetant and 7.0% on placebo), Fatigue (6.7% on elinzanetant and 2.9% on placebo), and Somnolence (5.1% on elinzanetant and 1.3% on placebo).

Table 49 OASIS 3 - TEAEs reported in ≥5% of participants (any treatment arm) by PT (SAF)

Preferred term MedDRA version 26.1	Elinzanetant 120 mg N=313 (100%)	Placebo N=314 (100%)
Headache	30 (9.6%)	22 (7.0%)
COVID-19	22 (7.0%)	32 (10.2%)
Fatigue	21 (6.7%)	9 (2.9%)
Somnolence	16 (5.1%)	4 (1.3%)
Nasopharyngitis	15 (4.8%)	21 (6.7%)

MedDRA = Medical dictionary for regulatory activities, PT = preferred term, SAF = safety analysis set, TEAE = treatment-emergent adverse event

Pooled safety analysis (SWITCH-1, OASIS 1, 2 and 3)

Overall frequency of treatment emergent adverse events (TEAE)

Up to Week 12 (placebo-controlled phase)

During the first 12 weeks of treatment, women who received elinzanetant had higher incidences of TEAEs [389 (50.8%) vs. 326 (43.2%)], TEAEs assessed to be related to study drug by the investigator [173 (22.6%) vs. 81 (10.7%)], AESIs [84 (11.0%) vs. 34 (4.5%)], and TEAEs leading to discontinuation [60 (7.8% vs. 27 (3.6%)] compared to women who received placebo. Most of the TEAEs in both groups were

mild or moderate. The proportion of women with serious TEAEs was low [9 (1.2%) vs.7 (0.9%)], and none were assessed as related to the study drug or procedure by the investigator.

Table 50 Pooled safety population - Summary of TEAEs up to Week 12

Number of women with:	EZN 120 mg (Week 1-12) N=765 (100%)	Placebo (Week 1-12) N=754 (100%)	Risk difference (%) (95% CI)	Risk ratio (95% CI)
Any TEAE	**389 (50.8%)**	**326 (43.2%)**	**7.55 (2.56, 12.54)**	**1.17 (1.06, 1.31)**
Maximum intensity				
Mild	235 (30.7%)	188 (24.9%)	5.72 (1.24, 10.19)	1.23 (1.04, 1.45)
Moderate	132 (17.3%)	114 (15.1%)	2.15 (-1.55, 5.85)	1.14 (0.91, 1.44)
Severe	22 (2.9%)	24 (3.2%)	-0.31 (-2.03, 1.41)	0.90 (0.51, 1.60)
Drug-related TEAEs	**173 (22.6%)**	**81 (10.7%)**	**11.89 (8.20, 15.58)**	**2.10 (1.65, 2.69)**
Maximum intensity				
Mild	106 (13.9%)	43 (5.7%)	8.15 (5.20, 11.09)	2.43 (1.73, 3.41)
Moderate	59 (7.7%)	32 (4.2%)	3.49 (1.11, 5.87)	1.81 (1.19, 2.74)
Severe	8 (1.0%)	6 (0.8%)	0.27 (-0.75, 1.30)	1.32 (0.46, 3.78)
Procedure-related TEAEs	**5 (0.7%)**	**4 (0.5%)**	**0.14 (-0.68, 0.96)**	**1.20 (0.37, 3.91)**
Action taken with study drug				
Drug withdrawn	60 (7.8%)	27 (3.6%)	4.29 (1.97, 6.60)	2.17 (1.40, 3.37)
Drug interrupted	27 (3.5%)	19 (2.5%)	1.01 (-0.71, 2.73)	1.40 (0.78, 2.49)
Dose not changed	338 (44.2%)	296 (39.3%)	4.83 (-0.10, 9.76)	1.12 (1.00, 1.26)
Not applicable	10 (1.3%)	9 (1.2%)	0.10 (-1.02, 1.22)	1.09 (0.45, 2.65)
AEs of special interest (AESIs) [a)]	**84 (11.0%)**	**34 (4.5%)**	**6.48 (3.83, 9.14)**	**2.44 (1.66, 3.59)**
Any serious TEAE	**9 (1.2%)**	**7 (0.9%)**	**0.25 (-0.78, 1.27)**	**1.25 (0.48, 3.22)**
Drug-related	0	0		
Procedure-related	0	0		
Led to study drug discontinuation	4 (0.5%)	1 (0.1%)		
Action taken with serious TEAE				
Drug withdrawn	4 (0.5%)	1 (0.1%)		
Drug interrupted	3 (0.4%)	1 (0.1%)		
Dose not changed	2 (0.3%)	3 (0.4%)		
Not applicable	1 (0.1%)	3 (0.4%)		

CI = confidence interval, SAF = safety analysis set, TEAE = treatment-emergent adverse event
a) Potential liver event, somnolence or fatigue, phototoxicity, and postmenopausal uterine bleeding

TEAEs reported in ≥2% of patients by PT up to week 12 (placebo-controlled phase)

With regard to TEAEs reported in ≥2% of patients by PT somnolence, fatigue, dizziness, and headache were more frequently reported in the elinzanetant arm compared to placebo arm.

Table 51 Pooled safety population - TEAEs up to Week 12 by MedDRA PT with a relative frequency of ≥2% in any group (SAF, pooled safety population)

Preferred Term MedDRA Version 26.1	EZN 120 mg (Week 1-12) N=765 (100%)	Placebo (Week 1-12) N=754 (100%)	Risk difference (%) (95% CI)	Risk ratio (95% CI)
Headache	57 (7.5%)	32 (4.2%)	3.17 (0.83, 5.52)	1.74 (1.15, 2.66)
Fatigue	41 (5.4%)	10 (1.3%)	4.04 (2.25, 5.83)	3.91 (2.00, 7.64)
Somnolence	26 (3.4%)	4 (0.5%)	2.87 (1.48, 4.25)	5.78 (2.14, 15.57)
Arthralgia	23 (3.0%)	20 (2.7%)	0.33 (-1.33, 1.99)	1.12 (0.62, 2.03)
Dizziness	23 (3.0%)	8 (1.1%)	1.94 (0.53, 3.35)	2.73 (1.25, 5.96)
COVID-19	21 (2.7%)	25 (3.3%)	-0.58 (-2.42, 1.26)	0.84 (0.47, 1.48)
Depression rating scale score increased	21 (2.7%)	28 (3.7%)	-1.87 (-5.22, 1.48)	0.74 (0.43, 1.28)
Nausea	19 (2.5%)	14 (1.9%)	0.63 (-0.84, 2.09)	1.34 (0.68, 2.65)
Diarrhoea	16 (2.1%)	14 (1.9%)	0.20 (-1.19, 1.60)	1.11 (0.55, 2.24)

CI = confidence interval, MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, SAF = safety analysis set, TEAE = treatment-emergent adverse event
Mantel-Haenszel estimates stratified by study for risk difference and risk ratio are displayed.

Table 52 Study drug-related TEAEs up to Week 12 with a relative frequency of >1 woman in both groups (SAF, pooled safety population)

Preferred Term (PT) MedDRA Version 26.1	EZN 120 mg (Week 1-12) N=765 (100%)	Placebo (Week 1-12) N=754 (100%)
Fatigue	36 (4.7%)	5 (0.7%)
Headache	30 (3.9%)	12 (1.6%)
Somnolence	23 (3.0%)	3 (0.4%)
Dizziness	15 (2.0%)	6 (0.8%)
Nausea	12 (1.6%)	9 (1.2%)
Diarrhoea	11 (1.4%)	5 (0.7%)
Dry mouth	8 (1.0%)	3 (0.4%)
Dyspepsia	8 (1.0%)	6 (0.8%)
Constipation	6 (0.8%)	5 (0.7%)
Arthralgia	5 (0.7%)	3 (0.4%)
Alopecia	5 (0.7%)	3 (0.4%)
Abdominal distension	4 (0.5%)	2 (0.3%)
Depression rating scale score increased	4 (0.5%)	5 (0.7%)
Depression	3 (0.4%)	3 (0.4%)
Anxiety	2 (0.3%)	2 (0.3%)

See Definitions of terms for treatment groups description. CI = confidence interval, SAF = safety analysis set, TEAE = treatment-emergent adverse event

Up to Weeks 26 and 52 (extension phase with all patients on elinzanetant)
TEAE incidence rates per 100 person-years were comparable between women under elinzanetant and those under placebo treatment. Higher rates under elinzanetant than initially reported during under placebo treatment were observed in TEAEs assessed as related to the study drug by the investigator, as well as AESIs. Somnolence, fatigue and headache were the TEAEs with the largest difference.

Treatment of moderate to severe VMS caused by AET

OASIS 4, Part A placebo-controlled phase Weeks 1 to 12

Up to Week 12 (placebo-controlled phase)
As reflected in the table below, during Weeks 1-12, the percentage of participants with overall TEAEs [220 (69.8%) vs. 98 (62.0%)] and TEAEs assessed by the investigator to be related to study intervention [109 (34.6%) vs. 43 (27.2%)] were slightly higher in elinzanetant compared to placebo. The proportion of participants with TEAEs of special interest was higher on elinzanetant compared to placebo [81 (25.7%) vs. 18 (11.4%)]. In most participants, TEAEs were reported as mild or moderate in intensity.

Serious TEAEs were reported in a small number of participants [elinzanetant 8: (2.5%) vs. placebo: 1 (0.6%)]. Serious TEAEs that were assessed by the investigator as related to study intervention were reported in 2 participants in the elinzanetant arm. The number of TEAEs leading to permanent discontinuation was higher on elinzanetant compared to placebo during Weeks 1-12 [23 (7.3%) vs. 4 (2.5%)].

Table 53 OASIS 4 – Treatment-emergent adverse events: overall summary (SAF)

Number (%) of women	EZN 120 mg Wk 1-12 N=315 (100%)	PLC Wk 1-12 N=158 (100%)	EZN 120 mg Wk 13-26 N=294 (100%)	PLC - EZN 120 mg Wk 13-26 N=150 (100%)	EZN 120 mg Wk 1-26 N=465 (100%)	EZN 120 mg Wk 27-52 N=409 (100%)	EZN 120 mg Wk 1-52 N=465 (100%)
Any TEAE	220 (69.8%)	98 (62.0%)	154 (52.4%)	81 (54.0%)	333 (71.6%)	217 (53.1%)	368 (79.1%)
Study drug-related TEAE	109 (34.6%)	43 (27.2%)	36 (12.2%)	28 (18.7%)	154 (33.1%)	38 (9.3%)	171 (36.8%)
TEAE leading to study drug discontinuation	23 (7.3%)	4 (2.5%)	5 (1.7%)	6 (4.0%)	34 (7.3%)	3 (0.7%)	37 (8.0%)
AESI	81 (25.7%)	18 (11.4%)	28 (9.5%)	19 (12.7%)	120 (25.8%)	22 (5.4%)	133 (28.6%)
Serious TEAE	8 (2.5%)	1 (0.6%)	8 (2.7%)	4 (2.7%)	18 (3.9%)	18 (4.4%)	33 (7.1%)
Study drug-related serious TEAE	2 (0.6%)	0	1 (0.3%)	0	2 (0.4%)	0	2 (0.4%)
Serious TEAE leading to study drug discontinuation	2 (0.6%)	0	1 (0.3%)	1 (0.7%)	4 (0.9%)	1 (0.2%)	5 (1.1%)
TEAE with outcome death	0	0	0	0	0	0	0

See Definitions of terms for label descriptions. AESI = adverse event of special interest, defined in Section 2.1.2.4.1, EZN = elinzanetant, PLC = placebo, SAF = safety analysis set, TEAE = treatment-emergent adverse event, Wk = week Module 5.3.5.1, B003761 (OASIS 4),

Primary SOCs with most frequently reported TEAEs (placebo-controlled phase)

The primary SOCs with most (5) frequently reported TEAEs are presented below. In week 1-12, the SOCs Nervous system disorders, Gastrointestinal disorders, and General disorders and administration site conditions were more frequently reported on elinzanetant compared to placebo, see table below.

Table 54 OASIS 4 – TEAEs: 5 most frequent primary SOCs (in any group) (SAF)

Primary SOC MedDRA Version 27.1	EZN 120 mg Wk 1-12 N=315 (100%)	PLC Wk 1-12 N=158 (100%)	EZN 120 mg Wk 13-26 N=294 (100%)	PLC - EZN 120 mg Wk 13-26 N=150 (100%)	EZN 120 mg Wk 1-26 N=465 (100%)	EZN 120 mg Wk 27-52 N=409 (100%)	EZN 120 mg Wk 1-52 N=465 (100%)
Nervous system disorders	78 (24.8%)	34 (21.5%)	30 (10.2%)	17 (11.3%)	117 (25.2%)	30 (7.3%)	135 (29.0%)
Gastrointestinal disorders	69 (21.9%)	28 (17.7%)	30 (10.2%)	22 (14.7%)	108 (23.2%)	44 (10.8%)	131 (28.2%)
General disorders and administration site conditions	60 (19.0%)	12 (7.6%)	26 (8.8%)	14 (9.3%)	90 (19.4%)	22 (5.4%)	106 (22.8%)
Infections and infestations	59 (18.7%)	25 (15.8%)	51 (17.3%)	26 (17.3%)	120 (25.8%)	73 (17.8%)	164 (35.3%)
Musculoskeletal and connective tissue disorders	55 (17.5%)	27 (17.1%)	37 (12.6%)	25 (16.7%)	104 (22.4%)	61 (14.9%)	139 (29.9%)
Investigations	35 (11.1%)	20 (12.7%)	13 (4.4%)	7 (4.7%)	53 (11.4%)	21 (5.1%)	68 (14.6%)

EZN = elinzanetant, MedDRA = Medical dictionary for regulatory activities, PLC = placebo, SAF = Safety analysis set, SOC = System organ class, TEAE = Treatment-emergent adverse event, Wk = week Placebo - Elinzanetant 120 mg = placebo for 12 weeks, followed by elinzanetant 120 mg for 40 weeks. See Definitions of terms for label descriptions.

TEAEs reported in ≥2% of the participants by PT at week 12

TEAEs reported in ≥2% of the participants by PT are presented in the table below. In week 1-12, somnolence [34 (10.8%) vs. 6 (3.8%)], fatigue [30 (9.5%) vs. 8 (5.1%)], diarrhoea [16 (5.1%) vs. 3 (1.9%)], depression [14 (4.4%) vs. 1 (0.6%)], asthenia [13 (4.1%) vs. 2 (1.3%)], and dizziness [12 (3.8%) vs. 2 (1.3%)] were more frequently reported on elinzanetant compared to placebo, while Headache [30 (9.5%) vs. 20 (12.7%), insomnia [5 (1.6%) vs. 6 (3.8%)], and abdominal pain [8 (2.5%) vs. 5 (3.2%)] were more frequently reported on placebo compared to elinzanetant.

Table 55 OASIS 4 – TEAEs reported in ≥2% of the participants (in any group) by PT (SAF)

Preferred term (PT) MedDRA Version 27.1	EZN 120 mg Wk 1-12 N=315 (100%)	PLC Wk 1-12 N=158 (100%)	EZN 120 mg Wk 13-26 N=294 (100%)	PLC - EZN 120 mg Wk 13-26 N=150 (100%)	EZN 120 mg (Wk 1-26) N=465 (100%)	EZN 120 mg Wk 27-52 N=409 (100%)	EZN 120 mg Wk 1-52 N=465 (100%)
Somnolence	34 (10.8%)	6 (3.8%)	4 (1.4%)	5 (3.3%)	42 (9.0%)	1 (0.2%)	42 (9.0%)
Fatigue	30 (9.5%)	8 (5.1%)	7 (2.4%)	5 (3.3%)	41 (8.8%)	3 (0.7%)	43 (9.2%)
Headache	30 (9.5%)	20 (12.7%)	13 (4.4%)	7 (4.7%)	48 (10.3%)	11 (2.7%)	56 (12.0%)
Depression rating scale score increased	21 (6.7%)	13 (8.2%)	1 (0.3%)	0	22 (4.7%)	2 (0.5%)	24 (5.2%)
Arthralgia	20 (6.3%)	10 (6.3%)	19 (6.5%)	6 (4.0%)	42 (9.0%)	15 (3.7%)	52 (11.2%)
Nausea	19 (6.0%)	10 (6.3%)	6 (2.0%)	5 (3.3%)	28 (6.0%)	3 (0.7%)	29 (6.2%)
Diarrhoea	16 (5.1%)	3 (1.9%)	6 (2.0%)	4 (2.7%)	25 (5.4%)	7 (1.7%)	32 (6.9%)
Depression	14 (4.4%)	1 (0.6%)	7 (2.4%)	2 (1.3%)	23 (4.9%)	5 (1.2%)	27 (5.8%)
Asthenia	13 (4.1%)	2 (1.3%)	7 (2.4%)	3 (2.0%)	22 (4.7%)	5 (1.2%)	26 (5.6%)
Dizziness	12 (3.8%)	2 (1.3%)	4 (1.4%)	1 (0.7%)	16 (3.4%)	4 (1.0%)	19 (4.1%)
Nasopharyngitis	12 (3.8%)	5 (3.2%)	9 (3.1%)	8 (5.3%)	28 (6.0%)	9 (2.2%)	37 (8.0%)
Back pain	10 (3.2%)	7 (4.4%)	5 (1.7%)	2 (1.3%)	16 (3.4%)	14 (3.4%)	29 (6.2%)
Pyrexia	10 (3.2%)	2 (1.3%)	5 (1.7%)	1 (0.7%)	15 (3.2%)	6 (1.5%)	20 (4.3%)
Dyspepsia	9 (2.9%)	5 (3.2%)	1 (0.3%)	0	10 (2.2%)	4 (1.0%)	13 (2.8%)
Abdominal pain	8 (2.5%)	5 (3.2%)	1 (0.3%)	0	9 (1.9%)	0	9 (1.9%)
Depressed mood	8 (2.5%)	2 (1.3%)	5 (1.7%)	1 (0.7%)	14 (3.0%)	5 (1.2%)	19 (4.1%)
Urinary tract infection	8 (2.5%)	2 (1.3%)	4 (1.4%)	3 (2.0%)	14 (3.0%)	7 (1.7%)	17 (3.7%)
Muscle spasms	7 (2.2%)	3 (1.9%)	4 (1.4%)	3 (2.0%)	14 (3.0%)	6 (1.5%)	19 (4.1%)
Influenza	6 (1.9%)	2 (1.3%)	4 (1.4%)	3 (2.0%)	13 (2.8%)	6 (1.5%)	18 (3.9%)
Abdominal pain upper	5 (1.6%)	6 (3.8%)	4 (1.4%)	3 (2.0%)	11 (2.4%)	5 (1.2%)	14 (3.0%)
Constipation	5 (1.6%)	3 (1.9%)	4 (1.4%)	0	9 (1.9%)	1 (0.2%)	10 (2.2%)
Hypertension	5 (1.6%)	4 (2.5%)	7 (2.4%)	1 (0.7%)	13 (2.8%)	5 (1.2%)	18 (3.9%)
Insomnia	5 (1.6%)	6 (3.8%)	0	2 (1.3%)	7 (1.5%)	2 (0.5%)	8 (1.7%)
Pain in extremity	5 (1.6%)	4 (2.5%)	3 (1.0%)	4 (2.7%)	12 (2.6%)	1 (0.2%)	13 (2.8%)
Vertigo	5 (1.6%)	0	0	2 (1.3%)	7 (1.5%)	4 (1.0%)	10 (2.2%)
Alopecia	4 (1.3%)	1 (0.6%)	6 (2.0%)	2 (1.3%)	12 (2.6%)	3 (0.7%)	15 (3.2%)
Bronchitis	4 (1.3%)	2 (1.3%)	0	1 (0.7%)	5 (1.1%)	6 (1.5%)	11 (2.4%)
COVID-19	4 (1.3%)	4 (2.5%)	9 (3.1%)	4 (2.7%)	17 (3.7%)	13 (3.2%)	30 (6.5%)
Gastrooesophageal reflux disease	4 (1.3%)	4 (2.5%)	3 (1.0%)	5 (3.3%)	11 (2.4%)	5 (1.2%)	16 (3.4%)
Neck pain	4 (1.3%)	2 (1.3%)	5 (1.7%)	1 (0.7%)	10 (2.2%)	1 (0.2%)	11 (2.4%)
Cough	3 (1.0%)	0	6 (2.0%)	1 (0.7%)	10 (2.2%)	5 (1.2%)	15 (3.2%)
Myalgia	3 (1.0%)	1 (0.6%)	2 (0.7%)	4 (2.7%)	9 (1.9%)	5 (1.2%)	14 (3.0%)
Vaginal haemorrhage	3 (1.0%)	0	3 (1.0%)	2 (1.3%)	8 (1.7%)	7 (1.7%)	14 (3.0%)
Breast pain	2 (0.6%)	1 (0.6%)	3 (1.0%)	1 (0.7%)	6 (1.3%)	5 (1.2%)	10 (2.2%)
Hot flush	2 (0.6%)	1 (0.6%)	1 (0.3%)	2 (1.3%)	5 (1.1%)	9 (2.2%)	14 (3.0%)
Gamma-glutamyltransferase increased	1 (0.3%)	1 (0.6%)	1 (0.3%)	3 (2.0%)	5 (1.1%)	2 (0.5%)	7 (1.5%)
Sleep disorder	0	1 (0.6%)	1 (0.3%)	3 (2.0%)	4 (0.9%)	1 (0.2%)	5 (1.1%)

See Definitions of terms for label descriptions. EZN = elinzanetant, MedDRA = Medical dictionary for regulatory activities, PLC = placebo, PT = Preferred term, SAF = Safety analysis set, TEAE = Treatment-emergent adverse event, Wk = week.

TEAEs (≥2%) assessed by the investigator as related to the study intervention (Week 1-12)

TEAEs (≥2%) assessed by investigator as related to the study intervention were somnolence and fatigue, nausea, and diarrhoea on elinzanetant and headache and depression rating scale score increased on placebo.

Table 56 Study intervention-related TEAEs reported in ≥2% of the participants (in any group) by PT (SAF) (Table 5–9 CSR)

PT MedDRA Version 27.1	EZN 120 mg Wk 1-12 N=315 (100%)	PLC Wk 1-12 N=158 (100%)	EZN 120 mg Wk 13-26 N=294 (100%)	PLC - EZN 120 mg Wk 13-26 N=150 (100%)	EZN 120 mg Wk 1-26 N=465 (100%)	EZN 120 mg Wk 27-52 N=409 (100%)	EZN 120 mg Wk 1-52 N=465 (100%)
Somnolence	28 (8.9%)	6 (3.8%)	3 (1.0%)	5 (3.3%)	35 (7.5%)	1 (0.2%)	35 (7.5%)
Fatigue	26 (8.3%)	5 (3.2%)	4 (1.4%)	2 (1.3%)	31 (6.7%)	0	31 (6.7%)
Nausea	14 (4.4%)	4 (2.5%)	3 (1.0%)	4 (2.7%)	20 (4.3%)	2 (0.5%)	21 (4.5%)
Headache	13 (4.1%)	11 (7.0%)	2 (0.7%)	2 (1.3%)	16 (3.4%)	3 (0.7%)	19 (4.1%)
Diarrhoea	9 (2.9%)	0	1 (0.3%)	1 (0.7%)	11 (2.4%)	2 (0.5%)	13 (2.8%)
Depression rating scale score increased	8 (2.5%)	6 (3.8%)	0	0	8 (1.7%)	1 (0.2%)	9 (1.9%)
Abdominal pain upper	5 (1.6%)	2 (1.3%)	1 (0.3%)	2 (1.3%)	7 (1.5%)	4 (1.0%)	11 (2.4%)
Alopecia	4 (1.3%)	1 (0.6%)	3 (1.0%)	2 (1.3%)	9 (1.9%)	2 (0.5%)	11 (2.4%)

MedDRA = Medical dictionary for regulatory activities, PT = Preferred term, SAF = Safety analysis set, TEAE = Treatment-emergent adverse event Placebo - Elinzanetant 120 mg = Placebo for 12 weeks, followed by elinzanetant 120 mg for 40 weeks.

2.6.8.2.1. AEs of special interest (AESI)

In the OASIS 1-4 studies, the following were defined as AESI, based on non-clinical or clinical experience, if the event took place after the first intake of study drug:

- Any condition triggering close liver observation (CLO) (i.e., ALT and/or AST ≥3 x ULN or AP ≥2 x ULN and confirmed at retest),
- Somnolence or fatigue,
- Phototoxicity,
- Postmenopausal uterine bleeding.

In the SWITCH-1 study, only postmenopausal uterine bleeding was defined as AESI. However, other AESIs from the SWITCH-1 study as defined in OASIS 1-4 studies are included in the pooled safety analysis based on the preferred terms (PTs).

Treatment of moderate to severe VMS associated with menopause

Liver event

In the OASIS 1-3 studies, liver safety was monitored through AE reporting and AESI, (defined as any condition triggering CLO, specific liver laboratory parameters, and CLO based on reaching predefined thresholds of specific liver laboratory parameters according to FDA guidance (FDA July 2009). Prior to the start of the studies an independent external liver safety monitoring board (LSMB) was installed, who assessed all CLO cases independently in a blinded fashion.

OASIS 3 – long-term study

Close liver observation (CLO)

At screening, liver enzymes and bilirubin values for all participants met the eligibility criteria (exclusion criterion: abnormal liver parameters (AST, ALT or AP > 2xULN, or TBL or INR>ULN).

Elevated post-baseline values of ALT/AST ≥ 3 x ULN were observed in 7 (2.3%) participants in the elinzanetant arm and 6 (2.0%) participants in the placebo arm. A potential AESI of liver event based on the pre-defined Standardized MedDRA Query was reported in 7 (2.2%) participants in the elinzanetant 120 mg arm and 12 (3.8%) participants in the placebo arm.

Table 57 Potential TEAE of special interest– liver event: number of subjects by primary SOC and PT (SAF)

Primary System Organ Class Preferred Term MedDRA Version 26.1	Elinzanetant 120mg N=313 (100%)	Placebo N=314 (100%)
Number (%) of subjects with at least one such adverse event	7 (2.2%)	12 (3.8%)
Hepatobiliary disorders	0	1 (0.3%)
Cholestasis	0	1 (0.3%)
Investigations	7 (2.2%)	11 (3.5%)
Alanine aminotransferase increased	5 (1.6%)	4 (1.3%)
Aspartate aminotransferase increased	1 (0.3%)	4 (1.3%)
International normalised ratio increased	1 (0.3%)	2 (0.6%)
Liver function test abnormal	1 (0.3%)	1 (0.3%)
Alanine aminotransferase abnormal	0	1 (0.3%)
Aspartate aminotransferase abnormal	0	1 (0.3%)
Gamma-glutamyltransferase increased	0	2 (0.6%)
Hepatic enzyme increased	0	1 (0.3%)
Liver function test increased	0	1 (0.3%)
Prothrombin time prolonged	0	1 (0.3%)

The protocol-defined criteria triggering CLO were confirmed in the re-test and reported for 6 participants in the elinzanetant arm and 4 participants in the placebo arm. Causality to study intervention was assessed as possible for 1 case in the elinzanetant arm and probable for 1 case in the placebo arm by the LSMB. In total, 1 case in the elinzanetant arm and 2 cases in the placebo arm met the liver injury criteria as assessed by the LSMB see table below.

Table 58 Number of subjects meeting close liver observation and assessment by liver safety monitoring board (safety analysis set)

		Elinzanetant 120mg (N=313)	Placebo (N=314)
Case Met Close Liver Observation	n	6 (1.9%)	4 (1.3%)
Case Met Liver Injury Criteria	No	5 (83.3%)	2 (50.0%)
	Yes	1 (16.7%)	2 (50.0%)
	Missing	0	0

n = the number of subjects meeting close liver observation criteria as per Table 10-2 of the protocol
Percentage for Case Met Close Liver Observation is based on total number of subjects (N), percentage for Cases Met Liver Injury Criteria is based on total number of Case Met Close Liver Observation (n).

Somnolence or fatigue

Note: In the studies OASIS 1-3 and SWITCH-1, women took the study drug at bedtime and were instructed neither to drive nor operate machinery if they experienced somnolence or fatigue.

Somnolence or fatigue were reported more frequently in the elinzanetant arm compared to the placebo arm. None of the events were assessed as serious or severe. The difference was mostly driven by the higher number of participants with fatigue (PT) and somnolence (PT).

Somnolence or fatigue was assessed as related to study intervention by the investigator as follows:

- Fatigue (PT): 13 participants on elinzanetant and 5 participants on placebo
- Somnolence (PT): 15 participants on elinzanetant and 3 participants on placebo

Asthenia (PT) events that were reported in 2 participants in the elinzanetant 120 mg arm were assessed as unrelated to study intervention by the investigator.

Table 59 OASIS 3 - Treatment-emergent AESIs - somnolence or fatigue: number of participants by primary SOC and PT (SAF)

Primary SOC **Preferred term** **MedDRA version 26.1**	**Elinzanetant 120 mg N=313 (100%)**	**Placebo N=314 (100%)**
Number (%) of participants with at least one such TEAE	**37 (11.8%)**	**12 (3.8%)**
General disorders and administration site conditions:	23 (7.3%)	9 (2.9%)
Fatigue	21 (6.7%)	9 (2.9%)
Asthenia	2 (0.6%)	0
Nervous system disorders:	16 (5.1%)	4 (1.3%)
Somnolence	16 (5.1%)	4 (1.3%)

AESI = adverse events of special interest, MedDRA = Medical dictionary for regulatory activities, PT = preferred term, SAF = safety analysis set, SOC = system organ class, TEAE = treatment-emergent adverse event. A participant is counted only once within each primary SOC and preferred term.

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 234-fold the Cmax at the human therapeutic dose. These effects were not observed at a concentration of 73-fold the Cmax at the human therapeutic dose. The number of participants reporting phototoxicity was small (2 participants on elinzanetant and 1 participant on placebo). None of the events were assessed as serious or severe. For 1 participant in the elinzanetant arm and 1 participant in the placebo arm, the phototoxicity event was assessed as related to the study intervention by the investigator. The observed cases of mild to moderate photosensitivity mostly resolved spontaneously during ongoing treatment with elinzanetant.

Postmenopausal uterine bleeding

The number of participants reporting postmenopausal uterine bleeding was small (8/225 participants with an intact uterus in the elinzanetant arm and 11/221 participants with an intact uterus in the placebo arm). None of the events were assessed as serious. 1 participant in the elinzanetant arm had a vaginal haemorrhage assessed as severe by the investigator. Postmenopausal uterine bleeding was assessed as related to study intervention by the investigator as follows:

- Postmenopausal haemorrhage (PT): 3 participants on elinzanetant and 2 participants on placebo
- Vaginal haemorrhage (PT): 2 participants on elinzanetant and 1 participant on placebo
- Uterine haemorrhage (PT): 1 participant on elinzanetant

Table 60 OASIS 3 - Treatment-emergent AESIs - postmenopausal uterine bleeding: number of participants by primary SOC and PT (SAF)

Primary SOC Preferred term MedDRA version 26.1	**Elinzanetant 120 mg N=225 (100%)**	**Placebo N=221 (100%)**
Number (%) of participants with at least one such TEAE	**8 (3.6%)**	**11 (5.0%)**
Reproductive system and breast disorders:	8 (3.6%)	11 (5.0%)
Postmenopausal haemorrhage	5 (2.2%)	7 (3.2%)
Vaginal haemorrhage	4 (1.8%)	2 (0.9%)
Uterine haemorrhage	1 (0.4%)	1 (0.5%)
Coital bleeding	0	1 (0.5%)

AESI = adverse events of special interest, MedDRA = Medical dictionary for regulatory activities, PT = preferred term, SAF = safety analysis set, SOC = system organ class, TEAE = treatment-emergent adverse event.
A participant is counted only once within each primary SOC and preferred term.

N = number of participants with uterus.

In addition to the postmenopausal uterine bleeding AESIs described above, 1 intermenstrual bleeding (PT) was reported (reported term: "ovulation bleeding") in 1 participant in the elinzanetant arm, assessed as unrelated to the study intervention by the investigator.

Pooled safety analysis (SWITCH 1, OASIS 1, OASIS 2, OASIS 3)

Week 1-12

In Week 1-12, the difference in the overall incidence of AESIs between women treated with elinzanetant and placebo during the first 12 weeks (11.0% vs 4.5%) was mainly driven by the AESI somnolence or fatigue. AESIs potential liver event occurred in similar proportions of women in the two groups. The incidence of postmenopausal uterine bleeding considered drug-related was higher in the elinzanetant arm than in the placebo arm [9 (1.8%) vs.1 (0.2%)]. Phototoxicity was reported for 2 women (both in the elinzanetant 120 mg group), of which 1 was assessed as study drug-related by the investigator, and led to discontinuation.

Table 61 Pooled safety population - Summary of AESIs up to Week 12 (SAF, pooled safety population)

AESI grouping	Elinzanetant 120 mg (Week 1-12) N=765 (100%) n (%) / IR (100 py) [a)]	Placebo (Week 1-12) N=754 (100%) n (%) / IR (100 py) [a)]
Potential liver event		
Any event	9 (1.2%) / 5.25	9 (1.2%) / 5.32
Study drug-related	3 (0.4%) / 1.76	3 (0.4%) / 1.75
Leading to discontinuation	1 (0.1%) / 0.59	1 (0.1%) / 0.58
Serious	0	0
Somnolence or fatigue		
Any event	66 (8.6%) / 41.26	15 (2.0%) / 8.98
Study drug-related	58 (7.6%) / 36.08	8 (1.1%) / 4.74
Leading to discontinuation	14 (1.8%) / 8.26	0
Serious	0	0
Phototoxicity		
Any event	2 (0.3%) / 1.15	0
Study drug-related	1 (0.1%) / 0.57	0
Leading to discontinuation	0	0
Serious	0	0
Postmenopausal uterine bleeding		
Number of women with intact uterus	512 (100%)	495 (100%)
Any event	11 (2.1%) / 9.71	10 (2.0%) / 9.00
Study drug-related	9 (1.8%) / 7.99	1 (0.2%) / 0.88
Leading to discontinuation	1 (0.2%) / 0.88	0
Serious	0	0

AESI = adverse events of special interest, SAF = safety analysis set
a) IR (100 py) = incidence rate per 100 person-years

The same pattern was seen in AESIs reported during the 26-week and 52-week periods. No serious AESIs were reported at any time point.

Table 62 Pooled safety population - Summary of AESIs up to Weeks 26 and 52 (SAF, pooled safety population)

	Week 1–26		Week 1–52	
AESI grouping	EZN 120 mg N=1113 (100%)	Placebo N=754 (100%)	EZN 120 mg N=1113 (100%)	Placebo N=754 (100%)
Number of women	n (%) / IR (100 py)[a)]	n (%) / IR (100 py)[a)]	n (%) / IR (100 py)[a)]	n (%) / IR(100 py)[a)]
Potential liver event				
Any event	14 (1.3%) / 3.35	11 (1.5%) / 3.61	16 (1.4%) / 2.89	13 (1.7%) / 3.10
Study drug-related	6 (0.5%) / 1.38	3 (0.4%) / 0.88	6 (0.5%) / 1.01	4 (0.5%) / 0.87
Leading to discontinuation	1 (<0.1%) / 0.30	2 (0.3%) / 0.58	1 (<0.1%) / 0.22	2 (0.3%) / 0.43
Serious	0	0	0	0
Somnolence or fatigue				
Any event	78 (7.0%) / 20.32	17 (2.3%) / 8.10	80 (7.2%) / 15.42	22 (2.9%) / 7.07
Study drug-related	62 (5.6%) / 15.85	10 (1.3%) / 4.30	62 (5.6%) / 11.61	11 (1.5%) / 3.38
Leading to discontinuation	14 (1.3%) / 3.36	0	14 (1.3%) / 2.45	0
Serious	0	0	0	0
Phototoxicity				
Any event	4 (0.4%) / 0.88	0	5 (0.4%) / 0.86	1 (0.1%) / 0.22
Study drug-related	2 (0.2%) / 0.39	0	3 (0.3%) / 0.50	1 (0.1%) / 0.22
Leading to discontinuation	0	0	1 (<0.1%) / 0.22	0
Serious	0	0	0	0
Postmenopausal uterine bleeding				
Number of women with intact uterus	726 (100%)	495 (100%)	726 (100%)	495 (100%)
Any event	14 (1.9%) / 5.38	11 (2.2%) / 7.00	15 (2.1%) / 4.17	15 (3.0%) / 6.35
Study drug-related	10 (1.4%) / 3.76	1 (0.2%) / 0.44	10 (1.4%) / 2.67	3 (0.6%) / 0.96

Leading to discontinuation	2 (0.3%) / 0.74	0	2 (0.3%) / 0.53	0
Serious	0	0	0	0

AESI = adverse events of special interest, SAF = safety analysis set

a) IR (100 py) = incidence rate per 100 person-years. IRs are study size adjusted incidence rates according to Crowe et al (2016).

Switchers from OASIS 1 and 2 are included in all groups but the event is assigned only to the treatment they received when the event started.

Somnolence or fatigue

During week 1-12, the incidence of somnolence and fatigue was 66 (8.6%) in the elinzanetant arm vs. 15 (2.0%) in the placebo arm. The majority of the events occurred during the first two weeks of treatment, were mild or moderate and resolved.

Liver event (any condition triggering close liver observation (CLO))

During week 1-12, no numerical differences between elinzanetant and placebo were observed in AE reporting and AESI (any condition triggering CLO). In addition, no clear differences were observed from baseline between elinzanetant 120 mg and placebo for specific liver laboratory parameters, see tables below.

Up to week 12, ALT or AST elevations of ≥3 x ULN were observed in 0.5% of participants treated with elinzanetant 120 mg (4 of 755 participants who had measurements of transaminases) and in 0.4% of participants treated with placebo (3 of 735 participants who had measurements of transaminases). There were no AST or ALT elevations ≥5 x ULN or total bilirubin elevations ≥2 x ULN across the treatment groups. ALP elevations were comparable between both treatment groups (ALP ≥2 x ULN were observed in 0.1% of participants treated with elinzanetant 120 mg (1 of 755 participants) and in 0.3% of participants treated with placebo (2 of 735 participants). None of the participants had elevations of total bilirubin elevations ≥2 x ULN.

Table 63 Number of subjects and study size and exposure-adjusted incidence rate by cumulative hepatic safety laboratory parameter category up to week 12 (pooled studies (SWITCH-1, OASIS 1, 2, and 3).

Parameter		EZN 120 mg (week 1-12) (N=765) n (%)	IR* (100 py)	Placebo (week 1-12) (N=754) n (%)	IR* (100 py)
ALT	n	753 (100.0%)		735 (100.0%)	
	Category				
	>=1 x ULN	129 (17.1%)	73.73	172 (23.4%)	108.29
	>=3 x ULN	3 (0.4%)	1.54	2 (0.3%)	1.10
	>=5 x ULN	0		0	
	>=8 x ULN	0		0	
	>=10 x ULN	0		0	
	>=20 x ULN	0		0	
AST	n	755 (100.0%)		735 (100.0%)	
	Category				
	>=1 x ULN	82 (10.9%)	44.75	107 (14.6%)	63.22
	>=3 x ULN	3 (0.4%)	1.54	1 (0.1%)	0.55
	>=5 x ULN	0		0	
	>=8 x ULN	0		0	
	>=10 x ULN	0		0	
	>=20 x ULN	0		0	
ALT or AST	n	755 (100.0%)		735 (100.0%)	
	Category				
	>=3 x ULN	4 (0.5%)	2.05	3 (0.4%)	1.65
	>=5 x ULN	0		0	
	>=8 x ULN	0		0	
	>=10 x ULN	0		0	
	>=20 x ULN	0		0	
Total bilirubin	n	753 (100.0%)		735 (100.0%)	
	Category				
	>=1 x ULN	24 (3.2%)	12.58	17 (2.3%)	9.43
	>=2 x ULN	0		0	
	>=5 x ULN	0		0	
	>=8 x ULN	0		0	
ALP	n	755 (100.0%)		735 (100.0%)	
	Category				
	>=1.5 x ULN	6 (0.8%)	3.10	11 (1.5%)	6.09
	>=2 x ULN	1 (0.1%)	0.50	2 (0.3%)	1.12
	>=3 x ULN	1 (0.1%)	0.50	0	
INR	n	703 (100.0%)		688 (100.0%)	
	Category				
	>=1.5	5 (0.7%)	2.83	8 (1.2%)	4.80
	>=2	2 (0.3%)	1.13	3 (0.4%)	1.80

n = number of subjects with parameter assessment done at respective time point. Unscheduled visits were included in the analysis. ULN = Upper Limit of Normal. AST = Aspartate Aminotransferase, ALT = Alanine Transferase, ALP = Alkaline Phosphatase, INR = International Normalized Ratio, py = person years, SAF = safety analysis set. Results are provided per 100 person-years, where one person-year is defined as 365.25 days. *IRs are study size and exposure adjusted incidence rates according to Crowe et al (2016).

Table 64 Number of women by cumulative hepatic safety laboratory parameter category (SAF, pooled safety analysis) (pooled studies (SWITCH-1, OASIS 1, 2, and 3) (Table 2-12 safety summary)

	Week 1-12		Week 1-26		Week 1-52	
Any time post-baseline	EZN 120 mg N=765	Placebo N=754	EZN 120 mg N=1113	Placebo-EZN N=754	EZN 120 mg N=1113	Placebo-EZN N=754
ALT						
n	753 (100.0%)	735 (100.0%)	1098 (100.0%)	735 (100.0%)	1098 (100.0%)	735 (100.0%)
≥1 ULN	129 (17.1%)	172 (23.4%)	229 (20.9%)	196 (26.7%)	253 (23.0%)	219 (29.8%)
≥3 ULN	3 (0.4%)	2 (0.3%)	10 (0.9%)	4 (0.5%)	13 (1.2%)	6 (0.8%)
≥5 ULN	0	0	1 (<0.1%)	1 (0.1%)	2 (0.2%)	2 (0.3%)
≥8 ULN	0	0	0	1 (0.1%)	1 (<0.1%)	1 (0.1%)
≥10 ULN	0	0	0	0	0	0
AST						
n	755 (100.0%)	735 (100.0%)	1100 (100.0%)	735 (100.0%)	1100 (100.0%)	735 (100.0%)
≥1 ULN	82 (10.9%)	107 (14.6%)	155 (14.1%)	122 (16.6%)	176 (16.0%)	137 (18.6%)
≥3 ULN	3 (0.4%)	1 (0.1%)	4 (0.4%)	2 (0.3%)	5 (0.5%)	4 (0.5%)
≥5 ULN	0	0	0	1 (0.1%)	0	1 (0.1%)
≥8 ULN	0	0	0	1 (0.1%)	0	1 (0.1%)
≥10 ULN	0	0	0	0	0	0
ALT or AST						
n	755 (100.0%)	735 (100.0%)	1100 (100.0%)	735 (100.0%)	1100 (100.0%)	735 (100.0%)
≥3 ULN	4 (0.5%)	3 (0.4%)	10 (0.9%)	4 (0.5%)	13 (1.2%)	7 (1.0%)
≥5 ULN	0	0	1 (<0.1%)	1 (0.1%)	2 (0.2%)	2 (0.3%)
≥8 ULN	0	0	0	1 (0.1%)	1 (<0.1%)	1 (0.1%)
≥10 ULN	0	0	0	0	0	0
Total bilirubin						
n	753 (100.0%)	735 (100.0%)	1098 (100.0%)	735 (100.0%)	1098 (100.0%)	735 (100.0%)
≥1 ULN	24 (3.2%)	17 (2.3%)	39 (3.6%)	18 (2.4%)	40 (3.6%)	19 (2.6%)
≥2 ULN	0	0	1 (<0.1%)	0	1 (<0.1%)	0
≥5 ULN	0	0	0	0	0	0
AP						
n	755 (100.0%)	735 (100.0%)	1100 (100.0%)	735 (100.0%)	1100 (100.0%)	735 (100.0%)
≥1.5 ULN	6 (0.8%)	11 (1.5%)	19 (1.7%)	13 (1.8%)	22 (2.0%)	16 (2.2%)
≥2 ULN	1 (0.1%)	2 (0.3%)	3 (0.3%)	3 (0.4%)	4 (0.4%)	3 (0.4%)
≥3 ULN	1 (0.1%)	0	1 (<0.1%)	1 (0.1%)	2 (0.2%)	1 (0.1%)
INR						
n	703 (100.0%)	688 (100.0%)	1048 (100.0%)	688 (100.0%)	1048 (100.0%)	688 (100.0%)
≥1.5 ULN	5 (0.7%)	8 (1.2%)	16 (1.5%)	8 (1.2%)	18 (1.7%)	13 (1.9%)
≥2 ULN	2 (0.3%)	3 (0.4%)	7 (0.7%)	3 (0.4%)	7 (0.7%)	5 (0.7%)

n = number of subjects with parameter assessment done at respective time point. At any time post-baseline for OASIS 3, the event onset is up to day 182 (inclusive) for EZN 120 mg (week 1-26) and Placebo (week 1-26)

During week 1-52, a total of 12 cases fulfilled the criteria for CLO. Overall, the LSMB assessed 7 out of 8 CLO cases in the elinzanetant group and 3 out of 4 CLO cases in the placebo group as unlikely related to study drug. The LSMB assessed one case as probably related to study drug without the availability of an alternative etiology on placebo treatment. There were no cases in the pooled safety population indicating potential cholestatic DILI.

Out of 1113 women treated with elinzanetant, only one CLO case was assessed by the LSMB as being possibly related to elinzanetant that did not meet the international consensus definition of being probably drug induced liver injury (DILI) (*Aithal et al. 2011*). For this case an alternative etiology was identified, namely possible passage of gallstone as it was associated with acute onset of biliary type pain after 57 days on study and resolved very quickly. No cases of DILI causally related to elinzanetant (i.e., probably related likelihood >50%) were identified based on blinded assessment by the LSMB and no potential Hy's law case was identified. There was no indication for cholestatic injury either.

Overall, based on these results the Applicant considers that the risk for hepatotoxicity for elinzanetant is considered to be very low and liver monitoring is not required for elinzanetant in the post-approval setting.

Phototoxicity

In the pooled safety analysis, 5 women under elinzanetant and 1 woman under placebo treatment reported photosensitivity reaction (PTs) during the period Week 1 to 52. Of these, 3 women under elinzanetant and in 1 woman under placebo treatment were assessed as related to the study drug by the investigator. In 3 women, onset of photosensitivity was more than 120 days after start of treatment. In a woman with an earlier onset (Day 46), concomitant use of another medication was recorded which may cause photosensitivity (dexibuprofen). All cases were mild or moderate in intensity and non-serious. One woman treated with elinzanetant 120 mg withdrew from the study because of a photosensitivity reaction (onset Day 290), while the other 4 cases resolved despite continued treatment with elinzanetant 120 mg, and no actions were taken for these events. Additionally, one woman in SWITCH-1 study who received 160 mg elinzanetant developed a mild intermittent photosensitivity reaction (PT) after 45 days of treatment, which resolved after 15 days while continuing the study drug.

Postmenopausal uterine bleeding

In OASIS 1, 2 and 3, any woman experiencing postmenopausal bleeding after randomization had to undergo a TVU with subsequent investigation and management (including endometrial biopsy, if indicated) according to the investigator's clinical judgment and usual practice.

In the pooled safety analysis, over week 1-52, in total 15 (2.1%) cases were reported in the elinzanetant arms vs. 15 (3.0%) in the placebo arm. Of the 15 cases in the elinzanetant arm, 10 (1.4%) were considered drug-related. Overall, these cases were mild in intensity, except for one case which was severe, and were associated with a benign endometrium. No cases of endometrial hyperplasia or malignant neoplasm were reported.

Phase I studies (pooled)

Liver event

Overall, 8 out of 782 subjects in the pooled Phase 1 studies had clinically relevant increases of liver parameters. Among these 8 participants, there were 3 participants from a dedicated study 21668 with pre-existing hepatic impairment, as well as 3 participants who had increased liver parameters only at the follow-up visit (i.e. 7-11 days after last elinzanetant dose).

Table 65 Overview of clinically relevant liver parameter results in Phase 1 studies (pooled)

	Elinzanetant n=537 (100%)	Placebo n=245 (100%)	Total n=782 (100%)
ALT or AST ≥3 x ULN	3 (0.6%)*	0	3 (0.4%)
ALP ≥2 X ULN	1 (0.2%)**	0	1 (0.1%)
Total Bilirubin ≥2 x ULN	4 (0.7%)***	1 (0.4%)	5 (0.6%)****
ALT or AST ≥ 3xULN and TB ≥2xULN	0	0	0

* Includes 1 participant with pre-existing hepatic impairment (Study 21668, a dedicated hepatic impairment study)
** Includes 1 participant with pre-existing hepatic impairment (Study 21668, a dedicated hepatic impairment study)
*** Includes 2 participants with pre-existing hepatic impairment (Study 21688, a dedicated hepatic impairment study). None of the 4 participants had concomitant increases of ALT/AST/ALP.
**** One subject is counted twice, because he showed elevated total bilirubin during both the placebo and elinzanetant period of a cross-over study (subject 012, study 21676)

Liver-related stopping criteria were met for 2 female participants: one participant in study 21680) and one participant in study 22653). These 2 participants are considered relevant for the hepatic safety assessment. One case was considered not related and the other case (120 mg dose), which remained below the threshold of > 5 x ULN with normal bilirubin, was considered probable related due to the positive dechallenge. The alternative etiology was identified as non-alcoholic steatohepatitis.

Phase 2 study Nirvana (only liver safety data)

Liver event

Two participants in the recently completed phase 2 NIRVANA study (not submitted in this MAA) had ALT and/or AST > 3 x ULN. These cases were reviewed by each LSMB member independently in blinded fashion. One case was on elinzanetant treatment and one case on placebo treatment. One case (placebo) was unlikely related in a patient over chronic liver injury, the other case with mildly elevated baseline ALT/AST (likely due to her underlying fatty liver) developed a progressive rise in ALT to >5X ULN (120 mg elinzanetant) with normal bilirubin was considered probably related due to time to onset and the positive dechallenge.

Treatment of moderate to severe VMS Caused by AET

OASIS 4, Part A + B (Weeks 1 to 52 of the study)

A tabulated summary of AESIs in the OASIS 4 up to Week 12 and up to Week 52 is presented in the tables below.

Table 66 Summary of AESIs up to Week 12 (SAF) –OASIS 4

AESI grouping	EZN 120 mg (Week 1-12) N=315 (100%) n (%) / IR (100 py) [a]	Placebo (Week 1-12) N=158 (100%) n (%) / IR (100 py) [a]
Potential liver event		
Any event	9 (2.9%) / 12.59	2 (1.3%) / 5.54
Study drug-related	4 (1.3%) / 5.55	0
Leading to discontinuation	2 (0.6%) / 2.77	0
Serious	1 (0.3%) / 1.38	0
Study drug-related	0	0
Leading to discontinuation	1 (0.3%) / 1.38	0
Somnolence or fatigue		
Any event	70 (22.2%) / 116.07	15 (9.5%) / 44.12
Study drug-related	56 (17.8%) / 89.73	11 (7.0%) / 31.84
Leading to discontinuation	6 (1.9%) / 8.37	0
Serious	0	0
Phototoxicity		
Any event	3 (1.0%) / 4.15	1 (0.6%) / 2.74
Study drug-related	3 (1.0%) / 4.15	0
Leading to discontinuation	0	0
Serious	0	0
Postmenopausal uterine bleeding		
Number of women with intact uterus	274 (100%)	141 (100%)
Any event	5 (1.8%) / 7.98	0
Study drug-related	0	0
Leading to discontinuation	0	0
Serious	0	0

AESI = adverse event(s) of special interest, EZN = elinzanetant, SAF = safety analysis set. a IR (100 py) = incidence rate per 100 person-years, where one person-year is defined as 365.25 days.

Table 67 Summary of AESIs up to Week 52 (SAF) – OASIS 4

AESI grouping	EZN 120 mg (Week 1-52) N=465 (100%) n (%) / IR (100 py) [a]	Placebo/EZN 120 mg (Week 1-52) N=158 (100%) n (%) / IR (100 py) [a]
Potential liver event		
Any event	22 (4.7%) / 5.78	2 (1.3%) / 5.54
Study drug-related	7 (1.5%) / 1.79	0
Leading to discontinuation	3 (0.6%) / 0.76	0
Serious	1 (0.2%) / 0.25	0
Study drug-related	0	0
Leading to discontinuation	1 (0.2%) / 0.25	0
Somnolence or fatigue		
Any event	100 (21.5%) / 31.14	15 (9.5%) / 44.12
Study drug-related	70 (15.1%) / 20.42	11 (7.0%) / 31.84
Leading to discontinuation	9 (1.9%) / 2.30	0
Serious	0	0
Phototoxicity		
Any event	4 (0.9%) / 1.03	1 (0.6%) / 2.74
Study drug-related	4 (0.9%) / 1.03	0
Leading to discontinuation	0	0
Serious	0	0
Postmenopausal uterine bleeding		
Number of women with intact uterus	408 (100%)	141 (100%)
Any event	19 (4.7%) / 5.69	0
Study drug-related	2 (0.5%) / 0.58	0
Leading to discontinuation	0	0
Serious	2 (0.5%) / 0.58	0
Study drug-related	0	0
Leading to discontinuation	0	0

AESI = adverse event(s) of special interest, EZN = elinzanetant, SAF = safety analysis set.
a IR (100 py) = incidence rate per 100 person-years, where one person-year is defined as 365.25 days.

Liver event

Close liver observation

The table below presents an overview of exposure adjusted incidence rates (EAIRs) by treatment group at week 12 (for both elinzanetant and placebo), and at week 52 (elinzanetant) for liver events identified with the SMQ "Drug related hepatic disorders – comprehensive search".

Table 68 Treatment-emergent AESI - Liver event: overview of exposure-adjusted incidence rate by treatment group (OASIS 4, SAF) Appendix Q176

AESI	EZN 120 mg Week 1-12 N=315 (100%) n(%) IR* (100 py)	Placebo Week 1-12 N=158 (100%) n(%) IR* (100 py)	EZN 120 mg Week 1-26 c N=465 (100%) n(%) IR* (100 py)	EZN 120 mg Week 1-52 c N=465 (100%) n(%) IR* (100 py)
Any event	9 (2.9%) 12.59	2 (1.3%) 5.54	4 (2.7%) 4.45	22 (4.7%) 5.38
Study drug-related	4 (1.3%) 5.55	0	4 (0.9%) 1.02	7 (1.5%) 1.38
Leading to discontinuation	2 (0.6%) 2.77	0	2 (0.4%) 0.51	3 (0.6%) 0.27
Serious	1 (0.3%) 1.38	0	1 (0.2%) 0.25	1 (0.2%)
Study drug-related	0	0	0	0
Leading to discontinuation	1 (0.3%) 1.38	0	1 (0.2%) 0.25	1 (0.2%)

py = person-years. *IRs are exposure adjusted incidence rates according to Crowe et al (2016).
c Reported AEs, during the exposure period to elinzanetant, for both treatment groups.

ALT/AST, bilirubin, AP elevations

Elevated post-baseline values of ALT/AST ≥ 3 x ULN were observed in 1% (3 of 311 participants) in the elinzanetant arm at Week 12 no elevations of ALT/AST were observed in the placebo group. The protocol-defined criteria triggering CLO were confirmed in the re-test and reported for the 2 participants in the elinzanetant arm. Both cases met the liver injury criteria as assessed by the LSMB. For one case the assessment by the LSMB was completed. 32 days after starting study intervention (elinzanetant), the participant was reported with hepatic enzyme increased (reported term: elevated liver enzymes) (AST 866 U/L [24.74ULN], ALT 599 U/L [17.11ULN], AP 187 U/L [1.80ULN] and total bilirubin 1.5 mg/dL [1.25ULN]), which the investigator considered serious because it met the following seriousness criterion or criteria: “other medically important serious event”. The causality to study intervention was assessed as possible, but biliary disease was identified as plausible alternative explanation.

ALT or AST post-baseline elevations of ALT/AST ≥ 3 x ULN were observed in 1.5% (7 of 461 participants) at week 52. At week 52, AP was elevated ≥2xULN in 0,7% (n=3, EAIR 0,77) participants on EZN compared to no participants exposed to placebo. Only in the case mentioned above the elevation of AP ≥2 x ULN was combined with an increase of bilirubin ≥2 x ULN.

Table 69 Number of subjects and exposure-adjusted incidence rate by cumulative hepatic safety laboratory parameter category up to week 52 (OASIS 4, SAF)

Parameter		EZN 120 mg (week 1-12) (N=315) n (%) IR* (100 py)	Placebo (week 1-12) (N=158) n (%) IR* (100 py)	EZN 120mg (week 1-52) (N=465) n (%) IR* (100 py)
ALT	n	311 (100.0%)	157 (100.0%)	461 (100.0%)
	Category			
	>=1 x ULN	37 (11.9%) 54.20	28 (17.8%) 84.77	98 (21.3%) 27.03
	>=3 x ULN	3 (1.0%) 4.11	0	6 (1.3%) 1.28
	>=5 x ULN	2 (0.6%) 2.74	0	3 (0.7%) 0.77
	>=8 x ULN	2 (0.6%) 2.74	0	2 (0.4%) 0.51
	>=10 x ULN	2 (0.6%) 2.74	0	2 (0.4%) 0.51
	>=20 x ULN	0	0	0
AST	n	311 (100.0%)	157 (100.0%)	461 (100.0%)
	Category			
	>=1 x ULN	30 (9.6%) 43.41	16 (10.2%) 46.03	88 (19.1%) 23.48
	>=3 x ULN	2 (0.6%) 2.74	0	5 (1.1%) 1.28
	>=5 x ULN	2 (0.6%) 2.74	0	2 (0.4%) 0.51
	>=8 x ULN	1 (0.3%) 1.37	0	1 (0.2%) 0.25
	>=10 x ULN	1 (0.3%) 1.37	0	1 (0.2%) 0.25
	>=20 x ULN	1 (0.3%) 1.37	0	1 (0.2%) 0.25
ALT or AST	n	311 (100.0%)	157 (100.0%)	461 (100.0%)
	Category			
	>=3 x ULN	3 (1.0%) 4.11	0	7 (1.5%) 1.54
	>=5 x ULN	2 (0.6%) 2.74	0	3 (0.7%) 0.77
	>=8 x ULN	2 (0.6%) 2.74	0	2 (0.4%) 0.51
	>=10 x ULN	2 (0.6%) 2.74	0	2 (0.4%) 0.51
	>=20 x ULN	1 (0.3%) 1.37	0	1 (0.2%) 0.25
Total bilirubin	n	311 (100.0%)	157 (100.0%)	461 (100.0%)
	Category			
	>=1 x ULN	7 (2.3%) 9.68	2 (1.3%) 5.45	11 (2.4%) 2.86
	>=2 x ULN	1 (0.3%) 1.37	0	1 (0.2%) 0.25
	>=5 x ULN	0	0	0
	>=8 x ULN	0	0	0
ALP	n	311 (100.0%)	157 (100.0%)	461 (100.0%)
	Category			
	>=1.5 x ULN	4 (1.3%) 5.49	1 (0.6%) 2.71	9 (2.0%) 2.32
	>=2 x ULN	3 (1.0%) 4.11	0	3 (0.7%) 0.77
	>=3 x ULN	2 (0.6%) 2.73	0	2 (0.4%) 0.51

A total of 5 cases under elinzanetant fulfilled the criteria for CLO, of which after blinded assessment by the LSMB, two cases were considered unlikely and 3 cases were considered possibly related, of which 2 met the international consensus definition for mild liver injury (DILI) (Aithal et al. 2011). For all three cases an alternative etiology was identified. No cases of DILI causally related to elinzanetant (i.e., probably related likelihood >50%) and no Hy's law cases were identified (based on hepatocellular and cholestatic analysis).

Somnolence or fatigue

During week 1-12, somnolence or fatigue were reported more frequently in participants in elinzanetant arm compared to those in the placebo arm. The difference was mostly driven by the higher number of participants with fatigue (PT) and somnolence (PT). None of the events were assessed as serious. One TEAE (asthenia) was assessed as severe.

Somnolence or fatigue was assessed as related to study intervention by the investigator as follows:

- Fatigue (PT): 26 participants who received elinzanetant during Weeks 1-12, 5 participants who received placebo during Weeks 1-12, 4 participants who received elinzanetant during Weeks 13-26 and 2 participants who switched to elinzanetant at Week 13.
- Somnolence (PT): 28 participants who received elinzanetant during Weeks 1-12, 6 participants who received placebo during Weeks 1-12, 3 participants who received elinzanetant 120 mg during Weeks 13-26 and 5 participants who switched to elinzanetant at Week 13.
- Hypersomnia (excessive sleepiness) (PT): 2 participants who received elinzanetant 120 mg during Weeks 1-12 and 1 participant who received elinzanetant during Weeks 13-26.
- Asthenia (PT): 6 participants who received elinzanetant during Weeks 1-12, 1 participant who received placebo during Weeks 1-12, 1 participant who received elinzanetant during Weeks 13-26.

During Weeks 27-52, the frequency of somnolence and fatigue was decreased compared to the corresponding frequencies during Weeks 13-26. None of the events were assessed as serious. One TEAE (asthenia) was assessed as severe.

Phototoxicity

During Weeks 1-12, phototoxicity was reported 3 participants on elinzanetant and 1 participant on placebo, and during week 13-52, in 1 participant who switched to elinzanetant at Week 13. None were assessed as serious or severe. All 4 TEAEs on elinzanetant were assessed as related to study intervention by the investigator.

Postmenopausal uterine bleeding

During Weeks 1-12, 3/274 participants with an intact uterus who received elinzanetant, and during weeks 13-26, 3/256 participants who received elinzanetant, and 2/134 participants with an intact uterus who switched to elinzanetant at Week 13 reported postmenopausal uterine bleeding. One case of postmenopausal haemorrhage was assessed as serious. None of the events were assessed as severe. One TEAE (uterine haemorrhage) was assessed as related to study intervention by the investigator.

From week 1-52, the number of participants with postmenopausal uterine bleeding was small (19/408 participants with an intact uterus who received elinzanetant 120 mg and no cases in participants who received placebo). Two participants, both receiving tamoxifen as the background therapy, had postmenopausal uterine bleeding events (PTs "postmenopausal haemorrhage" and "abnormal uterine bleeding") that were assessed as serious. None of the events were assessed as severe. For 2 participants, the events (PTs "vaginal haemorrhage" and "uterine haemorrhage") were assessed as related to the study intervention by the investigator, and for 1 participant, the event (PT "vaginal haemorrhage") was assessed as related to the study procedures.

2.6.8.2.2. Other findings on safety

Cardiac safety

In OASIS 1, 2, 3, and 4 studies, a single 12-lead ECG was to be obtained for eligibility check at screening. If clinically indicated, unscheduled 12-lead ECGs could be performed at any point during the study. Clinically relevant abnormalities had to be reported as AEs (e.g., new onset atrial fibrillation). Palpitations (PT) was the most frequently reported TEAE under the SOC "cardiac disorders" among those women who received elinzanetant 120 mg, during weeks 1 to 52 both in the pooled safety population for women with VMS associated with menopause (8 women) and in women with VMS caused by AET (8 women). In the SWITCH-1 study, a 12-lead ECG was to be obtained at all visits except Screening Visit 1. There were no clinically relevant findings in the SWITCH-1 study.

Effects on QT interval (study 21670)

The cardiac safety of elinzanetant, including effects on the QT interval, has also been investigated by means of standard 12-lead ECG and continuous 12-lead Holter ECG in various Phase 1 studies in healthy volunteers. Doses in these studies were up to elinzanetant 600 mg. The highest clinically observed geometric mean plasma concentration in these studies was up to approximately 5-fold higher than the geometric mean steady-state exposure of the planned therapeutic dose of 120 mg as obtained in Phase 3 studies. Based on the study results there is no indication of a QTc interval prolongation or other relevant cardiac safety risks by elinzanetant after single oral administration of elinzanetant at doses up to 5 times the maximum recommended dose. Evaluations also showed no relationship between elinzanetant plasma concentration and QTc interval. This assessment is supported by the absence of relevant findings in the non-clinical cardiac safety studies.

Bone mineral density

In OASIS 3, BMD was measured at designated sites and had to be done for all women enrolled at those sites. Measurements were done via DEXA scan (femoral neck, hip and lumbar spine) at screening, Week 24 and Week 52. 343 women (173 in the elinzanetant 120 mg arm and 170 women in the placebo arm) had DEXA scan performed. To standardize the procedures across sites, detailed instructions were provided to the sites in the imaging manual. For both elinzanetant and placebo groups, the observed mean percentage changes in BMD were within the expected age-related loss per year, which per literature is approximately 1-2% bone loss per year (*Finkelstein et al. 2008*), and comparable between treatment arms.

Endometrial safety

In OASIS 1-3, in women with intact uterus, endometrial biopsies were taken at screening, end of treatment and in the event of abnormal findings in the TVU or postmenopausal bleeding. In OASIS 4, biopsies were taken at screening, end of treatment (i.e., premature discontinuation of Part A of the study), and during the study if the women had symptoms (e.g., unexplained vaginal bleeding). All biopsies were assessed by three blinded independent pathologists, and the main result was based on majority read, in line with the FDA guideline on HRT.

Transvaginal ultrasound (TVU) of endometrial thickness was required in OASIS 1-4 studies at screening and end of treatment, and in OASIS 4 also during the study if the woman had unexplained vaginal bleeding. Endometrial thickness (measured in the medio-sagittal section as double-layer in millimeters) and overall safety assessment of the pelvic organs, especially for evaluation of the uterus, ovaries and fallopian tubes. In the SWITCH-1 study, a TVU was required in the event of postmenopausal bleeding, according to the investigator's clinical judgment and usual clinical practice. Endometrial biopsies were not performed.

With regard to *Endometrial biopsy outcome* in pivotal safety trial OASIS 3, in 140 of 170 women treated with elinzanetant 120 mg with an intact uterus who completed 52 weeks (≥326 days of treatment), biopsy samples were obtained providing 116 samples with adequate tissue. Of 30 women treated with elinzanetant 120 mg with no end-of-treatment biopsy sample, this was due to patient refusal (n=22) or unsuccessful attempts (n=6). However, TVU results at EoT indicated that these women had relatively thin endometrium. At *unscheduled visits* after <326 days of treatment, adequate endometrial tissue was obtained from 5 out of 5 participants in the elinzanetant arm and 5 out of 6 participants in the placebo arm. Of these, a benign endometrium was observed for all participants in both treatment arms. Disordered proliferative endometrium was diagnosed in 2 participants in the elinzanetant 120 mg arm and 1 participant in the placebo arm. No cases of endometrial hyperplasia or malignant neoplasm were reported at any visits in this study.

In OASIS 1-2, adequate EoT endometrial biopsies (week 26) were obtained in from 143 women on elinzanetant vs. 146 women on placebo. All were judged a benign endometrium, and no cases of endometrial hyperplasia or malignant neoplasm were reported (based on majority read).

In week 1-52 of OASIS 4, Endometrial biopsies were performed in women with an intact uterus if they had symptoms (e.g., unexplained vaginal bleeding) during the study. Endometrial biopsies were evaluated according to the FDA guideline (FDA 2003) and the operational manual. The assessment for main result and subcategories was based on majority read. At baseline, endometrial biopsies were performed in 64/415 participants with an intact uterus. Adequate endometrial tissue was obtained from 35/38 participants (92.1%) in the elinzanetant arm and 22 out of 25 participants (88.0%) in the placebo-elinzanetant arm. At the EoT visit after ≥326 days of treatment, endometrial biopsies were performed in 27/230 participants in the elinzanetant arm and 9/122 participants in the placebo-elinzanetant arm. A benign endometrium was observed in all cases. Endometrial polyps were reported in 1 participant in the elinzanetant 120 mg arm (background therapy: tamoxifen), No cases of disordered proliferative endometrium were reported. 2 cases of endometrial hyperplasia were reported as AEs, but these diagnoses were not based on the biopsies performed as part of the study.

Regarding ***TVU***, in OASIS 1-3, no clinically relevant changes in TUV were observed in any of the treatment arms. In OASIS 4, Mean and median baseline values for endometrial thickness were comparable between the treatment arms. At Week 52, clinically significant changes on ultrasound were reported in 4 participants in the elinzanetant arm and 1 participant in the placebo-elinzanetant arm. All these participants received tamoxifen as the background therapy. The following AEs corresponding to these abnormal findings were reported (PTs): uterine cyst (1 participant), uterine polyp (3 participants), and endometrial thickening (2 participants). In addition, there were 3 participants (1 in the elinzanetant arm and 2 in the placebo-elinzanetant arm) with clinically significant findings on the gynaecological ultrasound during unscheduled visits. Vaginal haemorrhage (PT) was reported as a corresponding AE in 2 of these 3 participants and ovarian cyst (PT) in 1 participant. All of them received tamoxifen as the background therapy.

Mammogram

In OASIS 1-4, mammograms were required at screening and at the end-of-treatment visit (EoT) (if applicable). Prior mammogram results could be used performed no more than 6 months prior to start of screening in the OASIS 1-3 and no more than 12 months in the OASIS 4 study. At EoT, a mammogram had to be obtained if time elapsed since the previous mammogram was in line with local medical guidelines in the respective age group (OASIS 1, 2, and 3 studies) or for the follow-up of a specific participant (OASIS 4). In the SWITCH-1, a mammogram was required for eligibility and only for women who had not had a mammogram within the national guidelines.

OASIS 3 *At baseline* mammogram was obtained in 309/313 participants (98.7%) in the elinzanetant arm and in 308/314 participants (98.1%) in the placebo arm. Normal results were obtained for 291 participants (94.2%) in the elinzanetant arm and 286 participants (92.9%) in the placebo arm. An abnormal result was obtained for 16 participants in the elinzanetant arm and 16 participants in the placebo arm, but all were judged as clinically insignificant. *At Week 52*, a mammogram was obtained in 99/243 participants (40.7%) in the elinzanetant arm and in 107/242 participants (44.2%) in the placebo arm. A normal result was observed for 91 participants (91.9%) in the elinzanetant and 98 participants (91.6%) in the placebo arm. For participants who *prematurely discontinued the treatment*, a mammogram was obtained at EoT in 5/75 participants (6.7%) in the elinzanetant arm and in 2/61 participants (3.3%) in the placebo arm. All results were judged as normal. At *unscheduled visits*, 2 participants in the elinzanetant arm with normal results at baseline had a clinically significant abnormal result, i.e. PTs Invasive breast carcinoma and Invasive ductal breast carcinoma, after completion of the 52-week treatment. For 1 of these 2 participants, an SAE of invasive breast carcinoma was reported accordingly, which was considered not drug-related by the investigator. The other participant had a normal mammogram result at Week 52, but had an unscheduled mammogram one month later, from which a clinically significantly abnormal result of Invasive breast carcinoma was reported. A follow-up procedure was performed 2 weeks later, and a clinically insignificant result was reported.

OASIS 1 + 2: No cases of clinically significant abnormal mammogram findings were reported.

OASIS 4 (week 1-52) *At baseline*, a mammogram/ultrasound was obtained in 302/309 participants (97.7%) in the elinzanetant and 153/156 participants (98.1%) in the placebo-elinzanetant arm. A normal result was obtained for 255 participants (84.4%) in the elinzanetant arm and 130 participants (85.0%) in the placebo-elinzanetant arm. An abnormal result was obtained for 47 participants in the elinzanetant arm and 23 participants in the placebo-elinzanetant arm. Of these, 6 participants with a clinically significant abnormal mammogram at baseline were erroneously randomized, 4 to the elinzanetant arm and 2 to the placebo-elinzanetant arm. In total, 3 of 4 participants in the elinzanetant arm and all 2 participants in the placebo-elinzanetant arm had an *unscheduled procedure* and a normal or clinically insignificant breast imaging was confirmed. Breast imaging of the 4 participants of OASIS 4 showed that in two participants, follow-up mammograms were normal, and in the other two patients were abnormal, but clinically insignificant.

At Week 52, a mammogram11/ultasound was obtained in 167 out of 270 participants (61.9%) in the elinzanetant 120 mg arm and 76 out of 132 participants (57.6%) in the placebo-elinzanetant 120 mg arm. Of these, a normal result was observed for 154 participants (92.2%) in the elinzanetant 120 mg arm and for 70 participants (92.1%) in the placebo-elinzanetant 120 mg arm. A clinically significant abnormal result was obtained for 1 participant in the elinzanetant 120 mg arm (Table 8.3.7/1). The corresponding SAE (reported term "Ductal carcinoma low degree of papillary pattern right breast") was reported during Part C of the study and therefore this SAE is not included in the AE tables or AE listings of the CSR.

Seizure

In OASIS 1-3, 7 women were included with a medical history of epilepsy or seizure (PT epilepsy: 2 in the elinzanetant group and 2 in the placebo group; PT seizure: 2 in the elinzanetant group; PT generalised tonic-clonic seizure: 1 in the elinzanetant group).

In OASIS 1-3 studies there was one seizure case reported in a woman with a medical history (>30 years) of generalized tonic-clonic seizures. She experienced two episodes of generalised tonic-clonic seizure (SAE) on the same day. The event occurred 46 days after switching from placebo to elinzanetant treatment and was considered drug-related by the investigator and led to discontinuation. The last recorded outcome was recovered/resolved. In OASIS 4, none of the women had a medical history of epilepsy or seizure, and no epilepsy or seizure events were reported during Part A + B of the study.

Suicidal ideation and behaviour

Suicidal ideation and behaviour were monitored by the Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) questionnaire in the SWITCH-1 and in the OASIS 1-3 studies. In the SWITCH-1, and OASIS 1-2, none reported suicidal ideation or behaviour. In OASIS 3 none reported suicidal behaviour. The number of women with suicidal ideation was low in both treatment arms (ranging from 2 to 5 women in elinzanetant arm and 2 to 4 women in placebo arm at all timepoints measured). In conclusion, no cases of suicidal behaviour were reported; in OASIS 3, the number of cases of suicidal ideation was very low and comparable between treatment arms, indicating no relevant effect of elinzanetant on suicidal ideation and behaviour.

2.6.8.3. Serious adverse event/deaths/other significant events

2.6.8.3.1. Deaths

No deaths were reported in any of the studies.

2.6.8.3.2. Serious adverse events

Treatment of moderate to severe VMS associated with menopause

OASIS 3 study

Serious TEAEs were reported in 13 (4.2%) women in the elinzanetant arm and 6 (1.9%) women in the placebo arm. All serious TEAEs were distributed over several SOCs and were reported as single PTs without a pattern. None were assessed as related to the study drug or study procedure. 3 women in the elinzanetant arm discontinued the study drug because of the serious TEAEs (injury, multiple sclerosis and epiglotitis).

Table 70 Serious TEAEs: number of participants by PT (SAF) (Table 5–11 CSR OASIS 3)

Preferred term MedDRA version 26.1	Elinzanetant 120 mg N=313 (100%)	Placebo N=314 (100%)
Number (%) of participants with at least one such TEAE	**13 (4.2%)**	**6 (1.9%)**
Acute myocardial infarction	1 (0.3%)	0
Vertigo	1 (0.3%)	0
Epiglottitis	1 (0.3%)	0
Fusobacterium infection	1 (0.3%)	0
Meningitis meningococcal	1 (0.3%)	0
Concussion	1 (0.3%)	0
Injury	1 (0.3%)	0
Blood glucose increased	1 (0.3%)	0
Osteoarthritis	1 (0.3%)	1 (0.3%)
Rotator cuff syndrome	1 (0.3%)	0
Invasive ductal breast carcinoma	1 (0.3%)	0
Multiple sclerosis	1 (0.3%)	0
Syncope	1 (0.3%)	0
Transient ischaemic attack	1 (0.3%)	0
Cholecystitis chronic	0	1 (0.3%)
Infected bite	0	1 (0.3%)
Post procedural haemorrhage	0	1 (0.3%)
Encephalitis toxic	0	1 (0.3%)
Hemiparaesthesia	0	1 (0.3%)

MedDRA = Medical dictionary for regulatory activities, PT = preferred term, SAF = safety analysis set, TEAE = treatment-emergent adverse event

Pooled safety analysis

Up to Week 52, 31 of 1113 women (2.8%) who received elinzanetant had at least one serious TEAE (incidence rate of 5.46 per 100 person-years). All events were distributed over multiple SOCs with no observed pattern. Most of the events were reported as single PTs, and all except one were assessed as unrelated to the study drug by the investigator. In the OASIS 2 study, one serious TEAE was considered related to the study drug by the investigator (generalized tonic-clonic seizure). Next to the 13 serious TEAEs reported in OASIS 3 depicted above, serious TEAEs were reported in 18 patients in SWITCH-1/OASIS 1+2 studies (15 women in the elinzanetant arm, see the table below:

Table 71 Serious TEAEs up to week 52 by primary System Organ Class and by PT (SAF, pooled safety population)

Primary System Organ Class Preferred Term MedDRA Version 26.1	**EZN 120 mg (week 1-52) N=1113 (100%) n (%) IR* (100 py)**	**Placebo (week 1-52) N=754 (100%) n (%) IR* (100 py)**
Number of subjects with at least one such event	**31 (2.8%) 5.46**	**10 (1.3%) 2.92**
Cardiac disorders	**1 (<0.1%) 0.22**	**0**
Acute myocardial infarction	1 (<0.1%) 0.22	0
Ear and labyrinth disorders	**1 (<0.1%) 0.22**	**0**
Vertigo	1 (<0.1%) 0.22	0
Gastrointestinal disorders	**2 (0.2%) 0.28**	**0**
Abdominal pain	1 (<0.1%) 0.14	0
Mechanical ileus	1 (<0.1%) 0.14	0
Hepatobiliary disorders	**2 (0.2%) 0.28**	**3 (0.4%) 1.14**
Cholecystitis acute	0	1 (0.1%) 0.46
Cholecystitis chronic	0	1 (0.1%) 0.22
Cholelithiasis	2 (0.2%) 0.28	1 (0.1%) 0.46
Infections and infestations	**8 (0.7%) 1.37**	**3 (0.4%) 0.91**
Diverticulitis	1 (<0.1%) 0.14	0
Epiglottitis	1 (<0.1%) 0.22	0
Fusobacterium infection	1 (<0.1%) 0.22	0
Infected bite	0	1 (0.1%) 0.21
Infective exacerbation of chronic obstructive airways disease	0	1 (0.1%) 0.24
Meningitis meningococcal	1 (<0.1%) 0.22	0
Otitis externa	1 (<0.1%) 0.14	0
Pneumonia	1 (<0.1%) 0.14	0
Pyelonephritis	1 (<0.1%) 0.14	1 (0.1%) 0.45
Urinary tract infection	1 (<0.1%) 0.14	0
Urosepsis	0	1 (0.1%) 0.45
Injury, poisoning and procedural complications	**4 (0.4%) 0.72**	**1 (0.1%) 0.21**
Accident	1 (<0.1%) 0.14	0
Concussion	1 (<0.1%) 0.22	0
Injury	1 (<0.1%) 0.22	0
Post procedural haemorrhage	0	1 (0.1%) 0.21
Tibia fracture	1 (<0.1%) 0.14	0
Investigations	**1 (<0.1%) 0.22**	**0**
Blood glucose increased	1 (<0.1%) 0.22	0
Musculoskeletal and connective tissue disorders	**3 (0.3%) 0.58**	**1 (0.1%) 0.21**
Joint range of motion decreased	1 (<0.1%) 0.14	0
Osteoarthritis	1 (<0.1%) 0.22	1 (0.1%) 0.21
Rotator cuff syndrome	1 (<0.1%) 0.22	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (<0.1%) 0.22**	**0**
Invasive ductal breast carcinoma	1 (<0.1%) 0.22	0
Nervous system disorders	**5 (0.4%) 0.94**	**2 (0.3%) 0.43**
Encephalitis toxic	0	1 (0.1%) 0.21
Generalised tonic-clonic seizure	1 (<0.1%) 0.14	0

Primary System Organ Class Preferred Term MedDRA Version 26.1	**EZN 120 mg (week 1-52) N=1113 (100%) n (%) IR* (100 py)**	**Placebo (week 1-52) N=754 (100%) n (%) IR* (100 py)**
Hemiparaesthesia	0	1 (0.1%) 0.22
Multiple sclerosis	1 (<0.1%) 0.22	0
Syncope	2 (0.2%) 0.36	0
Transient ischaemic attack	1 (<0.1%) 0.22	0
Product issues	**1 (<0.1%) 0.14**	**0**
Device loosening	1 (<0.1%) 0.14	0
Respiratory, thoracic and mediastinal disorders	**2 (0.2%) 0.28**	**0**
Pulmonary embolism	2 (0.2%) 0.28	0
Surgical and medical procedures	**3 (0.3%) 0.43**	**0**
Arthrodesis	1 (<0.1%) 0.14	0
Bunion operation	1 (<0.1%) 0.14	0
Mammoplasty	1 (<0.1%) 0.14	0
Vascular disorders	**1 (<0.1%) 0.14**	**0**
Deep vein thrombosis	1 (<0.1%) 0.14	0

MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, py = person years, SAF = safety analysis set, TEAE = treatment-emergent adverse event * IR = incidence rate per 100 person-years. IRs are study size adjusted incidence rates according to Crowe et al (2016). Switchers from OASIS 1 and 2 are included in all groups but the event is assigned only to the treatment they received when the event started.

Serious TEAEs that led to discontinuation of study drug were reported in 7 of the 31 women with serious TEAEs in the elinzanetant 120 mg (Week 1-52) treatment group which included Epiglottitis, Urinary tract infection, Urosepsis, Injury, Generalised tonic-clonic seizure, Multiple sclerosis, Syncope, and Pulmonary embolism.

Treatment of moderate to severe VMS Caused by AET

OASIS 4, Part A + B (Weeks 1 to 52 of the study)

Serious TEAEs were reported in 33 women during 52 weeks of treatment:

- 8 women in the elinzanetant arm during Week 1-12: atrial fibrillation, intestinal obstruction, infection, hepatic enzyme increased and metastases to liver, tremor, hypoxia, and breast reconstruction
- 1 woman in the placebo arm during Week 1-12: ligament operation
- 8 women in the elinzanetant arm during Week 13-26: metastases to liver and metastases to bone in one patient, tremor, cataract, bile duct stone, post procedural sepsis, lumbar spinal stenosis, abnormal uterine bleeding, and postmenopausal haemorrhage
- 4 women in the placebo-elinzanetant 120 mg arm during Week 13-26 (i.e., after the switch to elinzanetant 120 mg): COVID-19, concussion, hypokalaemia, and breast cancer recurrent
- 18 women in the elinzanetant + placebo-elinzanetant arm during Week 27-52: breast reconstruction, cataract, Gastroenteritis, Respiratory tract infection (2), Cervical vertebral fracture, Ligament injury, Osteoarthritis, Breast cancer female, Breast cancer stage IV, Malignant melanoma, Thyroid adenoma, Trigeminal neuralgia, Uterine polyp (2), Anisomastia, Endometrial hyperplasia with cellular atypia, Ovarian cyst.

Serious TEAEs that were assessed as related to the study drug by the investigator were reported in 1 woman in the elinzanetant arm during Weeks 1-12 (intestinal obstruction) and 1 woman in the elinzanetant during Weeks 1-52 (tremor, reported twice, during Weeks 1-12 and 13-26). No serious TEAEs that were assessed as related to study intervention by the investigator were reported during Weeks 27-52.

Serious TEAEs that led to discontinuation of study drug were reported in 5 women:

- 2 women in the elinzanetant arm during Weeks 1-12 (hepatic enzyme increased and metastases to liver),
- 1 woman in the elinzanetant 120 mg arm during Weeks 13-26 (tremor),
- 1 woman in the placebo-elinzanetant 120 mg arm during Weeks 13-26 after switching to elinzanetant (breast cancer recurrent),
- 1 participant receiving elinzanetant 120 mg during Weeks 27-52 (breast cancer stage IV)

Study intervention-related TEAEs resulting in discontinuation of study intervention are presented in the table below:

Table 72 Study intervention-related TEAEs resulting in discontinuation of study intervention by PT (SAF)

PT MedDRA Version 27.1	EZN 120 mg Wk 1-12 N=315 (100%)	PLC Wk 1-12 N=158 (100%)	EZN 120 mg Wk 13-26 N=294 (100%)	PLC - EZN 120 mg Wk 13-26 N=150 (100%)	EZN 120 mg Wk 1-26 N=465 (100%)	EZN 120 mg Wk 27-52 N=409 (100%)	EZN 120 mg Wk 1-52 N=465 (100%)
Number (%) of participants with at least one such TEAE	**17 (5.4%)**	**4 (2.5%)**	**4 (1.4%)**	**5 (3.3%)**	**26 (5.6%)**	**2 (0.5%)**	**28 (6.0%)**
Headache	4 (1.3%)	2 (1.3%)	1 (0.3%)	0	5 (1.1%)	0	5 (1.1%)
Fatigue	3 (1.0%)	0	1 (0.3%)	0	4 (0.9%)	0	4 (0.9%)
Asthenia	2 (0.6%)	0	0	0	2 (0.4%)	0	2 (0.4%)
Diarrhoea	2 (0.6%)	0	0	0	2 (0.4%)	0	2 (0.4%)
Dizziness	2 (0.6%)	0	0	0	2 (0.4%)	0	2 (0.4%)
Somnolence	2 (0.6%)	0	0	1 (0.7%)	3 (0.6%)	0	3 (0.6%)
Abdominal pain upper	1 (0.3%)	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.4%)
Alopecia	1 (0.3%)	1 (0.6%)	1 (0.3%)	0	2 (0.4%)	0	2 (0.4%)
Arthralgia	1 (0.3%)	0	1 (0.3%)	0	2 (0.4%)	0	2 (0.4%)
Constipation	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Depression	1 (0.3%)	0	1 (0.3%)	0	2 (0.4%)	0	2 (0.4%)
Dry mouth	1 (0.3%)	0	0	1 (0.7%)	2 (0.4%)	0	2 (0.4%)
Dyspepsia	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Hyperthermia	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Loss of libido	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Myalgia	1 (0.3%)	0	0	1 (0.7%)	2 (0.4%)	0	2 (0.4%)
Nasal dryness	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Trichorrhexis	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Yellow skin	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Abdominal distension	0	0	0	1 (0.7%)	1 (0.2%)	0	1 (0.2%)
Alanine aminotransferase increased	0	0	0	0	0	1 (0.2%)[a]	1 (0.2%)
Aspartate aminotransferase increased	0	0	0	0	0	1 (0.2%)[a]	1 (0.2%)
Nausea	0	0	0	1 (0.7%)	1 (0.2%)	0	1 (0.2%)
Pruritus	0	1 (0.6%)	0	0	0	0	0
Tremor	0	0	1 (0.3%)	0	1 (0.2%)	0	1 (0.2%)
Vertigo	0	0	0	1 (0.7%)	1 (0.2%)	0	1 (0.2%)

EZN = elinzanetant, MedDRA = Medical dictionary for regulatory activities, PLC = placebo, PT = Preferred term, SAF = Safety analysis set, TEAE = Treatment-emergent adverse event, Wk = week Placebo - Elinzanetant 120 mg = placebo for 12 weeks, followed by elinzanetant 120 mg for 40 weeks. a Both instances were reported for the same participant. See Definitions of terms for label descriptions.

2.6.8.4. Laboratory findings

Clinical safety laboratory assessments were done at screening, throughout the study and at the end of treatment in all 5 studies (SWITCH-1 and OASIS 1, 2, 3, and 4). The laboratory values for both treatment groups were comparable at baseline and following the initiation of treatment, the laboratory results in both treatment groups were also comparable, remained stable, exhibiting only minor, non-clinically significant fluctuations which eventually returned or were returning to baseline levels in the follow-up period. The fluctuations did not exceed the established reference ranges throughout the duration of the study treatment. Overall, no clinically significant differences were observed from baseline between elinzanetant 120 mg and placebo groups for clinical laboratory assessments in any study.

In OASIS 3, 6 women in the elinzanetant 120 mg arm and 4 women in the placebo arm had liver function tests increased that fulfilled the CLO as per the study protocol.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Age

Clinical pharmacology studies with elinzanetant included participants with an age range of 18 to 75 years. There were no apparent age-related differences in the safety and tolerability of elinzanetant.

Impaired hepatic or renal function

Elinzanetant was investigated clinically in heathy participants with impaired hepatic (Study 21668) or renal (Study 21669) function. See PK sections for details.

Subgroup analyses were also done in participants with renal and hepatic impairment in the pooled safety analyses (SWITCH-1, OASIS 1, 2 and 3). However, the results cannot be conclusive because of the small size of the subgroups (30 women with baseline eGFR <60 mL/min/1.73 m^2 and 30 women with hepatic impairment).

Studies in Chinese and Japanese women

Two Phase 1 studies conducted in healthy Chinese (Study 21756) and Japanese (Study 21774) women aged 40-65 years to investigate PK, safety and tolerability showed that elinzanetant 120 mg was safe and well tolerated. Overall, the number of AEs in the studies was low, and there were no clinically relevant differences in the frequency of TEAEs between women in elinzanetant and placebo groups.

Subgroup analyses by race, ethnicity and BMI

TEAEs up to Weeks 12, 26 and 52, including serious TEAEs and TEAEs resulting in discontinuation, were analyzed by race, ethnicity, and BMI. Overall incidence of TEAEs was numerically higher in women of White race compared to women of Black or African American race (52.8% vs 36.8%), in particular in such TEAEs as headache (7.9% vs 3.7%), fatigue (5.9% vs 2.2%) and dizziness (3.2% vs 1.5%). Other subgroups with sufficient sample size showed consistent results with the overall.

2.6.8.7. Immunological events

Not applicable

2.6.8.8. Safety related to drug-drug interactions and other interactions

See PK sections

2.6.8.9. Discontinuation due to adverse events

Treatment of moderate to severe VMS associated with menopause

OASIS 3

The number of participants discontinuing due to an AE was higher in the elinzanetant arm in comparison to the placebo arm [39 (12.5%) vs. 13 (4.1%). Fatigue and headache were the most frequently reported TEAEs that led to discontinuation in the elinzanetant arm. In total 5 (1.6%) participants in the elinzanetant arm reported fatigue that led to discontinuation, and in 4 of them, the event was assessed as related to the study intervention by the investigator. 4 participants in the elinzanetant arm reported headache (1.3%) that led to discontinuation, of which 3 cases were assessed as related to elinzanetant by the investigator. Other TEAEs leading to discontinuation of study intervention were reported were abdominal pain and depressed mood.

Table 73 TEAEs resulting in discontinuation of study intervention reported in ≥1% of the participants (in any treatment arm) by PT (SAF) (Table 5–12 CR OASIS 3)

Preferred term MedDRA version 26.1	Elinzanetant 120 mg N=313 (100%)	Placebo N=314 (100%)
Fatigue	5 (1.6%)	0
Headache	4 (1.3%)	0
Abdominal pain upper	3 (1.0%)	0
Depressed mood	3 (1.0%)	0

Pooled safety population

The majority of TEAE resulting in discontinuation of study drug occurred during the first 12 weeks (60 of 83 women under elinzanetant and 27 of 31 women under placebo treatment). During this period, the discontinuation rate due to TEAEs was more than twice as high in the elinzanetant group than in the placebo group, with a risk ratio of 2.17 (95% CI: 1.40, 3.37). The most pronounced difference and highest risk ratio between the two groups was seen in fatigue (see table below). The results were consistent across all 4 studies without any heterogenous treatment effect.

TEAEs up to week 12 resulting in discontinuation of the study drug in >2 women included Fatigue, Headache, Nausea, Dizziness, Diarrhoea, Gastroesophageal reflux disease, Arthralgia, Abdominal pain upper, Depressed mood which frequencies were all higher in the elinzanetant arm compared to the placebo arm.

Table 74 Pooled safety population - TEAEs up to Week 12 resulting in discontinuation of the study drug reported in >2 women in any group (SAF)

Preferred Term MedDRA Version 26.1	EZN 120 mg (Week 1-12) N=765 (100%)	Placebo (Week 1-12) N=754 (100%)	Risk difference (%) (95% CI)	Risk ratio (95% CI)
Fatigue	13 (1.7%)	0	1.82 (0.84, 2.80)	9.63 (1.79, 51.72)
Headache	11 (1.4%)	5 (0.7%)	0.77 (-0.25, 1.80)	1.96 (0.74, 5.18)
Nausea	6 (0.8%)	5 (0.7%)	0.13 (-0.78, 1.04)	1.18 (0.36, 3.85)
Dizziness	4 (0.5%)	3 (0.4%)		
Diarrhoea	4 (0.5%)	2 (0.3%)		
Gastrooesophageal reflux disease	4 (0.5%)	0		
Arthralgia	3 (0.4%)	5 (0.7%)	-0.41 (-1.49, 0.67)	0.62 (0.16, 2.36)
Abdominal pain upper	3 (0.4%)	1 (0.1%)		
Depressed mood	3 (0.4%)	0		

CI = confidence interval, MedDRA = Medical Dictionary for Regulatory Activities, SAF = safety analysis set, TEAE = treatment-emergent adverse event.

During the 26-week and 52-week periods, when comparing the incidence rates per 100 person-years, the differences in the discontinuation rates were less marked. After the first 12 weeks, no woman under elinzanetant treatment discontinued the study drug because of fatigue and only 1 woman discontinued because of headache (see the table below).

Table 75 Pooled safety population - TEAEs up to Weeks 26 and 52 resulting in study drug discontinuation reported in >2 women in any group (SAF)

Preferred Term (PT) MedDRA Version 26.1	Week 1–26				Week 1–52			
	EZN 120 mg N=1113 (100%)	IR (100 py) [a)]	Placebo 754 (100%)	IR (100 py) [a)]	EZN 120 mg N=1113 (100%)	IR (100 py) [a)]	Placebo 754 (100%)	IR (100 py) [a)]
Fatigue	13 (1.2%)	3.06	0	0	13 (1.2%)	2.23	0	0
Headache	12 (1.1%)	2.76	5 (0.7%)	2.83	12 (1.1%)	2.01	5 (0.7%)	2.08
Nausea	8 (0.7%)	1.76	6 (0.8%)	3.10	8 (0.7%)	1.29	6 (0.8%)	2.27
Dizziness	5 (0.4%)	1.18	3 (0.4%)	1.88	5 (0.4%)	0.86	3 (0.4%)	1.38
Abdominal pain upper	5 (0.4%)	1.29	1 (0.1%)	0.63	5 (0.4%)	0.94	1 (0.1%)	0.46
Diarrhoea	4 (0.4%)	0.88	2 (0.3%)	1.25	4 (0.4%)	0.64	2 (0.3%)	0.92
Gastrooesophageal reflux disease	4 (0.4%)	0.99	0	0	4 (0.4%)	0.72	1 (0.1%)	0.21
Arthralgia	3 (0.3%)	0.58	5 (0.7%)	2.82	3 (0.3%)	0.42	5 (0.7%)	2.07
Depression	3 (0.3%)	0.79	1 (0.1%)	0.63	3 (0.3%)	0.42	5 (0.7%)	2.07
Muscle spasms	3 (0.3%)	0.69	0	0	3 (0.3%)	0.50	0	0
Depressed mood	3 (0.3%)	0.79	0	0	4 (0.4%)	0.80	0	0

MedDRA = Medical Dictionary for Regulatory Activities, SAF = safety analysis set, TEAE = treatment-emergent adverse event

a) IR (100 py) = incidence rate per 100 person-years. IRs are study size adjusted incidence rates according to Crowe et al (2016).

Switchers from OASIS 1 and 2 are included in all groups but the event is assigned only to the treatment they received when the event started.

Treatment of moderate to severe VMS caused by AET

OASIS 4, Part A + B (Weeks 1 to 52 of the study)

TEAEs that led to discontinuation of study intervention

During week 1-12, headache and fatigue were the most frequently reported TEAEs that led to discontinuation of study intervention on elinzanetant 120 mg (4 participants and 3 participants, respectively), and headache was the most frequently reported TEAE that led to discontinuation of study intervention on placebo (2 participants). Other TEAEs leading to discontinuation of study intervention during Weeks 1-12 were reported for 1-2 participants.

Table 76 OASIS 4 - TEAEs resulting in discontinuation of study intervention by PT (SAF)

PT MedDRA Version 27.1	EZN 120 mg Wk 1-12 N=315 (100%)	PLC Wk 1-12 N=158 (100%)	EZN 120 mg Wk 13-26 N=294 (100%)	PLC - EZN 120 mg Wk 13-26 N=150 (100%)	EZN 120 mg Wk 1-26 N=465 (100%)	EZN 120 mg Wk 27-52 N=409 (100%)	EZN 120 mg Wk 1-52 N=465 (100%)
Number (%) of participants with at least one such TEAE	**23 (7.3%)**	**4 (2.5%)**	**5 (1.7%)**	**6 (4.0%)**	**34 (7.3%)**	**3 (0.7%)**	**37 (8.0%)**
Headache	4 (1.3%)	2 (1.3%)	1 (0.3%)	0	5 (1.1%)	0	5 (1.1%)
Fatigue	3 (1.0%)	0	2 (0.7%)	0	5 (1.1%)	0	5 (1.1%)
Arthralgia	2 (0.6%)	0	1 (0.3%)	0	3 (0.6%)	0	3 (0.6%)
Asthenia	2 (0.6%)	0	0	0	2 (0.4%)	0	2 (0.4%)
Diarrhoea	2 (0.6%)	0	0	0	2 (0.4%)	0	2 (0.4%)
Dizziness	2 (0.6%)	0	0	0	2 (0.4%)	0	2 (0.4%)
Somnolence	2 (0.6%)	0	0	1 (0.7%)	3 (0.6%)	0	3 (0.6%)
Abdominal pain	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Abdominal pain upper	1 (0.3%)	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.4%)
Alopecia	1 (0.3%)	1 (0.6%)	1 (0.3%)	0	2 (0.4%)	0	2 (0.4%)
Anxiety	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Constipation	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Depression	1 (0.3%)	0	1 (0.3%)	0	2 (0.4%)	0	2 (0.4%)
Dry mouth	1 (0.3%)	0	0	1 (0.7%)	2 (0.4%)	0	2 (0.4%)
Dyspepsia	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Hepatic enzyme increased	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Hyperthermia	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Loss of libido	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Metastases to liver	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Myalgia	1 (0.3%)	0	0	1 (0.7%)	2 (0.4%)	0	2 (0.4%)
Nasal dryness	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Oedema peripheral	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Paraesthesia	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Psoriasis	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Skin disorder	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Trichorrhexis	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Yellow skin	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (0.2%)
Abdominal distension	0	0	0	1 (0.7%)	1 (0.2%)	0	1 (0.2%)
Alanine aminotransferase increased	0	0	0	0	0	1 (0.2%)[a]	1 (0.2%)
Aspartate aminotransferase increased	0	0	0	0	0	1 (0.2%)[a]	1 (0.2%)
Breast cancer recurrent	0	0	0	1 (0.7%)	1 (0.2%)	0	1 (0.2%)
Breast cancer stage IV	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Nausea	0	0	0	1 (0.7%)	1 (0.2%)	0	1 (0.2%)
Pruritus	0	1 (0.6%)	0	0	0	0	0
Tremor	0	0	1 (0.3%)	0	1 (0.2%)	0	1 (0.2%)
Vertigo	0	0	0	1 (0.7%)	1 (0.2%)	0	1 (0.2%)

EZN = elinzanetant, MedDRA = Medical dictionary for regulatory activities, PLC = placebo, PT = Preferred term, SAF = Safety analysis set, TEAE = Treatment-emergent adverse event, Wk = week
Placebo - Elinzanetant 120 mg = placebo for 12 weeks, followed by elinzanetant 120 mg for 40 weeks.
a Both instances were reported for the same participant. See Definitions of terms for label descriptions.

2.6.8.10. Post marketing experience

There is no post-marketing experience. Elinzanetant was only very recently registered in the United Kingdom (08 July 2025).

2.6.9. Discussion on clinical safety

- ***Adverse events***

Treatment of moderate to severe VMS associated with menopause

Safety data collection: For this indication, the primary safety data are derived from the placebo-controlled study OASIS 3 with a duration of 52 weeks, supplemented by a pooled safety analysis of phase 3 studies OASIS 1, OASIS 2, OASIS 3, and the subgroup receiving the 120 mg dose vs. placebo in phase 2 study SWITCH-1. OASIS 1-2 had a placebo-controlled phase of 12 weeks, followed by an extension phase of 14 weeks. The SWITCH-1 study has a placebo-controlled duration of 12 weeks. Safety assessments based on the pooled analysis comprised TEAEs, laboratory parameters (including liver monitoring), vital signs, and physical examinations, mammogram, transvaginal ultrasound (TVU), endometrial biopsies, sleepiness scale, suicidal ideation and behaviour measured with Electronic Columbia Suicide Severity Rating Scale (eC-SSRS), and ECGs. Bone mineral density (BMD) was measured in OASIS 3 only.

The approach to select the placebo-controlled phase 3 study OASIS 3 of 52 weeks duration as the primary safety data source and the pooled safety data as supportive is considered adequate.

Patient exposure: In OASIS 3, 627 women started treatment: 312 with elinzanetant and 315 with placebo. The 52-week treatment period was completed by 226 women (72.2%) in the elinzanetant arm and 232 women (73.7%) in the placebo arm.

In the pooled safety analysis, 765 women started with elinzanetant and 754 women started with placebo. After 12 weeks, 348 women in OASIS 1 and 2 switched treatment from placebo to receive elinzanetant. Thus, a total of 1113 women from SWITCH-1 and OASIS 1, 2 and 3 studies were exposed to at least one dose of elinzanetant. Due to the different study designs, treatment duration varied across the 4 studies. Of 1113 women exposed to elinzanetant:

- 966 women were treated with elinzanetant 120 mg for at least 12 weeks
- 575 women were treated with elinzanetant 120 mg for at least 23 weeks
- 219 women were treated with elinzanetant 120 mg for at least 50 weeks

Of the 923/1113 (83%) women treated with elinzanetant, completed treatment as per protocol. As only in the OASIS 3 study lasted 52-week period, to allow for flexibility in scheduling while ensuring that data collection remains consistent and reliable, without exposing too many participants beyond 52 weeks of treatment, a visit window was allowed around the end of treatment visit. As a result, 219 women (19.7%) were treated with elinzanetant for at least 50 weeks and 32 women (2.9%) were treated for at least 52 weeks.

The documented safety data up to one year in support of the indication '*Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause*' exceeds the requirements of ICH-E1 and is considered sufficient for adequate assessment of the safety profile of elinzanetant 120 mg in the indication of 'Treatment of moderate to severe VMS associated with menopause'.

Adverse events *OASIS 3 (pivotal safety source)*

In OASIS 3, TEAEs were frequently reported. However, the percentage of subjects reporting any TEAE (70.0% vs. 61.1%), TEAEs assessed by the investigator to be related to study intervention (30.4% vs. 14.6%), and TEAEs of special interest (16.9% vs. 11.1%) were all higher in the elinzanetant arm compared to the placebo arm. In most participants, TEAEs were reported as mild or moderate in intensity. Serious TEAEs were reported in a small number of participants in both treatment arms [13 (4.2%) vs. 6 (1.9%)], of which none were assessed by the investigator as related to the study intervention. No deaths were reported. The number of TEAEs leading to permanent discontinuation of the study intervention was higher in the elinzanetant arm compared to the placebo arm [39 (12.5%) vs. 13 (4.1%)], of which 3 participants in the elinzanetant arm had a serious TEAE leading to permanent discontinuation.

The 5 most frequently TEAEs reported by primary SOC in both treatment arms included Infections and infestations, Nervous system disorders, Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, and Investigations. The frequencies were comparable between treatment arms except for Nervous system disorders, which were reported in a higher frequency in elinzanetant compared to the placebo arm (22.0% vs. 11.8%).

Of TEAEs reported in ≥5% of participants by PT, headache (9.6% vs. 7.0%), fatigue (6.7% vs. 2.9%), and somnolence (5.1% vs. 1.3%) were reported more frequently in the elinzanetant arm compared to the placebo arm.

The percentage of TEAEs considered related to study drug by the investigator was higher in the elinzanetant arm compared to the placebo arm [95 (30.4%) vs. 46 (14.6%)]. The most frequent drug-related AEs reported in ≥2% of subjects were Somnolence [15 (4.8%) vs. 3 (1.0%)], Fatigue [13 (4.2% vs. 5 (1.6%)], Headache [10 (3.2% vs. 5 (1.6%)], Dyspepsia [8 (2.6%) vs. 4 (1.3%)], and dizziness [7 (2.2% vs. 3 (1.0%)]. The TEAEs considered related to study drug by the investigator are included in section 4.8 of the SPC, with the exception of dyspepsia.(see the section on *Adverse drug reactions* for further details).

Pooled safety analysis (OASIS 1-3, SWITCH-1)

Week 1-12 (placebo-controlled)

Subjects who received elinzanetant had higher percentage of any TEAE [389 (50.8%) vs. 326 (43.2%)], TEAEs assessed to be related to study drug by the investigator [173 (22.6%) vs. 81 (10.7%)], AESIs [84 (11.0%) vs. 34 (4.5%)], and TEAEs leading to discontinuation [60 (7.8% vs. 27 (3.6%)] compared to women who received placebo. Most of the TEAEs in both groups were mild or moderate in intensity.

With regard to TEAEs reported in >2% of patients by PT, somnolence, fatigue, dizziness and headache were more frequently reported in the elinzanetant 120 mg group compared to placebo.

Based on above, the observed adverse event pattern in the pooled analysis in the placebo-controlled phase over 12 weeks is comparable with that observed in the placebo-controlled the OASIS 3 study over 52 weeks.

Week 26-52

TEAE incidence rates per 100 person-years were comparable between women under elinzanetant and those under former placebo treatment. The incidence of serious TEAEs was low, and only 1 event was assessed by the investigator as related to the study drug (generalized tonic-clonic seizure). With regard to TEAEs by PT with frequency of >2%, somnolence, fatigue, and headache were the TEAEs with the largest difference compared to former placebo participants.

In conclusion, the observed adverse event pattern in the extension phase where all patients received elinzanetant is comparable with that observed during in the OASIS 3 study and during the first 12 weeks of placebo-controlled treatment.

Treatment of VMS caused by adjuvant endocrine therapy (AET)

Safety data collection: For this indication, the safety data are derived from 52 weeks of one phase 3 study OASIS 4 (Part A + B), consisting of a 12-week placebo-controlled period followed by an uncontrolled extension up to 52 weeks. Part B is submitted at Day 120.

Patient exposure: In the OASIS 4 study, 315 women started treatment with elinzanetant 120 mg, and 158 women started with placebo. After 12 weeks, 150 women from the placebo arm switched treatment to elinzanetant 120 mg. Thus, a total of 465 women received at least one dose of elinzanetant 120 mg during Week 1-26. 410 women completed the 26-week treatment period (271 women (85.8%) in the elinzanetant 120 mg arm and 139 women (88.0%) in the former placebo-elinzanetant 120 mg arm). In addition, 395 women completed the 52-week treatment period (262 women (82.9%) in the elinzanetant 120 mg arm and 133 women (84.2%) in the former placebo-elinzanetant 120 mg arm).

All participants except one in the elinzanetant 120 mg arm had a medical history of breast cancer. Only one participant was included who had high risk for developing hormone-receptor positive breast cancer and experiencing VMS caused by adjuvant endocrine therapy. The type of AET concomitantly used was 55.4% and 57% for tamoxifen and 44.6% and 43% for aromatase inhibitors for elinzanetant and placebo group, respectively. The median duration of AET treatment prior to study start varied between 1.5 and 1.7 years.

The safety data set for the indication of 'moderate to severe VMS caused by AET' consists of 395 participants who 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% of participants have proceeded to the optional 2-year extension study (Part C). With the additional data provided of Part B the requirement of ICH E1 of at least 100 patients treated with elinzanetant for a minimum of one year at dosage levels intended for clinical use has been fulfilled. No specific new safety concerns have been observed in this second target population of patients with a history of breast cancer that would point to a necessity for a longer follow-up of safety beyond the currently provided one year safety data.

It is acceptable that the data collected in the additional extension of treatment for an optional 2 years (Part C) will be assessed post-marketing in future PSURs.

Adverse events OASIS *4 (Part A + B)*

Week 1-12 (placebo-controlled)

During the placebo-controlled weeks 1-12, TEAEs were frequently reported. However, the percentage of participants with any TEAEs [220 (69.8%) vs. 98 (62.0%)] and TEAEs assessed by the investigator to be related to study intervention [109 (34.6%) vs. 43 (27.2%)] were slightly higher in elinzanetant compared to placebo. The proportion of participants with TEAEs of special interest was higher on elinzanetant compared to placebo [81 (25.7%) vs. 18 (11.4%)]. In most participants, TEAEs were reported as mild or moderate in intensity.

The 5 most frequently TEAEs reported by primary SOC in both treatment arms included Nervous system disorders, Gastrointestinal disorders, General disorders and administration site conditions, Infections and infestations, Musculoskeletal and connective tissue disorders, and Investigations The frequencies were comparable between treatment arms, except for General disorders and administration site conditions, which were reported in a higher frequency in the elinzanetant arm compared to the placebo arm 60 (19.0%) vs. 12 (7.6%).

Of TEAEs reported in ≥2% of the participants by PT, somnolence [34 (10.8%) vs. 6 (3.8%)], fatigue [30 (9.5%) vs. 8 (5.1%)], diarrhea [16 (5.1%) vs. 3 (1.9%)], depression [13 (4.1%) vs. 1 (0.6%)], asthenia [13 (4.1%) vs. 2 (1.3%)], and dizziness [12 (3.8%) vs. 2 (1.3%)] were more frequently reported on elinzanetant compared to placebo, while Headache [30 (9.5%) vs. 20 (12.7%), insomnia [5 (1.6%) vs. 6 (3.8%)], and abdominal pain [8 (2.5%) vs. 5 (3.2%)] were more frequently reported on placebo compared to elinzanetant.

The incidence of TEAEs in ≥2% of subjects considered related to study drug by the investigator was higher in the elinzanetant arm (34.6%) compared with the placebo arm (27.2%). The most frequently reported TEAEs (≥2%) assessed by the investigator as related to the study intervention were somnolence and fatigue, nausea, and diarrhoea on elinzanetant and headache and depression rating scale score increased on placebo. These AEs related to study drug stated above are presented in section 4.8 of the SPC, with the exception of nausea. See section 4.3.1 for more details.

In conclusion, the adverse event pattern observed in the OASIS 4 in the placebo-controlled weeks 1-12 in participants with VMS using concomitant AET is suggested largely comparable with that observed in participants with VMS associated with natural menopause with regard to the most frequently observed AEs by PTs somnolence, fatigue. However, also asthenia, alopecia, and depression were reported in a higher frequency in the elinzanetant arm, which higher frequency was not observed in participants with VMS associated with natural menopause.

- ***Adverse drug reactions***

Treatment of moderate to severe VMS associated with menopause

OASIS 3: Proportions of participants with TEAEs that were assessed by the investigator to be related to study intervention were higher in the elinzanetant arm compared to the placebo arm [95 (30.4%) vs. 46 (14.6%)]. The most frequently reported TEAEs (PT) assessed by the investigator to be related to study intervention with a relative frequency of ≥2% in the elinzanetant arm were somnolence, Fatigue, Headache, and Dyspepsia.

Pooled safety analysis: During the first 12 weeks of treatment, women who received elinzanetant had higher incidences of drug-related TEAEs compared to women who received placebo [173 (22.6%) vs. 81 (10.7%)]. Study drug-related TEAEs up to Week 12 with a relative frequency of >1 woman in both groups were Fatigue, Headache, Somnolence, Dizziness, Nausea, Diarrhoea, Dry mouth, Dyspepsia, Constipation, Arthralgia, Alopecia, Abdominal distension, Depression rating scale score increased, Depression, and anxiety. Drug-related TEAEs somnolence, fatigue, dizziness and headache were more frequent in the elinzanetant arm during the first 12 weeks of treatment compared to the placebo arm, also among TEAEs assessed by the investigator as study drug-related.

Treatment of moderate to severe VMS Caused by AET

OASIS 4, placebo-controlled part of Part A (Weeks 1-12 of the study) Proportions of participants with TEAEs that were assessed by the investigator to be related to study intervention were slightly higher in elinzanetant 120 mg Week 1-12 compared to placebo Week 1-12. TEAEs assessed by the investigator to be related to

study intervention with a relative frequency of ≥2% of the participants reported were somnolence, fatigue, nausea, headache, diarrhoea, and depression rating scale score. These were similar as observed in the OASIS 3 study.

There are some differences in the reported TEAEs between the participants with VMS associated with menopause and those with VMS caused by AET. This may be due to differences in the two populations related to demographics, underlying diseases (such as a history of breast cancer in the women with VMS caused by AET) and use of concomitant medications (concurrent adjuvant endocrine therapy (AET) in the population of VMS caused by AET).

The differences in reported TEAEs based on the pooled placebo-controlled periods of studies SWITCH-1, OASIS 1-3 and the full data of OASIS 4 also led to differences in the ADRs determined for both populations. Based on the Applicant´s assessment, the ADRs `depressive mood´, `depression´, `vertigo´ and `alopecia´ are newly added to the ADR table for the population with VMS caused by AET, whereas for the ADRs `headache´, `abdominal pain´ and `rash´ have been deleted as there was no sufficient evidence to include those TEAEs as ADRs for the population with VMS caused by AET.

- ***AEs of special interest***

Liver event: In the OASIS 1-3 studies liver safety was monitored through AE reporting and AESI defined as any condition triggering *Close Liver Observation (CLO)*, specific liver laboratory parameters, and CLO based on reaching predefined thresholds of specific liver laboratory parameters according to FDA guidance (FDA 2009). An independent external liver safety monitoring board (LSMB) was installed, who blindly assessed all CLO cases.

OASIS 3: elevated post-baseline values of ALT/AST ≥3 x ULN were observed in a small number of 7 subjects in the clinical trials OASIS 1-3 in the elinzanetant arm and in 6 subjects in the placebo arm. Protocol-defined criteria triggering CLO were confirmed in the re-test for 6 participants in the elinzanetant arm and 4 participants in the placebo arm. Causality to study intervention was assessed by the LSMB as possible for 1 case in the elinzanetant arm and probable for 1 case in the placebo arm. In total, 1 case in the elinzanetant arm and 2 cases in the placebo arm met the liver injury criteria as assessed by the LSMB.

In the OASIS 1-3 studies during the 12-week placebo-controlled period, ALT or AST elevations of ≥3 x ULN were observed in 0.5% (4 out of 755) of the participants treated with elinzanetant 120 mg and in 0.4% (3 out of 735) of the participants treated with placebo. There were no AST or ALT elevations ≥5 x ULN or total bilirubin elevations ≥2 x ULN across the treatment groups. ALP elevations were comparable between both treatment groups (ALP ≥2 x ULN were observed in 0.1% (1 out of 755) of the participants treated with elinzanetant 120 mg and in 0.3% (2 of 735) of the participants treated with placebo, but none of these elevations in both treatment arms fulfilled CLO criteria. Up to 52 weeks, 1 case fulfilled CLO criteria in the elinzanetant arm which was considered possibly related to elinzanetant, for which case an alternative etiology was identified, i.e. possible passage of gallstone. No cases of DILI causally related to elinzanetant (i.e., probably related likelihood >50%) were identified based on blinded assessment by the LSMB and no potential Hy's law case was identified, and no indication for cholestatic injury was identified.

In OASIS 4 elevated post-baseline values of ALT/AST ≥3 x ULN were observed in 1% (3 of 315 participants) in the elinzanetant arm in Week 1-12 and no elevations were observed in the placebo group. ALT or AST post-baseline elevations of ALT/AST ≥3 x ULN were observed in 1.5% at week 52. At week 52, AP was elevated ≥2xULN in 0,7% (n=3, EAIR 0,77) participants on EZN compared to no participants exposed to placebo-elinzanetant. Only in one case the elevation of AP ≥2 x ULN was combined with an increase of bilirubin ≥2 x ULN. Elevations have typically been asymptomatic and have resolved rapidly with continued treatment or with discontinuing treatment.

In OASIS 4, a total of 5 cases fulfilled the criteria for CLO of which 3 cases were considered possibly related, of which 2 met the international consensus definition for mild liver injury (DILI) (*Aithal et al. 2011*). For all three cases an alternative etiology was identified (biliary disease, acetaminophen use, herbal/OTC treatment). No cases of DILI causally related to elinzanetant (i.e., probably related likelihood >50%) and no Hy's law cases were identified (based on hepatocellular and cholestatic analysis).

One case of liver event (120 mg) in phase 1 study and 1 case in phase 2 study (Nirvana study, not submitted in this MAA, except for liver event data) (120 mg) with ALT and/or AST ≥3 x ULN but normal bilirubin were considered probable related due to the positive de-challenge. Overall, the risk for hepatotoxicity for elinzanetant is considered to be low.

Based on additional evaluations taking into account non-clinical data (drug properties and animal studies) regarding hepatic safety, elinzanetant does not exhibit known chemical substructures with obvious alerts for an increased liver safety risk as evaluated in existing drugs known for DILI risk. Further, elinzanetant structure appears structurally more similar to NK-1 antagonists of which several are licenced and differs from that of NK-3 receptor antagonists like pavinetant and fezolinetant, for which hepatotoxic effects have been described resulting in cessation of development (pavinetant) and requiring frequent monitoring (fezolinetant). Further, the biotransformation and elimination pathways of elinzanetant as well as its interactions with enzymes and transporters do not suggest a signal of increased risk for DILI. Additionally, the biotransformation and elimination pathways differ from that known for fezolinetant. Lastly, evaluation of expression of NK1 and NK 3 receptors in the human liver suggested no on-target effect of the class of NK-1/NK-3 receptor antagonists as mode of action.

In conclusion, although the level of evidence is considered very low, as only few cases of ALT/AST elevations reaching CLO within the different studies have been identified, with only two cases with a probable causality assessment, one in a phase 1 study and one in a phase 2 study, none in the natural menopause population, and three cases with a possible causality in the AET population, a possible association cannot be ruled out. Therefore, "alanine aminotransferase (ALT) increased" and "aspartate aminotransferase (AST) increased", with a calculation on the respective frequency category of the ADRs, are mentioned as requested as an ADR in section 4.8 of the SmPC. Further, no update of the safety specifications was acceptable. A follow-up of liver events is to be included in future PSURs.

Somnolence or fatigue: In the studies used for pooled analysis, women took the study drug at bedtime and were instructed neither to drive nor operate machinery if they experienced somnolence or fatigue. The AESIs 'somnolence or fatigue' were identified using several preferred terms. The majority of the events occurred during the first two weeks of treatment, were mild or moderate and resolved.

During Weeks 1-12 of OASIS 4, somnolence or fatigue were reported more frequently in participants who received elinzanetant compared to those who received placebo, as well as the frequency of fatigue (26 vs. 5) and somnolence (28 vs. 6) assessed as related to study intervention by the investigator. Additionally, hypersomnia (excessive sleepiness) (PT) was reported in 2 participants who received elinzanetant 120 mg during Weeks 1-12. Asthenia (PT) related to study drug-related was reported in 6 participants in the elinzanetant arm. None of the events were assessed as serious except for one case of TEAE (asthenia between weeks 13-26) which was assessed as severe. Somnolence and fatigue were included in section 4.8 of the proposed SmPC as common ADRs (≥1/100 to < 1/10). To investigate the potential safety risk of somnolence and fatigue, a dedicated driving ability study with elinzanetant was conducted, see PD section.

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 234-fold the Cmax at the human therapeutic dose. These effects were not observed at a concentration of 73-fold the Cmax at the human therapeutic dose.

In the pooled safety analysis, all cases were mild or moderate in intensity and non-serious. During Weeks 1-12 of OASIS-4, 3 participants on elinzanetant, 1 participant on placebo and 1 participant who switched to elinzanetant 120 mg at Week 13 reported photosensitivity reaction (PTs). None of the events were assessed as serious or severe. For 3 participants who received elinzanetant 120 mg during Weeks 1-12 and one who switched to elinzanetant 120 mg at Week 13, the TEAEs were assessed as related to study intervention by the investigator.

Based on all data, there is no need to address phototoxicity in section 4.4, but the photosensitivity cases were considered an ADR and were mentioned in the ADR table with a corresponding frequency.

Postmenopausal uterine bleeding: An unexplained postmenopausal bleeding was an exclusion criterion. Any woman experiencing postmenopausal bleeding after randomization had to undergo a TVU with subsequent investigation and management (including endometrial biopsy, if indicated) according to the investigator's clinical judgment and usual practice.

In the pooled safety analysis, the number of cases assessed as drug-related were higher in the elinzanetant in comparison to the placebo arm [9 (1.8%) compared to the placebo arm [1 (0.2%)]. Overall, cases were mild in intensity, except for one severe case, and were associated with a benign endometrium. No cases of endometrial hyperplasia or malignant neoplasm were reported.

In OASIS 4, the overall number of postmenopausal uterine bleeding was low and comparable with the placebo arms, but the cases of postmenopausal bleeding assessed as related to study drug were higher in the elinzanetant arm compared to placebo. All cases were considered mild, except for one severe case associated with a benign endometrium. No cases of endometrial hyperplasia or malignant neoplasm were reported.

- ***Death and other Serious adverse events***

No **deaths** were reported in any of the studies.

Serious TEAEs The number of serious TEAEs was low in OASIS 3, but higher in the elinzanetant arm [13 (4.2%)] compared to the placebo arm [6 (1.9%)]. All serious TEAEs were distributed over several SOCs and were reported as single PTs without a pattern, and none were assessed as related to the study drug.

In the pooled safety analysis up to Week 52, 31 of 1113 women (2.8%) who received elinzanetant 120 mg had at least one serious TEAE (incidence rate of 5.46 per 100 person-years). All events were distributed over multiple SOCs with no observed pattern. Most events were reported as single PTs and were assessed as unrelated to the study drug by the investigator, except for one serious TEAE of generalized tonic-clonic seizure in a woman with a history of tonic-clonic seizures which was considered related to the study drug by the investigator.

In Part A and B of OASIS 4, 5 cases of breast cancer were recorded, as well as 5 cases in the ongoing optional extension of 2 years (Part C). Based on causality assessment of these cases, several plausible arguments were provided, including the severity of the initial breast cancer diagnosis, the limited efficacy of AET in preventing progression/recurrence of estrogen receptor positive breast cancer and reference to non-clinical data indicating no increased risk of breast cancer with elinzanetant. In this respect, the percentage of breast cancer progression/recurrence cases reported in the subgroups of patients treated with tamoxifen (1.49%) or aromatase inhibitor (2.7%) in OASIS 4 up to this date appears to be lower or in line with the percentage of breast cancer cases reported in patients treated with tamoxifen (3.14% per women year) or aromatase inhibitors (2.14%), respectively, reported in public literature (*EBCTCG 2011, 2015*). Further, there seems to be no trend between the numbers of recurrence between stage of breast cancer at baseline and between tamoxifen or aromatase inhibitors.

Notwithstanding above arguments which plead against a causal relation, follow-up of any future breast cancer cases in future PSURs was considered necessary. A warning was added in the SmPC that women with history of breast cancer were only treated with tamoxifen or aromatase inhibitors in the clinical trials, with or without GnRH agonists. Section 5.1 of the SmPC also includes information on the breast cancer recurrence rate in OASIS 4, as well as the data from published literature.

- ***Discontinuations due to TEAEs***

Based on the OASIS 3 and week 1-12 in the pooled safety analysis, the incidence of TEAEs leading to discontinuations of elinzanetant treatment were twice as high compared to the placebo arms. Of which headache and fatigue were the most frequent reason for discontinuation across studies. However, the pattern of AEs was comparable between studies, which is reassuring.

In OASIS 4 during week 1-12, headache and fatigue were the most frequently reported TEAEs that led to discontinuation of study intervention on elinzanetant 120 mg (4 participants and 3 participants, respectively), and headache was the most frequently reported TEAE that led to discontinuation of study intervention on placebo (2 participants).

- ***Other findings related to safety***

The **clinical laboratory findings** in the pooled safety data from weeks 1-52 are considered clinically insignificant. The fluctuations did not exceed the established reference ranges throughout the duration of the study treatment.

Cardiac safety: In the SWITCH-1/OASIS 1-4 studies, palpitations (PT) was the most frequently reported TEAE under the SOC "cardiac disorders" in the elinzanetant 120 mg, both in the pooled safety population (8 women) and in OASIS 4 study (8 women).

In the phase 2 RELENT-1 study and phase I study 21670, effects on the QT interval has been investigated. Doses in these studies were up to elinzanetant 600 mg. The highest clinically observed geometric mean plasma concentration in these studies was up to approximately 5-fold higher than the geometric mean steady-state exposure of the planned therapeutic dose of 120 mg as obtained in Phase 3 studies. Based on the study results there is no indication of a QTc interval prolongation or other relevant cardiac safety risks by elinzanetant after single oral administration of elinzanetant at doses up to 5 times the maximum recommended dose. Evaluations also showed no relationship between elinzanetant plasma concentration and QTc interval. This assessment is supported by the absence of relevant findings in the non-clinical cardiac safety studies. In conclusion, results provide support that there is no indication of a QTc interval prolongation or other relevant cardiac safety risks by elinzanetant after single oral administration of elinzanetant at doses up to 5 times the maximum recommended dose.

Bone mineral density: In OASIS 3, BMD was measured at designated sites. Measurements were done via DEXA scan (femoral neck, hip and lumbar spine) at screening, Week 24 and Week 52. 343 women (173 in the elinzanetant 120 mg arm and 170 women in the placebo arm) had DEXA scan performed. For both elinzanetant and placebo groups, the observed mean percentage changes in BMD were within the expected age-related loss per year, which per literature is approximately 1-2% bone loss per year (*Finkelstein et al. 2008*), and comparable between treatment arms. In conclusion, the results obtained in OASIS 3 at week 24 and week 52 do not indicate that elinzanetant has a relevant effect on BMD.

Endometrial safety: In OASIS 1-3, in women with intact uterus, endometrial biopsies were taken at screening, end of treatment and in the event of abnormal findings in the Transvaginal ultrasound (TVU) or postmenopausal bleeding. In OASIS 4, biopsies were taken at screening, end of treatment (i.e., premature discontinuation of Part A of the study), and during the study if the women had symptoms (e.g., unexplained vaginal bleeding). Women were excluded from participation in any of the studies if diagnosed at screening with a disordered proliferative endometrium, endometrial hyperplasia, polyp, or endometrial cancer. All biopsies were assessed by three blinded independent pathologists, and the main result was based on majority read, which is in line with the FDA guideline on HRT. The EMA guideline on HRT recommends that "*Biopsies should be assessed by two independent pathologists blinded to treatment and time of biopsy. In case of disagreement in the interpretation of results (e.g. on hyperplasia or carcinoma diagnosis) between the two pathologists, a third one, also blinded, should be called upon to make the final determination*." However, there is no objection against applying the strategy recommended in the FDA guideline.

TVU of endometrial thickness was required in OASIS 1-4 studies at screening and end of treatment, and in OASIS 4 also in case of unexplained vaginal bleeding. In the SWITCH-1 study, a TVU was required in case of postmenopausal bleeding, according to the investigator's clinical judgment and usual clinical practice. No endometrial biopsies were performed.

Endometrial biopsy outcome: In pivotal safety trial OASIS 3, in 140 of 170 women treated with elinzanetant 120 mg with an intact uterus who completed 52 weeks (≥326 days of treatment), biopsy samples were obtained providing 116 samples with adequate tissue. At *unscheduled visits* after <326 days of treatment, adequate endometrial tissue was obtained from 5 out of 5 participants in the elinzanetant arm and 5 out of 6 participants in the placebo arm. Of these, a benign endometrium was observed for all participants in both treatment arms. Disordered proliferative endometrium was diagnosed in 2 participants in the elinzanetant 120 mg arm and 1 participant in the placebo arm. No cases of endometrial hyperplasia or malignant neoplasm were reported at any visits in this study. However, using the approach described in the EMA guideline on HRT, the observed rate of endometrial hyperplasia or cancer after approximately 1 year of treatment was 0% (0/136) for elinzanetant, which results in an upper bound of the 95%-CI of 2.18% and

0% (0/130) for placebo, which results an upper bound of the 95%-CI of 2.28%. As expected, due to the lower sample size, the upper bound is somewhat higher than recommended in the guideline, which is accepted, in view of the EMA advice given that evaluation of endometrial safety in a subset of patients was considered sufficient.

In OASIS 1-2, adequate end-of-treatment endometrial biopsies (week 26) were obtained in from 143 women on elinzanetant vs. 146 women on placebo. All were judged a benign endometrium, and no cases of endometrial hyperplasia or malignant neoplasm were reported (based on majority read).

In week 1-26 of ongoing OASIS 4, end of treatment endometrial biopsies (i.e., *premature discontinuation of Part A of the study*) were obtained from 1 of 25 women in the elinzanetant 120 mg arm and 1 of 11 women in the placebo-elinzanetant 120 mg arm. For most women (18 women in the elinzanetant 120 mg arm and 7 women in the placebo-elinzanetant 120 mg arm), end-of-treatment endometrial biopsy was not required as the women had no symptoms.

In OASIS 1-3, no clinically relevant changes in TUV were observed in any of the treatment arms. In OASIS 4, one woman in the elinzanetant 120 mg arm using AET tamoxifen was reported as having an AE (suspicion endometrial thickening). In a follow-up ultrasound after 2 weeks, the endometrium thickness was normal (4.9 mm). Based on the endometrial biopsy data provided and supplemented with TVU outcomes, it can be concluded that the current data do not suggest a signal that the use of elinzanetant has an adverse effect on endometrial safety.

Mammogram: In OASIS 1-4, mammograms were required at screening and at the end-of-treatment visit (EoT) (if applicable). Prior mammogram results could be used performed no more than 6 months prior to start of screening in the OASIS 1-3 and no more than 12 months in the OASIS 4 study. At EoT, a mammogram had to be obtained if time elapsed since the previous mammogram was in line with local medical guidelines in the respective age group (OASIS 1, 2, and 3 studies) or for the follow-up of a specific participant (OASIS 4). In the SWITCH-1, a mammogram was required for eligibility and only for women who had not had a mammogram within the national guidelines.

For OASIS 3 all abnormal mammograms were judged as clinically insignificant at baseline. At Week 52, a mammogram was obtained in 99/243 participants (40.7%) in the elinzanetant arm and in 107/242 participants (44.2%) in the placebo arm. A normal result was observed for 91 participants (91.9%) in the elinzanetant and 98 participants (91.6%) in the placebo arm.

In OASIS 1 + 2, there were no cases of clinically significant abnormal mammogram findings were reported.

For OASIS 4 (week 1-26), a mammogram/ultrasound was obtained in 302/309 participants (97.7%) in the elinzanetant and 153/156 participants (98.1%) in the placebo-elinzanetant 120 mg arm, at baseline. All abnormal results were classified as clinically insignificant.

Seizure: In OASIS 1-3, 7 women were included with a medical history of epilepsy or seizure. In OASIS 4, none of the women had a medical history of epilepsy or seizure, and no events were reported during Part A of the study.

In OASIS 1-3 studies, one seizure case was reported in a woman with a medical history of generalized tonic-clonic seizures, who experienced two episodes of generalised tonic-clonic seizure (SAE) on the same day and it was considered drug-related by the investigator. In conclusion, the results do not indicate a relevant effect of elinzanetant on the development of seizures. The participant used loratadine and cetirizine dihydrochloride during the study, both of which have convulsions as an ADR of very rare to unknown frequency. Based on the case description, and positive dechallenge a probable association of the use of elinzanetant with the

occurrence of the event can be agreed upon. Seizures or other convulsive disorders reported in patients with a history of these conditions will be followed up in future PSURs.

Suicidal ideation and behaviour: Suicidal ideation and behaviour were monitored by the Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) questionnaire in the SWITCH-1 and in the OASIS 1-3 studies. The results of the clinical studies showed no relevant effect of elinzanetant on suicidal ideation and behaviour.

- ***Safety in special populations***

Subgroup analyses by race, ethnicity and BMI: TEAEs up to Weeks 12, 26 and 52, including serious TEAEs and TEAEs resulting in discontinuation, were analyzed by race, ethnicity, and BMI. Overall incidence of TEAEs was numerically higher in women of White race compared to women of Black or African American race (52.8% vs 36.8%), in particular in such TEAEs as headache (7.9% vs 3.7%), fatigue (5.9% vs 2.2%) and dizziness (3.2% vs 1.5%). Other subgroups with sufficient sample size showed consistent results with the overall.

In the Pooled safety analysis (OASIS 1-3, SWITCH-1), subgroup analyses in ***participants with renal and hepatic impairment*** were done. However, the results were not conclusive because of the small size of the subgroups (30 women with baseline eGFR <60 mL/min/1.73 m^2 and 30 women with hepatic impairment).

There were no clinically relevant differences in the frequency of TEAEs between women in elinzanetant and placebo groups having mild and moderate hepatic (Study 21668) or moderate and severe renal impairment (Study 21669), aged between 18-75 of age, and different ethnicity (Chinese (Study 21756) and Japanese (Study 21774) women).

Alcohol use: Psychomotor and cognitive effects of alcohol + elinzanetant were investigated in healthy participants. Alcohol was administered alone (blood alcohol concentration 0.05%) and together with 200 mg elinzanetant administered as immediate release (IR) tablets, see section on PD.

Pregnancy: No pregnancies were reported. The SmPC includes a contraindication for use during pregnancy.

Lactation: Section 4.6 of the SmPC reflects that it is unknown whether elinzanetant/or its metabolites are excreted in human milk and a decision must be made whether to discontinue breast feeding or to discontinue/abstain from elinzanetant therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Return to fertility: No clinical information is available on return of fertility and Section 4.6 of the SmPC was adapted to reflect this.

Overdose: There were no cases of accidental/ intentional overdose. Single doses of elinzanetant up to 600 mg have been tested in clinical studies in healthy volunteers. Type of AEs, primarily somnolence and headache, reported at higher doses were similar to those observed with the therapeutic dose of 120 mg but occurred more often and with moderately higher intensity. Multiple once daily doses up to 240 mg over 5 days were tested in a driving ability study and were well tolerated. In the case of overdose, the individual should be closely monitored, and supportive treatment should be considered based on signs and symptoms. There is no specific antidote for elinzanetant.

Drug abuse: As elinzanetant is a centrally acting dual NK-1/3 antagonist the abuse potential was assessed. Required non-clinical studies were in accordance with the FDA guidance for centrally acting drugs (FDA 2017) and agreed by FDA`s Controlled Substance Staff (CSS) to be conducted in parallel to the Phase 3 program. Based on the currently available data including non-clinical and clinical assessments, elinzanetant is not expected to have a clinically relevant abuse potential.

Post marketing experience: Not applicable. No post-marketing data are available for elinzanetant, since this product has only recently been approved in the United Kingdom

2.6.10. Conclusions on the clinical safety

Recently, the selective neurokinin NK-3 receptor antagonist fezolinetant has been approved for the treatment of moderate to severe VMS associated with menopause, so there is some previous safety experience.

Treatment of vasomotor symptoms associated with menopause

Based on the primary safety source (OASIS 3), elinzanetant appears to be generally well tolerated with only 39 (12.5%) participants in the elinzanetant 120 mg arm compared to 13 (4.1%) participants in the placebo arm, who discontinued due to adverse events during a 52-weeks treatment-period. A comparable frequency of TEAE leading to discontinuation was observed in the placebo-controlled periods (weeks 1-12) of the pooled safety analysis (60 (7.8%) in the elinzanetant arm compared to 27 (3.6%)] in the placebo arm. The most commonly reported drug-related TEAEs were somnolence, fatigue, headache, and dizziness, were mostly of mild or moderate intensity.

However, the adverse event pattern of elinzanetant deviates from fezolinetant; while GI-disorders are commonly reported for both products, nervous system disorders commonly reported consist of somnolence, fatigue, and dizziness, which is opposite of insomnia that is commonly reported with fezolinetant. This is possibly due to the additional antagonistic effects of elinzanetant on the NK-1 receptor, which is hypothesized as linked to sleep.

Further, no significant adverse effects regarding endometrial, breast, hepatic and bone safety were observed. Follow-up of liver events was included as an activity for future PSURs.

Treatment of vasomotor symptoms caused by adjuvant endocrine therapy

The adverse event pattern observed in the initial placebo-controlled weeks 1-12 of Part A of the ongoing OASIS 4 study in participants with VMS using concomitant AET is suggested largely comparable with that observed in participants with VMS associated with natural menopause with regard to the most frequently observed drug-related TEAEs somnolence and fatigue, nausea, and diarrhoea. But also asthenia, alopecia and depression were reported in a higher frequency compared to placebo, which was not observed in participants with VMS associated with natural menopause. Differences in ADR pattern between populations are reflected in the approved SmPC.

With the additional data provided of Part B of OASIS 4, the requirement of ICH E1 of at least 100 patients treated with elinzanetant for a minimum of one year at dosage levels intended for clinical use has been fulfilled. No specific new safety concerns have been observed in this second target population of patients with a history of breast cancer that would point to a necessity for a longer follow-up of safety beyond the currently provided one year safety data. It is therefore acceptable that the data collected in the additional extension of treatment for an optional 2 years will be assessed post-marketing in future PSURs.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 77 Summary of the safety concerns

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

2.7.2. Pharmacovigilance plan

Table 78 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 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

2.7.3. Risk minimisation measures

Table 79 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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 08 July 2025. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lynkuet (Elinzanetant) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Menopause is characterized by decreased oestradiol levels due to decreased ovarian function (*Freeman et al. 2005*). Kisspeptin/NKB/dynorphin (KNDy) neurons in the hypothalamus have been identified as playing a role in thermoregulation that is responsive to both oestrogen and ambient temperature (*Rance et al. 2013*). In the menopausal state, the KNDy neurons are in a state of hyperactivation, which disrupts baseline thermoregulation and triggers VMS.

VMS are transient (lasting between 1-5 minutes) episodes of flushing and intense heat sensation (*Bansal and Aggarwal 2019*). VMS are reported by up to 80% of women at some point during perimenopause and last for a median duration of 7.4 years (*El Khoudary et al. 2019, Avis et al. 2015*).

VMS can have a significant impact on the health-related quality of life of an individual, including impact on sleep and emotional well-being, which limit their ability to perform daily activities (*Nappi et al. 2021; Nappi et al. 2023; Stute et al. 2022b*). Sleep disturbances have been suggested to affect up to 60% of menopausal women (*Birkhaeuser and Genazzani 2018*).

Decreased oestrogen levels, causing VMS, occur also in situations when oestrogen levels are suppressed by medical intervention such as bilateral oophorectomy or adjuvant endocrine (anti-oestrogen) therapy (AET) (*Rance et al. 2013, Zhang et al. 2021*). VMS are common adverse reactions in breast cancer patients treated with AET, such as tamoxifen and aromatase inhibitors (*Arimidex SmPC 2021, Berkowitz et al. 2021, Biglia et al. 2003, Nolvadex SmPC 2021, Tamoxifen SmPC 2021*) that strongly impacts quality of life and treatment adherence (*Knobf 2006, Murphy et al. 2012*).

The aim of this new treatment, elinzanetant, is to antagonize neurokinin 1, 3 (NK-1,3) receptor which exerts its pharmacological effects through blockade of these receptors on kisspeptin/ neurokinin B (NKB)/dynorphin (KNDy) neurons in the hypothalamus, normalizing the activity of the KNDy neurons. Therefore, it is postulated that the use of elinzanetant results in improvements of VMS, sleep disturbances and menopause-related quality of life. Of note, an additional Phase 2 study (NIRVANA) to evaluate the effect of elinzanetant on sleep disturbances associated with menopause is ongoing.

3.1.2. Available therapies and unmet medical need

Available therapies

VMS associated with menopause

Hormonal treatment

HRT, also referred to as hormone replacement therapy, is currently the recommended first-line treatment for moderate to severe VMS associated with menopause according to international guidelines (*Neves-E-Castro et al. 2015, ACOG 2014, NAMS 2022, NICE 2019, Yuksel et al. 2021*). Oestrogen-only preparations are given to postmenopausal women without a uterus. In women with a uterus, oestrogen should be combined with a progestogen to protect the endometrium from development of hyperplasia and potential endometrial cancer (*Baber et al. 2016, de Villiers et al. 2016, Stuenkel et al. 2015, NAMS 2022, ACOG 2014, Yuksel et al. 2021*).

Although international guidelines recommend HRT as first-line treatment for moderate to severe VMS associated with menopause, women could be contraindicated (e.g. with a history of cardiovascular disease or hormonal-sensitive cancer, such as breast cancer) and cannot take HRT. In addition, there are patients who have discontinued HRT due to lack of efficacy, adverse events or intolerance. Other women are not willing to use hormonal treatment. (*Marlatt et al. 2018*).

Non-hormonal treatment

Up until recently, the only non-hormonal treatment option approved for the treatment of VMS in some EU countries and UK was clonidine, a centrally acting a2-adrenergic agonist (*Clonidine SmPC UK 2020*). Other non-hormonal medications, such as selective serotonin or serotonin and norepinephrine reuptake inhibitors (SSRIs/SNRIs), are included as alternative treatment options in international and European clinical guidelines (*RCOG 2010, DGGG 2020, NICE 2019; NHG guideline 2022*) for management of VMS despite not being approved by European regulatory authorities and thus being used off-label (*Mintziori et al. 2015*). Paroxetine (a SSRI) is only approved in the US for the treatment of VMS.

Further, since 2023, fezolinetant, an oral NK-3 receptor antagonist, has been approved for the treatment of moderate to severe VMS associated with menopause in Europe through centralized procedure EMEA/H/C/005851/0000 (EU, Switzerland, UK), US, Australia and other countries.

VMS caused by adjuvant endocrine therapy (AET)

There are no effective treatment options approved for the treatment of VMS caused by AET. Since the objective of AET is to reduce oestrogen levels, HRT cannot be used to manage these symptoms. HRT is also contraindicated in patients with or at high risk for developing hormone receptor (HR)-positive breast cancer.

The EU-approved non-hormonal treatments used in women with VMS caused by natural menopause (clonidine and fezolinetant) have not been studied in this population.

Unmet medical need

Despite treatment options available, a large group of women suffering from moderate to severe VMS associated with menopause remain untreated, even though they experience bothersome symptoms that can significantly impair their quality of life (*Kingsberg et al. 2024b*). Also, considering the patient population on AET, as there are no approved treatment options for this population, the unmet need is very high (*Hickey et al. 2005*).

Therefore, the availability of safe and efficacious non-hormonal options, such as elinzanetant, for the treatment of VMS associated with menopause and caused by AET is important to mitigate the burden of moderate to severe VMS on the patient.

This is supported by the results of the large Patient preference study (EMPOWER study), suggesting that an additional treatment choice, next to no treatment or HRT, would be valuable.

3.1.3. Main clinical studies

Four phase 3 studies have been submitted.

'Treatment of moderate to severe VMS associated with menopause':

Two pivotal replicate design studies, OASIS 1 and 2, and the long-term, placebo-controlled safety study, OASIS 3, to support durability of efficacy of elinzanetant.

'Treatment of moderate to severe VMS caused by adjuvant endocrine therapy (AET):

One single pivotal phase 3 efficacy and safety study, OASIS 4.

VMS associated with menopause

The pivotal OASIS 1 and OASIS 2 are two identical designed pivotal efficacy studies. Both studies are randomized (1:1), placebo-controlled, 12-week double-blind studies, followed by a 14-week treatment extension period for up to 26 weeks where placebo group switched to elinzanetant. A total of 796 women (n=199 on elinzanetant and n=197 on placebo in OASIS 1 and n=200 on elinzanetant and n=200 on placebo in OASIS 2), aged 45-60, inclusive, with at least 50 moderate to severe hot flushes (HFs) associated with menopause per week at baseline, including night-time HFs, and seeking treatment for this condition were included. The primary efficacy endpoints were change in the frequency of HF at week 4 and at week 12 for 120 mg elinzanetant vs placebo.

Additionally, OASIS 3 is a randomized, double-blind, placebo-controlled safety and efficacy study with a duration of 52 weeks, which investigated long-term efficacy and safety data of elinzanetant in 628 (n=315 on elinzanetant and n=313 on placebo) women with moderate to severe HFs associated with menopause (no minimum number of HFs at baseline) and seeking treatment for this condition were included. The primary efficacy endpoint was change in HF frequency of moderate to severe VMS from baseline to week 12.

VMS caused by adjuvant endocrine therapy (AET)

OASIS 4 is the pivotal efficacy study for the indication of 'VMS caused by adjuvant endocrine therapy (AET) related to the treatment of breast cancer'. This was a randomized (2:1), placebo-controlled, 12-week double-blind study, followed by a 40-week treatment extension period (total up to 52 weeks), where placebo group switched to elinzanetant after 12 weeks. A total of 474 women (n=316 on elinzanetant and n=158 on placebo) with, or at high risk for developing hormone-receptor positive breast cancer and on AET, with at least 35 moderate to severe HFs per week at baseline, were included. Part A of OASIS 4 (week 1-26 of the study) presents the data on the primary and key secondary endpoints in the initial placebo-controlled 12-week period, Part B (week 27-52 of the study presents longer term safety data and Part C (an optional 2 years extension) is currently ongoing. Part B has been provided at Day 120 response.

3.2. Favourable effects

VMS associated with menopause – OASIS 1 and 2

Regarding the **primary analysis of OASIS 1 and 2**, the two **primary endpoints** have been met. Treatment with elinzanetant resulted in a higher reduction in frequency of moderate to severe HF from baseline to week 4 and week 12, compared to placebo.

- The LS mean change (95% CI) of HF frequency at week 12 was -8.66 (-9.79, -7.53) and -9.72 (-10.70, -8.75) for elinzanetant in OASIS 1 and 2, respectively. For placebo, these differences were -5.44 (-6.60, -4.28) and –6.48 (-7.45, -5.52), respectively.
  The difference in LS means were statistically significant for elinzanetant vs placebo for both OASIS 1 and 2; respectively -3.22 (95% CI: -4.81, -1.63) and -3.24 (95% CI: -4.60, -1.88). Similar findings were seen of HF frequency at week 4.

The **sensitivity analysis** confirmed the robustness of the primary analysis. The sensitivity analysis included the addition of up to 10 missing data points (10 hot flush events) to the HF frequency, which did not lead to relevant deviations in the results. The sensitivity analysis of the severity was analysed by assuming a lower efficacy of the treatment, which only lead to non-significant results if the treatment was hypothesized to be extremely less efficacious.

With respect to the **key secondary endpoints**, i.e. severity of HF from baseline to week 4 and to week 12, PROMIS SD SF 8b total T-score from baseline to week 12, frequency of HF from baseline to week 1 and MENQOL total score from baseline to week 12, the following was observed:

- The LS mean difference in HF severity for elinzanetant vs placebo for both OASIS 1 and 2 was statistically significant at week 12 (difference in LS mean (95% CI) was -0.40 (-0.54, -0.25) for OASIS 1 and -0.29 (-0.44, -0.14) for OASIS 2). Similar findings were seen in difference in HF severity at week 4.
- PROMIS SD SF 8b total T-score (sleep disturbances score) from baseline to week 12, resulted in a greater reduction when treated with elinzanetant vs placebo. The differences in LS means (95% CI) were -5.58 (-7.18, -3.98) in OASIS 1 and -4.32 (-5.77, -2,86) in OASIS 2.
- The LS mean difference in HF frequency at week 1 for elinzanetant versus placebo for both OASIS 1 and 2 was statistically significant (difference in LS mean (95% CI) for OASIS 1 was –2.45 (-3.36, -1.55) and for OASIS 2 –1.66 (-2.73, -0.58)).
- On the PRO, change in MENQOL total score from baseline to week 12, on presence of menopausal symptoms and impact thereof, a statistically significant between-group difference between elinzanetant and placebo was observed. The difference in LS means (95% CI) was –0.42 (-0.64, -0.20) in OASIS 1 and -0.30 (-0.53, -0.07) in OASIS 2.

All five key secondary endpoints support the primary endpoints/ analyses. The **subgroup analyses** with respect to region, race, ethnicity, BMI, and smoking status, performed for the primary and key secondary analysis, suggested that none of these subgroups had an impact on the efficacy of elinzanetant. In general, results obtained were consistent between groups.

Other secondary outcomes, i.e. change in HF frequency over time, BDI II total score on presence of depressive symptoms suggested similar beneficial effects, in line with the findings in the primary analyses. The beneficial effect of elinzanetant was also seen in the **exploratory endpoint** proportion of responders (i.e. ≥50% reduction in HF). This analysis showed in the elinzanetant group at week 12 a proportion of 71-75% responders for the elinzanetant group and 42-48% in the placebo group. For those who reached the responder rate during the first 12 weeks, the median time to response was as soon as 3 weeks in the elinzanetant group.

Regarding the **long-term efficacy** data obtained in OASIS 3 over 52 weeks, the primary endpoint HF frequency from baseline to week 12, difference in elinzanetant versus placebo was -1.55 and statistically significant. The effect was sustained to 52 weeks of treatment.

VMS caused by adjuvant endocrine therapy – ongoing study OASIS 4

Regarding the **primary analysis**, the two **primary endpoints** have been met. Treatment with elinzanetant resulted in a higher reduction in HF frequency from baseline to week 4 and to week 12, compared to placebo.

- The LS mean change (95% CI) of HF frequency at week 12 was -7.53 (-8.02, -7.05) for elinzanetant, for placebo the difference was -4.16 (-4.84, -3.47). The difference in LS means (95% CI) was statistically significant for elinzanetant vs placebo (-3.38 (-4.21 to -2.54)). Similar findings were seen in HF frequency at week 4.

The key **secondary endpoints** of OASIS 4 were the change from baseline to week 12 of the PROs of PROMIS SD SF 8b total T-score and MENQOL total score. With regard to the PROMIS SD SF 8b total T-score, the difference in LS means of elinzanetant vs placebo was statistically significant (-6.12 (95% CI: -7.49, -4.75)). Concerning the MENQOL total score, the difference in LS means of elinzanetant vs placebo was also statistically significant (–0.68 (95% CI: -0.88, -0.48)).

The results of the primary and key secondary endpoints of OASIS 4 are comparable with the results for OASIS 1 and 2.

Another **secondary endpoint** was change in HF severity at weeks 4 and 12. The change from baseline both at weeks 4 and 12 was numerically higher in the elinzanetant group compared to the placebo group. At week 12, this was -0.98 and -0.53 for elinzanetant and placebo, respectively. The **exploratory endpoint** of the responder rates, i.e. participants with at least 50% reduction in number of HF, supported the beneficial effect of the primary analysis and showed in the elinzanetant group at week 12 a percentage of 74% of responders, compared to 36% responders in the placebo group.

The **subgroup analyses** with respect to region, race, ethnicity, BMI, smoking history for the primary and key secondary analysis, suggested that none of these subgroups had an impact on the efficacy analysis elinzanetant. In general, results obtained were consistent between groups.

3.3. Uncertainties and limitations about favourable effects

None

3.4. Unfavourable effects

Treatment of moderate to severe VMS associated with menopause

The overall percentage of patients reporting **any adverse events** (TEAEs) in OASIS 3 was higher in the elinzanetant group compared to placebo (70.0%) vs. (61.1%) and in the first 12 weeks of all placebo-controlled data in the pooled safety analysis (50.8%) vs. (43.2%). The **most frequently reported TEAEs** in OASIS 3 (>5%) that were reported more frequently in the elinzanetant arm compared to the placebo arm were headache (9.6% vs. 7.0%), fatigue (6.7% vs. 2.9%), and somnolence (5.1% vs. 1.3%). A similar adverse event pattern was observed in the placebo-controlled 12-weeks of the pooled safety analysis. Also the percentage of **TEAEs considered related to study drug by the investigator** was almost comparable with headache, somnolence, dizziness and dyspepsia that were reported in a higher frequency compared to placebo.

Treatment of moderate to severe VMS caused by adjuvant endocrine therapy (AET)

During the 12-week placebo-controlled period, the overall percentage of patients reporting **any adverse events** (TEAE) was slightly higher in the elinzanetant arm compared to the placebo arm (68.9%) vs. (62.0%)]. The **most frequently reported TEAEs** were comparable with the TEAEs reported in participants with VMS associated with menopause, with the exception of depression (4.1%) vs. (0.6%)], and asthenia (4.1%) vs. (1.3, which were also more frequently reported with elinzanetant compared to placebo. The incidence of TEAEs in ≥2% of subjects considered **related to study drug by the investigator** was higher in the elinzanetant arm (34.3%) compared with the placebo arm (27.2%), of which the adverse event pattern is suggested largely comparable with that observed in participants with VMS due to natural menopause. However, also asthenia and depression were reported in a higher frequency which was not observed in participants with VMS associated with natural menopause.

AE of special interest and other safety issues:

Liver event: In all 4 phase 3 studies, elevated post-baseline values of ALT/AST ≥ 3 x ULN were observed in a low number of patients in the elinzanetant and placebo arms, of which several cases were considered potential AESIs of liver event. Few fulfilled CLO criteria. Overall, no cases of DILI causally related to elinzanetant (i.e., probably related likelihood >50%) and no Hy's law cases were identified (based on hepatocellular and cholestatic analysis). Based on an additional comprehensive evaluation of these clinical data, supported by non-clinical (drug properties in comparison with fezolinetant and animal studies) liver monitoring is considered not required for elinzanetant in the post-approval setting. Subsequently, liver function monitoring is not addressed in the SmPC. However, follow-up of liver events in future PSURs is requested, as pharmacovigilance activity.

Somnolence or fatigue: In all 4 phase 3 studies somnolence and fatigue were reported more frequently in the elinzanetant arm compared to the placebo arm as well as the frequency of somnolence or fatigue assessed as related to study intervention by the investigator. Additionally, hypersomnia (excessive sleepiness) was reported in few participants who received elinzanetant. Asthenia (PT) was reported in some participants in the elinzanetant arm, of which one case was severe. In OASIS 1-3 and SWITCH-1, women were instructed to take the study drug at bedtime and neither to drive nor operate machinery if they experienced somnolence or fatigue. This recommendation is stricter due to uncertainties regarding the relevance of these AEs observed in studies prior to start of the SWITCH study, than recommended in the SmPC section 4.7.

Phototoxicity: Based on the non-clinical potential and the imbalances found in the number of cases within the safety datasets, phototoxicity is considered an ADR of elinzanetant.

Postmenopausal uterine bleeding: In the pooled safety analysis over week 1-52 the percentages were similar in both treatment arms. Overall, no cases of endometrial hyperplasia or malignant neoplasm were reported, see also below. In OASIS 4, the percentage of participants in both treatment arms who reported postmenopausal bleeding was very low. The background therapy for the cases was tamoxifen, whose SmPC reports vaginal bleeding as ADR with frequency "very common". Overall, these cases were associated with a benign endometrium. No cases of endometrial hyperplasia or malignant neoplasm were reported.

Other findings related to safety *Cardiac safety:* In OASIS 1-4 studies, a single 12-lead ECG was performed for eligibility at screening and could be performed during the studies if clinically indicated. Palpitations (PT) was the most frequently reported TEAE, both in the pooled safety population (8 women) and in OASIS 4 study (4 women). Based on the study results there was no indication of a QTc interval prolongation or other relevant cardiac safety risks by elinzanetant after single oral administration of elinzanetant at doses up to 5 times the maximum recommended dose, and no relationship between elinzanetant plasma concentration and QTc interval. This assessment is supported by the absence of relevant findings in the non-clinical cardiac safety studies.

Bone mineral density (BMD): In OASIS 3, in total, 173 in the elinzanetant 120 mg arm and 170 women in the placebo arm had DEXA scan performed. For both elinzanetant and placebo groups, the observed mean percentage changes in BMD at EoT were within the expected age-related loss per year, and comparable between treatment arms. In conclusion, the results obtained in OASIS 3 at week 24 and week 52 do not indicate that elinzanetant has a relevant effect on BMD.

With regard to **Endometrial safety**, based on the endometrial biopsy data provided and supplemented with TVU outcomes, it can be concluded that the currently available data do not suggest a signal that the use of elinzanetant has an adverse effect on endometrial safety.

Mammogram: Throughout all studies, there were either no cases of clinically significant abnormal mammogram findings were reported, or if, reported, they were not related to study intervention.

Seizure: One event occurred 46 days after switching from placebo to elinzanetant treatment and was considered drug-related by the investigator and led to discontinuation of elinzanetant. However, follow-up of seizures or other convulsive disorders reported in patients with a history of these conditions in future PSURs is requested, as pharmacovigilance activity.

Suicidal ideation and behaviour: Suicidal ideation and behaviour were monitored by the Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) questionnaire in the SWITCH-1 and OASIS 1-3 studies. The number of women with suicidal ideation was low in both treatment arms (ranging from 2 to 5 women in elinzanetant arm and 2 to 4 women in placebo arm at all timepoints measured). These results indicate no relevant effect of elinzanetant on suicidal ideation and behaviour, which is reassuring.

No **deaths** have been reported in the safety population of elinzanetant. Overall, the incidence of subjects with **serious adverse events** (SAEs) in all 4 phase 3 studies was low. In the pooled analysis, all serious TEAEs were distributed without a pattern. One *serious TEAE related to elinzanetant by the investigator* were reported, including 1 case of generalized tonic-clonic seizure in a woman with a history of tonic-clonic seizures, 1 case of intestinal obstruction, and 1 case of tremor (reported twice, during Weeks 1-12 and during week 13-26). In OASIS 4, Part A (Weeks 1 to 26) serious TEAEs were reported in 18 women during elinzanetant treatment, including one case of hepatic enzyme increased with metastases to liver, metastases to liver and metastases to bone in one patient, breast cancer recurrent, for which cases additional background and causality assessment has been provided, supporting that a causal relation with elinzanetant appears currently lacking. In Part B, one additional case of breast cancer stage IV was reported. Additionally, one case of breast cancer is reported in Part C (ongoing), for which cases also a detailed narrative and a thorough causality assessment is requested.

Serious TEAEs that led to discontinuation of study drug were reported in 3 women in the elinzanetant arm (1 case of hepatic enzyme increased and metastases to liver, 1 case of tremor (considered drug-related by the investigator), and 1 case of breast cancer recurrent during Weeks 13-26 after switching to elinzanetant.

The number of participants who discontinued due to a TEAE in the pooled safety analysis was twice as high in the elinzanetant arm compared to the placebo arm in the placebo-controlled periods (51/765) (6.6%) vs. 21/754) (2.9%). Most discontinuations due to a TEAE occurred in the first 12 weeks. Fatigue and headache were the most frequently reported TEAEs leading to discontinuation in the elinzanetant arm, of which the majority was assessed as related by the investigator. Other TEAEs leading to discontinuation were reported were somnolence, diarrhoea, abdominal pain, asthenia and depressed mood. In the ongoing OASIS 4, a similar pattern was observed, though also asthenia was reported as a frequent reason to discontinue elinzanetant. In conclusion, the incidence of TEAEs leading to discontinuation in both indications was low, which is reassuring, and the pattern of TEAEs leading to discontinuation in the elinzanetant arms was comparable between studies. However, follow-up of any future breast cancer cases is considered necessary. It was therefore proposed to request the applicant to follow up all breast cancer-related events in this target population in future PSURs, as pharmacovigilance activity.

No trends or patterns have been observed in **special populations**, i.e. subgroup analyses based on *race, ethnicity*, and *BMI, renal and hepatic impairment, ethnicity (Chinese and Japanese women)*. ***Use in Pregnancy***: There are no data of use of elinzanetant in pregnant women. Studies in animals have shown reproductive toxicity (see non-clinical AR). T Applicant proposed a CI for pregnancy for elinzanetant to prevent any risk, e.g. for a potential pregnancy in peri-menopausal women. This was agreed. ***Use during Lactation***: There are no data on the presence of elinzanetant or its metabolites in human milk. This is currently appropriately addressed in section 4.6 of the SmPC. The **risk of infertility** in women during and after elinzanetant treatment is likely low based on non-clinical and clinical data. ***Overdose***: No cases of accidental/ intentional overdose were reported. ***Drug abuse*** As elinzanetant is a centrally acting dual NK-1/3 antagonist, the abuse potential was assessed in non-clinical studies and elevated in clinical studies. Based on data including non-clinical and clinical assessments, elinzanetant is not expected to have a clinically relevant abuse potential. Based on the available clinical data, no indication of ***withdrawal or rebound effects*** after discontinuation of elinzanetant is observed, in which participants were followed up for up to 4 weeks after discontinuation of the study drug.

A discussion regarding the potential for **pharmacodynamic interactions** of elinzanetant with adjuvant endocrine treatments, e.g. aromatase inhibitors (anastrozole, letrozole, exemestane)), tamoxifen, GnRH analogues, and a combination with CDK 4/6 inhibitors in breast cancer treatment has been provided. Based

on review of MoAs of endocrine therapy and potential interference of elinzanetant based on its MoA with the therapeutic efficacy of these products, it can be agreed that no relevant PD interactions of elinzanetant with the endocrine therapies tamoxifen, aromatase inhibitors, and GnRH agonists used in OASIS 4 are expected that may impair anti-cancer therapeutic efficacy of these therapies for breast cancer treatment in pre- and post-menopausal women. As the use of elinzanetant with any additional breast cancer medication combined with AET has not been investigated (SERDs (e.g. fulvestrant), MoA CDK4/6 kinase inhibitors (e.g. Palbociclib), HER2 targeting treatments, PI3K inhibitors, immunotherapies, mTOR targeting treatments or chemotherapy, except that some were allowed to use CDK 4/6 inhibitors as rescue medication in the extension phase CDK 4/6 inhibitors (except for those which are strong CYP3A4 inhibitors) after 12 weeks of treatment with the study intervention, the MAH agrees to add a respective warning in the SmPC that women with history of breast cancer were only treated with tamoxifen or aromatase inhibitors, with or without GnRH agonists. The use of elinzanetant with any additional breast cancer medication combined with this AET has not been investigated. A decision to treat women with elinzanetant when reviewing other medication than evaluated in the clinical studies should be based on a benefit-risk consideration for the individual.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 80 Effects table for Elinzanetant in VMS associated with menopause and VMS caused by AET, based on OASIS 1, 2, 3 and 4 (data cut-off: May 2024).

Effect	Unit	Elinzanetant	Placebo	Uncertainties/ Strength of evidence
Favourable Effects				
HF frequency: Change from baseline in frequency of moderate to severe HF at week 12	Mean change, LS mean (95% CI)	-9.16 (-9.92, -8.40)[1] -7.53 (-8.02, -7.05)[2]	-5.97 (-6.73, -5.20)[1] -4.16 (-4.84, -3.47)[2]	Primary endpoint SoE: • Diff. in LS means vs. placebo (95% CI): -3.19 (-4.26, -2.13)[1] -3.38 (-4.21, -2.54)[2] • Clinically meaningful reduction of ≥2 HF difference with placebo • Consistent results in pivotal studies for both indications • Consistent in sensitivity analyses • Consistency across subgroups for both indications • Sustained effect until 50 weeks of treatment (OASIS 3)
	Range in responder rate at week 12 (50% reduction in HF freq.)	71.4%[4] to 74.7%[5]	35.8%[2] to 48.3%[5]	
PROMIS SD SF 8b: Change from baseline in self-reported sleep disturbance total T-score at week 12	Mean change, LS mean (95% CI)	-10.33 (-11.12, -9.54)[1] -10.06 (-10.85, -9.26)[2]	-5.39 (-6.19, -4.59)[1] -3.94 (-5.06, -2.82)[2]	Key secondary endpoint SoE: • Diff. in LS means vs. placebo (95% CI): -4.94 (-6.02, -3.85)[1] -6.12 (-7.49, -4.75)[2] • Consistent results in pivotal studies for both indications • Consistent in sensitivity analysis • No differences in subgroups
MENQOL: Change from baseline in menopause related health QoL total score at week 12	Mean change, LS mean (95% CI)	-1.32 (-1.44, -1.20)[1] -1.23 (-1.34, -1.11)[2]	-0.96 (-1.08, -0.85)[1] -0.55 (-0.77, -0.38)[2]	Key secondary endpoint SoE: • Diff. in LS means vs. placebo (95% CI): -0.36 (-0.52, -0.20)[1] -0.68 (-0.88, -0.48)[2] • Consistent results in pivotal studies for both indications • Consistent in sensitivity analysis • No differences in subgroups
Unfavourable Effects				
Discontinuations due to TEAE Week 1-12	n/N (%)	60/765 (7.8)[3] 23/315 (7.3)[2]	27/754 (3.6)[3] 4/158 (2.5)[2]	SoE: • Consistent results for both indications • TEAEs leading to discontinuation consistent with drug-related TEAEs (fatigue, somnolence, dizziness, headache, depressed mood, GI-symptoms)

[1] pooled efficacy data OASIS 1 and 2 for menopause indication, [2] OASIS 4 for AET indication, [3] pooled safety population (OASIS 1, 2 and 3), [4] OASIS 1, [5] OASIS 2
AET = adjuvant endocrine therapy, HF = Hot flushes, TEAE = treatment emergent adverse event, VMS = vasomotor symptoms

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

With regard to the indication, '*treatment of vasomotor symptoms (VMS) associated with menopause*', pivotal evidence for efficacy is based on the phase 3 studies OASIS 1 and 2, supported by the long-term, placebo-controlled safety study, OASIS 3, to evaluate durability of efficacy of elinzanetant. The OASIS 1 and 2 studies, of identical design, showed a considerable, and clinically meaningful (i.e. HFs were reduced with ≥2 HF per day) greater reduction in daily HF frequency from baseline to week 12, with elinzanetant compared to placebo, i.e. difference of -3.19. Treatment with elinzanetant resulted also in a higher proportion of participants with at least 50% reduction from baseline in number of HF at 12 weeks compared to placebo. The effect on HF frequency sustained over 50 weeks of treatment (OASIS 3), which is re-assuring. In line with the observed reductions frequency of HF, additional beneficial effects were seen in the PROs PROMIS SD SF 8b total T-score with improvements in sleep disturbance and in the MENQOL score regarding presence of menopausal symptoms and the impact thereof in the elinzanetant groups, as compared to placebo.

Notably, although these concern indirect comparisons, the reduction in frequency of HF for elinzanetant seems to be in the same range to even higher than for the recently EU-approved non-hormonal NK-3 receptor antagonist fezolinetant for which a HF frequency reduction of -2.55 for week 12 was reported, as well as for oestrogen replacement therapy reporting a reduction of -17.46 HF per week, which is ≈ -2.5 HF frequency reductions per day (*Cochrane Data Base Syst. Rev. 2001*).

Concerning the indication, '*treatment of VMS caused by adjuvant endocrine therapy'*, pivotal evidence is based on the 12-week placebo-controlled phase of a single phase 3 study OASIS 4. A generally similar beneficial effect as in OASIS 1 and 2, was observed in the reduction in HF frequency from baseline to week 12 (-3.38) compared to placebo. Also in OASIS 4, better improvements were seen as compared to placebo for the PROs on sleep disturbance and MENQOL score and a 2-fold higher responder rate in the elinzanetant arm compared to placebo arm at 12 weeks.

Of note, it can be considered that there is good concordance among the efficacy endpoints, both within the studies (primary and (key) secondary endpoints), as well as between the four OASIS studies for both proposed indications (i.e. VMS associated with menopause and VMS caused by AET). Therefore, it was agreed that the reduction in HF frequency, by approximately 3 hot flushes per day, relative to placebo, was to be considered to be clinically relevant in both target populations.

Further, the four OASIS studies were well-conducted, the patients were dosed in accordance to the proposed dosing regimen in the SmPC and the evidence of efficacy was considered highly statistically convincing, sensitivity analysis were supportive for the primary and key secondary endpoints and results were in general consistent across subgroups.

The clinical safety data set in support of the indication '*Treatment of moderate to severe vasomotor symptoms (VMS) associated to menopause'* is primarily based on the placebo-controlled OASIS 3 study with a duration of 52 weeks. In total 226 postmenopausal women with moderate to severe HF completed 52 weeks of treatment, which is considered sufficient. The presented safety data did not raise major concerns, with somnolence, fatigue, headache, dyspepsia and dizziness being the most common treatment-related adverse events (AEs). Elinzanetant is well-tolerated, since the majority of the adverse events are mild to moderate in severity, and the discontinuations due to drug-related adverse events were low, with a comparable pattern of AEs over OASIS 1, 2 and 3, which is re-assuring. The nervous system disorders

commonly reported with elinzanetant consist of somnolence, fatigue, and dizziness.. This is possibly due to the additional antagonistic effects of elinzanetant on the NK-1 receptor, which is hypothesized as linked to sleep. Based on extensive assessments, no significant effect on the risk of endometrial, hepatic, cardiac, breast, and bone safety could be revealed with the use of elinzanetant. Thorough evaluation of currently available clinical and non-clinical data supports that there is no clear signal indicating a risk of potential drug-induced liver failure unlike seen with fezolinetant. Therefore, no update of the safety specifications on this point is acceptable. However, follow-up of liver events will be performed in future PSURs .

The clinical safety data set for the indication '*Treatment of moderate to severe vasomotor symptoms (VMS) caused by adjuvant endocrine therapy (AET)* is based on one pivotal phase 3 study OASIS 4. The adverse event pattern observed in OASIS 4 in the placebo-controlled weeks 1-12 is suggested largely comparable with that observed in participants with VMS associated with natural menopause, however, also asthenia, alopecia, and depression were reported in a higher frequency compared to placebo, which was not observed in participants with VMS associated with menopause. The ADR table in section 4.8 of the SmPC has been revised to separately reflect ARDs in both target populations.

During the assessment, questions were raised on the initial proposed wording of indication, which specified that patients should not be candidates for hormonal therapy. However, this restriction was not an exclusion criterion in the phase 3 studies. In addition, the decision to prescribe HRT or another treatment option should be made on an individual basis, weighing the potential benefits and risks of all options, including the woman's personal preference in a shared decision-making process with her treating physician, as recommended in clinical guidelines. In conclusion, it was considered that keeping this requirement would have resulted in a restriction of the target population.

3.7.2. Balance of benefits and risks

In terms of benefit, elinzanetant provides a significant and clinically meaningful greater reduction in frequency of hot flushes compared to placebo in women with '*moderate to severe VMS associated with menopaus*e' and '*moderate to severe VMS caused by adjuvant endocrine therapy (AET) related to breast cancer'*. This reduction in HF frequency was accompanied by a greater reduction in severity of HF and sleep disturbances and VMS related QoL and a higher 50% responder rate in the elinzanetant group. Of note, while based on indirect comparison, the magnitude of the reduction in frequency (and severity) of elinzanetant seems to be similar to somewhat higher than observed for fezolinetant, and comparable to that noted with estrogen replacement therapy (*Cochrane Data Base Syst. Rev. 2001*). The obtained efficacy in reduction of VMS could be considered of special relevance for those patients in whom oestrogen use is contra-indicated, including women with, or at high risk for developing, hormone positive breast cancer who suffer from VMS caused by AET. The use of elinzanetant appeared to be well tolerated with an acceptable safety profile, and with no specific safety concerns observed regarding endometrial, breast, hepatic, cardiac and bone safety. However, it is considered appropriate to follow-up liver events, seizures or other convulsive disorders reported in patients with a history of these conditions, and breast cancer-related events in women with VMS *caused by adjuvant endocrine therapy (AET) related to breast cancer* in future PSURs.

Based on these results, the benefit/risk balance is positive for both indications.

3.7.3. Additional considerations on the benefit-risk balance

Engagement with patients was sought through written questions from the regulatory agencies to these organisations. They stressed that, in treating VMS in women who are undergoing adjuvant endocrine therapy and are not candidates for HRT, a patient-centred approach is essential. The emphasis should be on improving quality of life through symptom relief, while ensuring long-term safety, particularly for women with cancer or other chronic conditions. Further research and patient-centred development of such treatments are crucial for meeting the unmet medical needs of women in this group.
The input of patients was taken into account by the CHMP.

3.8. Conclusions

The overall benefit/risk balance of Lynkuet is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lynkuet is favourable in the following indications:

"Lynkuet is indicated for the treatment of moderate to severe vasomotor symptoms (VMS):

- associated with menopause (see section 5.1)

- caused by adjuvant endocrine therapy (AET) related to breast cancer (see section 5.1)."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Elinzanetant is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.