CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219469Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	219469
Priority or standard	Standard
Submit date(s)	7/26/2024
Received date(s)	7/26/2024
PDUFA goal date	10/26/2025
Division/office	Division of Urology, Obstetrics, and Gynecology (DUOG), Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Review completion date	10/22/2025
Established/proper name	Elinzanetant (BAY 3427080)
Proposed proprietary name	LYNKUET
Pharmacologic class	New molecular entity, non-hormonal, selective neurokinin 1, 3 (NK1/NK3) receptor antagonist
Other product name(s)	GSK1144814, NT-814
Applicant	Bayer Healthcare Pharmaceuticals Inc
Dosage form(s)/formulation(s)	Capsule
Dosing regimen	120 mg/day, two 60 mg (b) (4) at (b) (4) with or without food
Applicant-proposed indication(s)/ population(s)	Treatment of moderate to severe vasomotor symptoms associated with menopause
SNOMED CT code for proposed indication disease term(s)1	198436008 |Menopausal flushing (finding)|
Regulatory action	Approval
Approved dosage (if applicable)	120 mg/d, two 60 mg (b) (4) at (b) (4) one 60 mg (b) (4) at (b) (4) if taking moderate CYP3A4 inhibitors
Approved indication(s)/ population(s) (if applicable)	Treatment of moderate to severe vasomotor symptoms (VMS) due to menopause
SNOMED CT code for approved indication disease term(s)1	198436008 |Menopausal flushing (finding)|

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUCR	AUC ratio
BCRP	breast cancer resistance protein
BID	twice daily
BLA	basolateral amygdala
BMD	bone mineral density
BMI	body mass index
BSEP	bile salt export pump
Cb/Cp	blood-to-plasma concentration ratio
CDER	Center for Drug Evaluation and Research
CLO	close liver observation
C_{max}	maximum plasma concentration
$C_{max}R$	C_{max} ratio
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CSR	clinical study report
CTCS	Computational Toxicology Consultation Service
CYP	cytochrome P450
DBG	dabigatran
DDI	drug-drug interaction
DILI	drug-induced liver injury
DSMB	data safety monitoring board
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EOP2	end-of-phase 2
EOT	end-of-treatment
ePV	enhanced pharmacovigilance
ER	estrogen receptor
E-R	exposure-response
EZN	elinzanetant
FAS	full analysis set
FDA	Food and Drug Administration
fmUGT	fraction metabolized by UGT
FSH	follicle stimulating hormone
fu	unbound fraction
$GABA_A$	gamma-amino butyric acid type A

GCP	good clinical practice
GI	gastrointestinal
GLP	good laboratory practice
GnRH	gonadotropin-releasing hormone
HCl	hydrochloride
HF	hot flash
HFDD	Hot Flash Daily Diary
HPG	hypothalamic-pituitary-gonadal
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IND	investigational new drug
IV	intravenous
kcat_GI_factor	gut wall metabolism factor
K_I	half-maximal rate of inactivation
k_{inact}	maximal rate of inactivation
KNDy	kisspeptin/NKB/dynorphin
LH	luteinizing hormone
LS	least squares
LSMB	Liver Safety Monitoring Board
MATE1	multidrug and toxin extrusion protein 1
MATE2K	multidrug and toxin extrusion protein 2 splice variant K
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
MENQOL	Menopause Specific Quality of Life Scale
MI	multiple imputation
MMRM	mixed-effect model for repeated measures
MOE	multiple of exposure
MRHD	maximum recommended human dose
mRNA	messenger RNA
MRP2	multidrug resistance-associated protein 2
NDA	new drug application
NK1	neurokinin 1
NK1R	neurokinin 1 receptor
NK3	neurokinin 3
NK3R	neurokinin 3 receptor
NKB	neurokinin B
NME	new molecular entity
NOAEL	no-observed-adverse-effect level
NSB	nonspecific binding
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCMQ	OND custom medical query
OCT	organic cation transporter
OND	Office of New Drugs
OSI	Office of Scientific Investigations
PBPK	physiologically based pharmacokinetic

PD	pharmacodynamic
PET	positron emission tomography
P-gp	P-glycoprotein
PI	Prescribing Information
PK	pharmacokinetic
PR	progesterone receptor
PROMIS SD SF 8b	Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b
PT	preferred term
QD	once daily
(Q)SAR	quantitative structure-activity relationship
SA1	sensitivity analysis 1
SA2	sensitivity analysis 2
SAE	serious adverse event
SAF	safety analysis set
SD:Hsd	Harlan Sprague-Dawley
SDLP	standard deviation of lateral position
SEE	substantial evidence of effectiveness
SOC	system organ class
SPA	special protocol assessment
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TR	total radioactivity
UGT	uridine diphosphate glucuronosyltransferase
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
USPI	United States Prescribing Information
UV	ultraviolet
VMS	vasomotor symptoms

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Bayer Healthcare Pharmaceuticals (hereafter referred to as the Applicant), submitted NDA 219469 under the 505(b)(1) regulatory pathway, proposing to market the new molecular entity (NME) elinzanetant for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause.

A multidisciplinary review team has reviewed this application, and each discipline recommends approval of this application. The signatory authority for this application concurs and recommends approval for this indication.

Menopause is a natural process in a woman's life that marks the decline of ovarian hormone production and cessation of reproductive capacity. This process is associated with profound physiological changes, resulting in symptoms such as VMS or hot flashes (HFs), and symptoms of vulvovaginal atrophy (vaginal dryness, irritation, and pain with intercourse). Menopausal symptoms, such as vasomotor symptoms, can negatively affect women's daily activities and quality of life (Whiteley et al. 2013a). In addition, menopausal symptoms can persist for long periods in some individuals.

Vasomotor symptoms, also known as hot flashes or HFs, occur as a result of estrogen withdrawal and represent a disorder of hypothalamic thermoregulation. The kisspeptin/neurokinin B (NKB)/dynorphin (KNDy) neurons in the thermoregulatory center in the hypothalamus are thought to be responsive to both estrogen and ambient temperature. In response to decreasing estrogen levels, hypertrophy and activation of the KNDy neurons are thought to disrupt thermoregulation and trigger VMS. Elinzanetant is a neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist that blocks NK1,3 receptors on the KNDy neurons. The Applicant hypothesizes that blockade of the KNDy neurons attenuates vasomotor symptoms associated with menopause.

Substantial evidence of effectiveness (SEE) of elinzanetant for treatment of moderate to severe vasomotor symptoms due to menopause was established with two adequate and well-controlled studies. For full details, refer to Section 1.2.

The available clinical data show that elinzanetant is safe for its intended use. Common adverse reactions include headache, fatigue, dizziness, somnolence, abdominal pain, rash, diarrhea, and muscle spasm.

Central nervous system depressant effects and daytime impairment were seen, and patients should refrain from driving or engaging in hazardous occupations or activities until the effects have resolved. Hepatic transaminase elevations were seen in the clinical development program and hepatic transaminases should be measured prior to initiating therapy and 3 months after initiation. In addition, there will be enhanced pharmacovigilance for hepatic adverse events.

Animal studies suggest that elinzanetant may cause pregnancy loss or stillbirth. Females of reproductive potential should have pregnancy excluded prior to initiating elinzanetant and should use effective contraception for 2 weeks after stopping elinzanetant. In addition, animal studies showed convulsions and there was one patient with a history of seizures who experienced a seizure during the clinical program. The identified risks for elinzanetant can be adequately mitigated through labeling and routine pharmacovigilance.

As described in Section 2.2, we conclude that the reduction in frequency and severity of hot flashes observed with elinzanetant outweighs the risks when elinzanetant is used as recommended in the approved labeling.

1.2. Conclusions on Substantial Evidence of Effectiveness

We conclude that substantial evidence of effectiveness for elinzanetant 120 mg daily (taken as two 60 mg (b) (4) for moderate to severe VMS in postmenopausal women has been demonstrated with two adequate and well-controlled studies (Study 21651 [OASIS 1] and Study 21652 [OASIS 2]).

A total of 796 postmenopausal women (396 in OASIS 1 and 400 in OASIS 2) aged 40 to 65 years who had a minimum of 50 moderate to severe HFs, including nighttime HFs, per week, were enrolled in OASIS 1 and OASIS 2. Subjects were randomized to elinzanetant 120 mg or placebo.

The primary efficacy endpoints in both studies were the mean change in frequency and in severity of moderate to severe vasomotor symptoms from baseline to Weeks 4 and 12, including day and night HFs measured using the Hot Flash Daily Diary (HFDD). In both studies, elinzanetant showed a statistically significant and clinically meaningful reduction (≥2 hot flashes over 24 hours) in the frequency of HFs from baseline to Weeks 4 and 12 compared to placebo. Also, in both studies, there was a statistically significant reduction in the severity of HFs from baseline to Weeks 4 and 12 compared to placebo.

Substantial evidence of effectiveness for elinzanetant 120 mg for the treatment of moderate to severe VMS associated with menopause has been demonstrated based on the results of two Phase 3 studies (OASIS 1 and OASIS 2).

2. Benefit–Risk Assessment

2.1. Benefit–Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Menopause is a natural and normal physiological process marking the decline of reproductive capacity in females. • In the United States, nearly 63 million women are past the average age of natural menopause of 51 years of age (50 years of age and older as of July 1, 2021) (United°States°Census°Bureau 2020). • Menopause is associated with profound physiological changes. Symptoms of menopause, such as vasomotor symptoms (VMS) [hot flashes/hot flushes] and vulvar and vaginal atrophy (VVA) symptoms (also referred to as genitourinary syndrome of menopause or GSM) [vaginal dryness, vaginal irritation/itching, and pain with sexual activity (dyspareunia)] can be debilitating with respect to a woman's ability to accomplish her normal activities, including sleep (Whiteley et al. 2013a). However, menopause is not directly a life-threatening condition. • VMS are experienced by up to 80% of individuals during menopause (Gold et al. 2006). The prevalence of moderate to severe VMS associated with menopause was 34% in the United States, 40% in Europe, and 16% in Japan (Nappi et al. 2021). • Hot flashes involve sudden sensations of heat in the upper body, particularly in the head, neck, chest and upper back. These symptoms occur as episodes that usually last 1 to 5 minutes and are characterized by perspiration, flushing, chills, clamminess, anxiety and, on occasion, heart palpitations. • An individual's experience can vary based on a combination of genetic background, psychological and socio-economic factors and other health conditions and/or treatments. • The duration of VMS from the time of symptom onset is typically 7.4 years and symptoms commonly persist for nearly a decade (Freeman et al. 2011; Avis et al. 2015).	Although menopause is a natural and normal physiological process, VMS associated with menopause can persist for long periods in some individuals, with a substantial impact on quality of life. Menopause symptoms, though not life threatening, constitute a significant public health concern often requiring medical intervention.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Current approved treatment options for the treatment of moderate to severe vasomotor symptoms include multiple oral, transdermal systems, topical gels/emulsion/spray, vaginal system products with estrogen-alone for use in a woman without a uterus or in combination with a progestogen for use in a woman with a uterus. These approved products offer a range of dosage strengths allowing titration of dose to relieve vasomotor symptoms based on treatment goals and risk for the individual woman. These products are contraindicated in women who have breast cancer (or a history of breast cancer), venous thromboembolism (or a history of venous thromboembolism), or thrombophilia, and those with a history of stroke or myocardial infarction. • Two nonhormonal products are approved (Brisdelle (paroxetine) and Veozah (fezolinetant)).	While there are numerous hormone therapy products for the treatment of vasomotor symptoms associated with menopause, there are only two nonhormonal options currently approved. Since some women cannot take or choose not to take hormone therapy, it is desirable to have additional nonhormonal treatments available to manage menopausal symptoms.
Benefit	• The efficacy of elinzanetant 120 mg orally once daily at bedtime was demonstrated in two adequate and well-controlled Phase 3 studies (OASIS 1 and OASIS 2) in postmenopausal women aged 40-65 years with moderate to severe VMS. • A total of 796 women (396 in OASIS 1 and 400 in OASIS 2) who had a minimum of 50 moderate to severe hotflashes, including nighttime HFs, per week, were enrolled in OASIS 1 and 2. Subjects were randomized to elinzanetant 120 mg or placebo. • In both studies, elinzanetant showed a statistically significant and clinically meaningful reduction (≥2 hot flashes over 24 hours) in the frequency of HFs from baseline to Weeks 4 and 12 compared to placebo. Also, in both studies, there was a statistically significant reduction in the severity of HFs from baseline to Weeks 4 and 12 compared to placebo.	Substantial evidence of efficacy of elinzanetant 120 mg for the treatment of moderate to severe VMS associated with menopause has been demonstrated based on the results of two Phase 3 studies (OASIS 1 and OASIS 2).
Risk and risk management	• The primary safety evaluation for elinzanetant was based on studies OASIS 1, OASIS 2 and OASIS 3 (a 52-week placebo-controlled study). Across the three clinical studies, a total of 713 women received elinzanetant, with approxiamtely 2200 women receiving at least one dose of elinzanetant (soft gel capsule formulation) in the clinical development program (including approxiamtely 550 for at least 23 weeks, and approxiamtely 220 for at least 50 weeks). • Common adverse reactions included headache, fatigue, dizziness, somnolence, abdominal pain, rash, diarrhea, and muscle spasms. • Concomitant use of strong and moderate CYP3A4 inhibitors increase elizanentant exposure and may increase the risk of adverse reactions associated with elizanentant. Therefore, concomitant use with strong CYP3A4 inhibiotrs is to	The safety profile of elinzanetant is well-characterized and the submitted safety data are supportive of the proposed 120 mg dose. To mitigate the risks of adverse reactions associated with increased elizanetant exposure, the recommended dose for patients taking moderate CYP3A4 inhibitors is 60 mg daily. Elinzanetant was associated with elevation in hepatic transaminases and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	be avoided. For patients taking moderate CYP3A4 inhibitors, dose adjustment to 60 mg (one capsule) daily is recommended. • In OASIS 3, serious adverse events (SAEs) were reported in 4.2% of subjects on elinzanetant compared to 1.9% of subjects on placebo. All events were reported as single preferred terms and distributed over several system organ classes. • By preferred term, the most frequently reported AEs leading to discontinuation were fatigue, headache, abdominal pain upper, and depressed mood, which occurred in 1.6%, 1.3%, 1%, and 1% of the elinzanetant group, respectively, compared to 0% of the placebo group. • Notable safety issues included hepatic transaminase elevation and nervous system disorders (including fatigue, somonolence, dizzziness, presyncope, and vertigo). For hepatic transaminase elevations, there were no cases of Hy's Law in the clinical program, but there were some imbalances in hepatic transaminase elevations. In addition, there were two cases of liver injury that were determined to be attributable to elinzanetant. The Applicant has agreed to enhanced pharmacovigilance to assess postmarketing adverse hepatic events occuring with elinzanetant use and provide expedited reporting, as well as summary reporting to be included in the periodic safety reports. For nervous system effects, imbalences in adverse events and adverse events leading to discontinuation were seen for fatigue, somnolence, dizziness and vertigo. In addition, a study evaluating driving performance indicated that driving ability was impaired in some subjects taking elinzanetant. • An additional notable safety consideration was the risk of seizure, which was identified in nonclinical data. In the clinical database there was one subject with a seizure who had a history of a seizure disorder. • Based on animal reproduction studies, elinzanetant may cause pregnancy loss or stillbirth when administered during pregnancy. Elinzanetant is intended for postmenapausal women. Labeling will note this risk for females of childbearing potential.	there was animal data suggesting risks related to hepatic safety. However, there were no cases of Hy's Law and there were a limited number of cases of hepatic transaminase elevation. Labeling and enhanced pharmacovigilence will be used to mitigate the risk of hepatic transaminase elevation. Elinzanetant was associated with CNS depressant effects (fatigue, somnolence) and daytime impairment in some patients. In addition, there were events of dizziness/vertigo and presyncope. The labeling will advise patients about the potential of CNS depressant effects and advise patients who experience these effects to refrain from driving or engaging in hazardous occupations or acvitivies until the effects have resolved. Based on nonclinical and clinical findings, the labeling will include information on the risk for seizures. Based on nonclinical findings, the labeling will include informaiton on the risk of pregnancy loss or stillbirth when adminstered during pregnancy. Importantly, elinzanetant is intended for postmenopausal women.

Abbreviations: CNS, central nervous system; HFs, hot flashes; VMS, vasomotor symptoms

2.2. Conclusions Regarding Benefit-Risk

Vasomotor symptoms are common during menopause and can negatively impact the quality of life for women and work productivity (Blumel et al. 2011; Whiteley et al. 2013a; Whiteley et al. 2013b). Vasomotor symptoms are characterized by problems with sleep, mood, joint pain, back pain, headaches, fatigue, loss of libido, mood swings and genitourinary problems (Nelson 2008; Berecki-Gisolf et al. 2009; Joffe et al. 2010; Moilanen et al. 2010; Seritan et al. 2010; Mishra and Kuh 2012; Whiteley et al. 2013a). In addition, menopausal symptoms can persist for long periods in some individuals (Freeman et al. 2014).

While there are numerous hormone therapy products for the treatment of vasomotor symptoms associated with menopause, there are only two nonhormonal options currently approved. Since some women cannot take or choose not to take hormone therapy, it is desirable to have additional nonhormonal treatments available to manage menopausal symptoms.

The efficacy of elinzanetant 120 mg orally once daily at bedtime was demonstrated in two adequate and well-controlled Phase 3 studies (OASIS 1 and OASIS 2) in postmenopausal women aged 40 to65 years with moderate to severe VMS. A total of 796 women (396 in OASIS 1 and 400 in OASIS 2) who had a minimum of 50 moderate to severe HFs, including nighttime HFs, per week, were enrolled in OASIS 1 and OASIS 2. Subjects were randomized to elinzanetant 120 mg or placebo. In both studies, elinzanetant showed a statistically significant and clinically meaningful reduction (≥2 hot flashes over 24 hours) in the frequency of HFs from baseline to Weeks 4 and 12 compared to placebo. At 4 and 12 weeks, respectively, the difference in the mean change from baseline in the frequency of HFs compared to placebo (least squares [LS]-mean [SE]) was -3.29 (0.61) and -3.22 (0.81) in OASIS 1 and -3.04 (0.69) and -3.24 (0.69) in OASIS 2. Also, in both studies, there was a statistically significant reduction in the severity of HFs from baseline to Weeks 4 and 12 compared to placebo. At 4 and 12 weeks, respectively, the difference in the mean change from baseline in severity of HFs compared to placebo ([LS]-mean [SE]) was -0.33 (0.06) and -0.40 (0.07) in OASIS 1 and -0.22 (0.06) and -0.29 (0.08) in OASIS 2.

The available clinical data show that elinzanetant is safe for its intended use. The safety database for elinzanetant for moderate to severe VMS was adequate. Dose adjustment to 60 mg daily is recommended for patients taking concomitant moderate CYP34 inhibitors due to increased elinzanetant exposure and the potential for associated increased adverse reactions. Common adverse reactions include headache, fatigue, dizziness, somnolence, abdominal pain, rash, diarrhea, and muscle spasms. Nervous system effects (i.e., somnolence, fatigue, vertigo, dizziness, and presyncope) were seen. Given the central nervous system depressant effects and daytime impairment, patients should refrain from driving or engaging in hazardous occupations or activities until these effects have resolved. Hepatic transaminase elevations were seen in the clinical development program and hepatic transaminases should be measured prior to initiating therapy and 3 months after initiation. In addition, there will be enhanced pharmacovigilance for hepatic adverse events. Animal studies suggest that elinzanetant may cause pregnancy loss or stillbirth. Females of reproductive potential should have pregnancy excluded prior to initiating elinzanetant and should use effective contraception for 2 weeks after stopping elinzanetant. In addition, animal studies showed convulsions and there was one patient with a history of seizures

who experienced a seizure during the clinical program. The identified risks for elinzanetant can be adequately mitigated through labeling and routine pharmacovigilance. Hepatic safety will also be monitored with enhanced pharmacovigilance.

Based on review of the available efficacy and safety data, NDA 219469 for elinzanetant provides substantial evidence of effectiveness and a favorable benefit-risk profile for the treatment of moderate to severe VMS in postmenopausal women.

II. Interdisciplinary Assessment

3. Introduction

Menopause is a natural and normal physiological process marking the decline of reproductive capacity in females. In the United States, nearly 63 million women are past the average age of natural menopause of 51 years of age (50 years of age and older as of July 1, 2021) (United°States°Census°Bureau 2020). Menopause is associated with profound physiological changes. Symptoms of menopause, such as vasomotor symptoms (VMS; hot flashes/hot flushes) and vulvar and vaginal atrophy symptoms (vaginal dryness, vaginal irritation/itching, and pain with sexual activity [dyspareunia]) can be debilitating with respect to a woman's ability to accomplish her normal activities, including sleep (Whiteley et al. 2013a). However, menopause is not directly a life-threatening condition. VMS are experienced by up to 80% of individuals during menopause (Gold et al. 2006). The prevalence of moderate to severe VMS associated with menopause was 34% in the United States, 40% in Europe, and 16% in Japan (Nappi et al. 2021).

Hot flashes involve sudden sensations of heat in the upper body, particularly in the head, neck, chest, and upper back. These symptoms occur as episodes that usually last 1 to 5 minutes and are characterized by perspiration, flushing, chills, clamminess, anxiety and, on occasion, heart palpitations. The duration of VMS from the time of symptom onset is typically 7.4 years and symptoms commonly persist for nearly a decade (Freeman et al. 2011; Avis et al. 2015). VMS can impact several areas of life and can affect work, social activities, leisure activities, sleep, mood, concentration, sexual activity, total energy level, and overall quality of life (Williams et al. 2009).

In menopause, there is a decrease in estradiol levels due to decreased ovarian function, resulting in increased gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus leading to increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations (Freeman et al. 2005). A group of neurons in the hypothalamus is an important regulator of GnRH. These neurons coexpress kisspeptin, dynorphin as well as NKB and are known as the kisspeptin/NKB/dynorphin neurons (KDNy neurons). The KDNy neurons in the hypothalamus have been identified as playing a role in thermoregulation that is responsive to estrogen and ambient temperature (Rance et al. 2013). In menopause, excessive KNDy neuron firing is thought to disrupt baseline thermoregulation and trigger VMS. Elinzanetant acts as an antagonist at NK1 and NK3 receptors, which are on KNDy neurons. Blocking these receptors is hypothesized to decrease hot flushes experienced by women with moderate to severe VMS during menopause.

Current Treatment Options

Women with mild symptoms of VMS (sensation of heat without sweating) typically do not require pharmacologic therapy. In contrast, women with moderate to severe symptoms of VMS may require pharmacologic therapy. The FDA has approved numerous postmenopausal hormone therapy products, both estrogens alone (Table 3) for use in a woman without a uterus, and estrogens plus progestogens products (Table 4 and Table 5) for use in a woman with a uterus, as well as two nonhormonal products for the treatment of moderate to severe VMS (Table 6). Hormone therapy has been the predominant treatment for moderate to severe VMS. Risks of estrogen plus progesterone therapy include deep venous thrombosis, pulmonary emboli, stroke, myocardial infarction, and breast cancer. Risks of estrogen-alone therapy include endometrial cancer, stroke, and deep venous thrombosis. Although hormone therapy is effective, these products are contraindicated in women who have breast cancer or a history of breast cancer, venous thromboembolism (or a history of venous thromboembolism) or thrombophilia, and those with a history of stroke or myocardial infarction. Currently, women who pursue treatment for VMS and are unable to take hormone therapy may try Brisdelle (paroxetine) or Veozah (fezolinetant), but additional options would be desirable.

Table 3. Estrogen-Alone Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

Estrogen-Alone Products	Available Dosage Strengths
Oral Estrogen-Alone Products	
Cenestin® (synthetic conjugated estrogens, A)*	0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
Enjuvia® (synthetic conjugated estrogens, B)*	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
Menest® (esterified estrogens)	0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
Ogen (estropipate)	0.625 mg, 1.25 mg, or 2.5 mg once daily
Premarin® (conjugated estrogens) Tablets	0.3 mg, 0.45 mg, 0.625 mg, 0.9 m, or 1.25 mg once daily
Various Generics (estradiol) Tablets	0.5 mg, 1.0 mg, 2.0 mg
Transdermal Products	
Alora® (estradiol matrix patch)	0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Climara® (estradiol matrix patch)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied once weekly
Estraderm® (estradiol reservoir patch)	0.05 mg or 0.1 mg; patch applied twice weekly
VivelleDot® (estradiol matrix patch)	0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Minivelle® (estradiol matrix patch)	0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Various Generics (estradiol matrix patch)	0.05 mg or 0.1 mg; patch applied once or twice weekly

Estrogen-Alone Products	Available Dosage Strengths
Topical Products	
Divigel (estradiol gel) 0.1%	0.25 mg, 0.5 mg, or 1.0 mg; 0.25 gram, 0.5 gram or 1.0 gram applied once daily
Elestrin® (estradiol gel)	0.87 gram containing 0.52 mg or 1.7 gram containing 1.04 mg applied once daily
Estrasorb® (estradiol topical emulsion)	0.05 mg; two 1.74 gram pouch applied once daily
EstroGel® 0.06% (estradiol gel)	1.25 grams containing 0.75 mg estradiol applied once daily
Evamist® (estradiol transdermal spray)	1, 2 or 3 spray(s) 90 mcL containing 1.53 mg estradiol applied once daily
Vaginal Rings	
Femring® (estradiol acetate)	Release of 0.05 mg estradiol or 0.10 mg estradiol; ring worn for 90 days

Source: Reviewer generated
* Discontinued

Table 4. Estrogen Plus Progestogen Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

Estrogen Plus Progestogen Products	Available Dosage Strengths
Oral	
Activella® (estradiol [E2] plus norethindrone acetate [NETA])	0.5 mg E2 plus 0.1 mg NETA taken daily or 1 mg E2 plus 0.5 mg NETA taken daily
Angeliq® (drospirenone [DRSP] plus estradiol [E2])	0.25 mg DRSP plus 0.5 mg E2 or 0.5 mg DRSP plus 1 mg E2 taken daily
femhrt® (norethindrone acetate [NETA] plus ethinyl estradiol [EE])	0.5 mg NETA plus 2.5 mcg EE taken daily or 1 mg NETA plus 5 mcg EE taken daily
Prefest® (estradiol [E2] plus norgestimate)	1 mg E2 taken daily for 3 days, then 1 mg E2 plus 0.09 mg norgestimate taken daily for 3 days, repeated continuously
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE taken daily for 14 days, then 0.625 mg CE plus 5.0 mg MPA taken daily on days 15-18
Prempro® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.3 mg or 0.45 mg CE plus 1.5 mg MPA taken daily or 0.625 mg CE plus 2.5 mg or 5.0 mg MPA taken daily
Bijuva® (estradiol [E2] and progesterone [P4])	0.5 mg estradiol/100 mg progesterone taken daily or 1 mg estradiol/100 mg progesterone taken daily
Transdermal	
ClimaraPro® (estradiol [E2] plus levonorgestrel)	0.045 mg E2 plus 0.015 mg levonorgestrel; patch applied once weekly
CombiPatch® (estradiol [E2] plus norethindrone acetate [NETA])	Release of 0.05 mg E2 plus 0.14 mg NETA; patch applied twice weekly or 0.05 mg E2 plus 0.25 mg NETA; patch applied twice weekly

Source: Reviewer generated

Table 5. Estrogen Plus Estrogen Agonist/Antagonist Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

Oral Tablet or Capsule	Available Dosage Strengths
Duavee® (conjugated estrogens/bazedoxifene)*	0.45 mg CE plus 20 mg bazedoxifene taken daily

Source: Reviewer generated
*Bazedoxifene is a SERM used with conjugated estrogen to treat osteoporosis and hot flashes in postmenopausal women. Bazedoxifene stimulates estrogen receptors in bone and has antagonistic effects in the breast and uterus.
Abbreviation: CE, conjugated estrogens

Table 6. Nonhormonal Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Oral Nonhormonal Tablet or Capsule	Available Dosage Strengths
Brisdelle™ (paroxetine)* capsules	7.5 mg at bedtime daily
Veozah® (fezolinetant)**	45 mg tablet once daily with or without food

Source: Reviewer generated
*selective serotonin reuptake inhibitor (SSRI).
**Neurokinin-3 (NK3) receptor antagonist.

In summary, while there are numerous approved treatment options for moderate to severe VMS in postmenopausal women, there are only two approved nonhormonal options. Symptoms of VMS can profoundly impact women, and it is important to have additional therapeutic options.

3.1. Review Issue List

The review team identified the key safety review issues listed in Section 3.1.2 below relevant to the evaluation of risk. In-depth assessment of these risk issues can be found in Section 7.7, respectively.

3.1.1. Key Efficacy Review Issues

The review team did not identify any substantive review issues related to efficacy. Substantial evidence of efficacy was established based on OASIS 1 and OASIS 2. See Section 6.2.5.3.1 for additional discussion.

3.1.2. Key Safety Review Issues

3.1.2.1. Hepatic Transaminase Elevation

3.1.2.2. Risk of Pregnancy Loss

3.1.2.3. Endometrial Tumor Abnormality

3.1.2.4. Seizures

3.1.2.5. Nervous System Effects

3.1.2.6. Photosensitivity

3.2. Approach to the Clinical Review

The primary evidence of efficacy and safety of elinzanetant in postmenopausal women with hot flashes is from three clinical studies: OASIS 1, OASIS 2, and OASIS 3. Two of these studies, OASIS 1 and OASIS 2, were submitted as the primary evidence of efficacy of elinzanetant in postmenopausal women. The primary assessment of safety was based on data from OASIS 1, OASIS 2, and OASIS 3.

The clinical studies conducted to support the primary benefit-risk assessment of elinzanetant for the treatment of moderate to severe hot flashes in postmenopausal women are summarized in Table 7.

Determination of Efficacy

Clinical data from the first 12 weeks of two randomized, double-blind, placebo-controlled studies (OASIS 1 and OASIS 2) in postmenopausal women with moderate to severe hot flashes, were submitted as the primary evidence of efficacy of elinzanetant. In each of these two studies, after the first 12 weeks, women on placebo were switched over to elinzanetant and all women were then treated with elinzanetant for a 14-week extension for up to 26 weeks total exposure. In OASIS 1 and OASIS 2, a total of 796 postmenopausal women were randomized to receive elinzanetant or placebo. Women who had at least 50 moderate to severe HFs, including nighttime HFs, per week, were enrolled in OASIS 1 and OASIS 2. The primary efficacy endpoints in both studies were the mean change in frequency and in severity of moderate to severe vasomotor symptoms from baseline to Weeks 4 and 12, including day and night HFs measured using the HFDD.

Determination of Safety

The primary safety evaluation is based on the 12-week placebo-controlled period of OASIS 1 and OASIS 2, in addition to a 52-week, randomized, placebo-controlled study (OASIS 3) in postmenopausal women with hot flashes. OASIS 3 was a multicenter Phase 3 study with a primary efficacy endpoint of mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 12 and a long-term safety evaluation up to 52 weeks in 628 postmenopausal women. Additional data from Phase 1/2 studies were evaluated to support the safety evaluation. See Section 7.3 for further details.

The assessment of AEs, laboratory evaluations, vital signs, and electrocardiograms (ECGs) was performed based on descriptive summaries and tables provided by the Applicant and Clinical Data Scientists from the FDA. Subject narratives were reviewed for death, treatment discontinuation, serious adverse events (SAEs), and adverse event of special interest. Clinical study data were independently analyzed using JMP and JMP Clinical as appropriate. All safety assessments and conclusions were those of the clinical review team unless otherwise specified.

Key review issues that were identified during the review are addressed in greater detail in Section 7.7 for safety. Overall, the submitted clinical studies were adequate for the safety and efficacy evaluation of elinzanetant.

Table 7. Clinical Trials Submitted in Support of the Efficacy and/or Safety Determinations for Elinzanetant

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
OASIS 1/21651 NCT05042362	Postmenopausal women with moderate to severe VMS aged 40 to 65 years.	Multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, intervention study	Elinzanetant 120 mg or matching placebo orally once daily. Arm 1: Elinzanetant 120 mg (26 weeks) Arm 2: placebo (12 weeks), followed by elinzanetant 120 mg (14 weeks)	Coprimary endpoints: • Mean change in frequency of moderate to severe HF from baseline to Week 4 • Mean change in frequency of moderate to severe HF from baseline to Week 12 • 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 Key Secondary Endpoints: • Mean change in frequency of moderate to severe HF from b 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	Planned: 1535 Randomized: 396	89 sites in total in the following countries: Austria (4), Czech Republic (8), Greece (4), Hungary (5), Israel (4), Italy (6), Netherlands (3), United States (55)

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
OASIS 2 21652 NCT05099159	Postmenopausal women with moderate to severe VMS aged 40 to 65 years	Multi-center, multi-country, double-blind, randomize, parallel-group, placebo-controlled, intervention study.	Elinzanetant 120 mg or matching placebo orally once daily. Arm 1: Elinzanetant 120 mg (26 weeks) Arm 2: placebo (12 weeks), followed by elinzanetant 120 mg (14 weeks)	Coprimary endpoints: • Mean change in frequency of moderate to severe HF from baseline to Week 4 • Mean change in frequency of moderate to severe HF from baseline to Week 12 • 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 Key Secondary Endpoints: • Mean change in frequency of moderate to severe HF from b 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	Planned: 1483 Randomized: 400	95 sites in total in the following countries: Canada (9), Czech Republic (5), Germany (10), Italy (4), Norway (5), Poland (6), Portugal (7), Slovakia (4), Switzerland (3), United States (42)

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
OASIS 3/21810 NCT05030584	Postmenopausal women with moderate to severe VMS aged 40 to 65 years	Multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, intervention study.	Elinzanetant 120 mg or matching placebo orally once daily. Arm 1: Elinzanetant 120 mg (52 weeks) Arm 2: placebo (52 weeks)	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	Planned:600 Randomized:300 per arm	83 sites in total in the following countries: Belgium (5), Bulgaria (10), Canada (7), Denmark (3), Finland (5), Poland (6), Spain (6), United Kingdom (5), United States (36)

Source: Reviewer Generated
Abbreviations: HF, hot flash; HFDD, Hot Flash Daily Diary; MENQOL, Menopause Specific Quality of Life Scale; PROMIS SD SF 8b, Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b; VMS, vasomotor symptoms

3.3. Approach To Establishing Substantial Evidence of Effectiveness

(1) Verbatim indication

Treatment of moderate to severe vasomotor symptoms (VMS) due to menopause

(2) SEE was established with

(a) Adequate and well-controlled clinical investigation(s):

(i) ☒ Two or more adequate and well-controlled clinical investigations, OR

(ii) ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

(b) ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1][2][3]

OR

(c) ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)[2]

(3) Complete response, if applicable

(a) ☐ SEE was established

(b) ☐ SEE was not established (if checked, omit item 2)

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998)

[3] FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

4. Patient Experience Data

Table 8. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		Section 6
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical pharmacological data indicate that elinzanetant acts as an antagonist at NK1 and NK3 receptors. These receptors on the KNDy neurons in the thermoregulatory center in the hypothalamus are thought to be responsive to both estrogen and ambient temperature. The activation of the KNDy neurons in response to declining estradiol levels during menopausal transition is thought to contribute to the hot flashes or HFs experienced by women with moderate to severe VMS during menopause.

5.1.1. Pharmacology

Elinzanetant is a NME that acts as a noncompetitive antagonist of both the human NK1 and NK3 receptors (NK1R and NK3R, respectively). In binding assays, elinzanetant displayed high affinity for human NK1R (pKi (negative base-10 logarithm of the inhibition constant) values of 8.71 to 10.15 [mean pKi of 9.43]) and NK3R (pKi values of 8.03 to 8.8[mean pKi of 8.42]). Elinzanetant has ~10-fold lower affinity towards human NK3R compared to human NK1R. Additionally, elinzanetant has higher affinity for human NK1R and NK3R receptors than for human NK2 receptors (pKi values of approximately 6.0). In functional in vitro assays, elinzanetant inhibited the activity of human NK1R and NK3R, with calculated pKB values of 9.02 to 9.1 for human NK1R and 8.17 to 8.5 for human NK3R. Ex vivo receptor occupancy studies in human putamen showed that elinzanetant occupied NK1Rs in the human putamen in a concentration-dependent manner with a pKi of 9.44.

Each of the principal metabolites of interest–M27, M30/34 and M18/21, which accounted for 6%, 11% and 5.5%, respectively, of total radioactivity in the human biotransformation clinical Study CPMX 50130/B002427–showed high affinity and noncompetitive antagonistic activity at the human NK1R and NK3R. The affinities and potencies of the metabolites at human NK1R and NK3R are similar to those of elinzanetant.

In vivo pharmacodynamic (PD) activity of elinzanetant was investigated in a gerbil foot tapping model of NK1 activity and in the guinea pig wet-dog shake model of NK3 activity. After oral dosing with elinzanetant, there was reversal of foot tapping induced by the NK1R agonist GR73632 in male gerbils (ID_{50} [dose resulting a 50% reduction in time spent foot tapping]=1.36 mg/kg). Similarly, elinzanetant doses of 8.5 and 25.5 mg/kg significantly reversed wet-dog shake behavior induced by the NK3R agonist senktide in the guinea pigs, indicating central NK3R antagonist activity. While the Applicant did not conduct studies in animal models to demonstrate the effects of elinzanetant in reducing HF-like symptoms, overall, the pharmacology data support the Applicant's therapeutic rationale for the use of elinzanetant to modulate neuronal activity in the vasomotor center. Refer to Section 5.1.2 below.

Selectivity screens were performed to evaluate the potential for off-target binding for elinzanetant and the three principal human metabolites of elinzanetant (M27, M30/34, and M18/21).

Elinzanetant was >100-fold more selective for the human NK3R and >300-fold for the human NK1R versus 88 other nontachykinin human receptors, enzymes, and transporters.

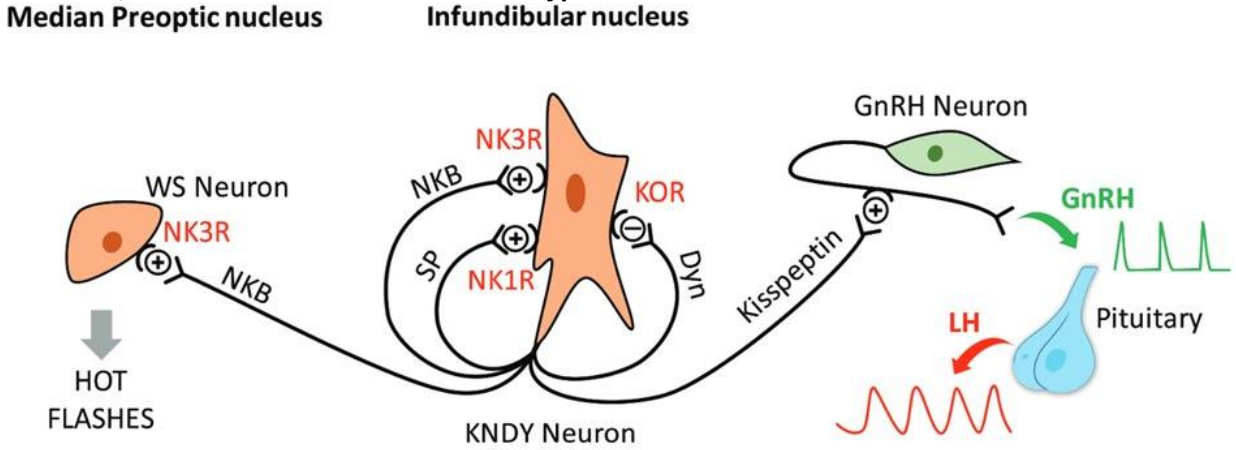
Refer to Section 13.2 for a full review of the pharmacological studies submitted by the Applicant.

The pharmacologic class term for elinzanetant is NK1 and NK3 receptor antagonist.

5.1.2. Mechanism of Action

NK1R and NK3R antagonists are thought to act by inhibiting the activity of KNDy neurons, which project to the vasomotor center in the median pre-optic nucleus to modulate neuronal activity involved in thermoregulation. This inhibition of KNDy neurons, which are thought to be in a hyperactivated state because of estrogen decline in menopause, is proposed to result in improvement of menopause-associated VMS (also called HFs).

Figure 1. NK1/NK3R and Schematic of the Links Between KNDy Neurons, the Regulation of GnRH Secretion, and the Vasomotor Area in the Hypothalamus



Source: Sassarini and Anderson (2024)
Abbreviations: Dyn, dynorphin A; GnRH, gonadotropin-releasing hormone; KOR, kappa opioid receptor; KNDY, kisspeptin/NKB/dynorphin; LH, luteinizing hormone; NK1, neurokinin 1; NK3R, neurokinin 3 receptor; NKB, neurokinin B; SP, substance P; WS, wavelet synapse

5.2. Clinical Pharmacology/Pharmacokinetics

The pharmacologic activity, pharmacokinetics, and clinical pharmacology of elinzanetant that are relevant to the interpretation of benefit and risk are summarized in Table 9.

Table 9. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
EPC	Neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist
Mechanism of action	Elinzanetant, as an NK1 and NK3 receptor antagonist, may decrease the activity of KNDy (kisspeptin/neurokinin B [NKB]/ dynorphin) neurons, which can be in a hyperactivated state due to declining estrogen levels in menopause. KNDy neurons project into the vasomotor center in the median pre-optic nucleus and modulate neuronal activity involved in thermoregulation. Inhibition of KNDy neurons is proposed to improve menopause-associated VMS (vasomotor symptoms), also called hot flashes.
Active moieties	Elinzanetant and its metabolite M18/21, M27, and M30/34 have similar potency for the human NK1 and NK3 receptors.
QT prolongation	At five times the maximum recommended daily dose of elinzanetant 120 mg, clinically significant QTc interval prolongation was not observed. However, there is insufficient information to characterize the effect of concomitant use of LYNKUET 120 mg with strong CYP3A4 inhibitors on the QTc interval. The supratherapeutic

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td></td><td>dose of 600 mg used in the QTc study did not cover at least two times higher than the highest expected clinical exposure achieved (with strong CYP3A4 inhibitors on board), which is approximately 3-fold for C_{max}. In the absence of a positive control in the QTc clinical study, the chosen supratherapeutic dose in this case should provide at least 6 times the clinical exposure at the recommended dose, but 600 mg only provided 5 times the clinical exposure.</td></tr>
<tr><td></td><td>General Information</td></tr>
<tr><td>Bioanalysis</td><td>Validated LC-MS/MS methods were used to determine the concentrations of elinzanetant and its metabolite M18/21, M27, and M30/34 in human plasma and urine (as applicable to individual studies)</td></tr>
<tr><td>Healthy subjects versus patients</td><td>The population PK analysis suggests healthy subjects have 59.6% higher clearance compared to patients with VMS.</td></tr>
<tr><td>Healthy subjects' drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)</td><td>Table 10. Elinzanetant Exposure at Steady State in Healthy Subjects
<table>
<tr><th></th><th colspan="2">Geometric Mean (%CV)</th></tr>
<tr><th>PK Parameters</th><th>$C_{max,md}$ (µg/L)</th><th>$AUC_{(0\text{-}24)md}$ (µg.h/L)</th></tr>
<tr><td>Elinzanetant[1]</td><td>2230 (42.4)</td><td>9330 (21.4)</td></tr>
<tr><td>M27[2]</td><td>628 (26.6)</td><td>4240 (30.1)</td></tr>
<tr><td>M30/34[2]</td><td>954 (17.8)</td><td>7370 (23.5)</td></tr>
<tr><td>M18/21[2]</td><td>515 (17.8)</td><td>3600 (24.1)</td></tr>
</table>
Source: Applicant's summary of clinical pharmacology, table 6-1
1. Study 21678, $AUC_{(0\text{-}24)md}$ and $C_{max,md}$ at Day 17
2. Study 21703, $AUC_{(0\text{-}24)md}$ and $C_{max,md}$ at Day 14
Dose: Elinzanetant 120 mg
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; M, metabolite; $_{md}$, multiple-dose; PK, pharmacokinetic</td></tr>
<tr><td>Range of effective dose(s) or exposure</td><td>Two 60 mg capsules orally once daily at bedtime with or without food.

One 60 mg capsule orally once daily at bedtime with or without food when moderate CYP3A4 inhibitor is administered concurrently.</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td>Maximum tolerated dose has not been determined. However, in Phase 1 Study 21670, the safety and PK of single ascending supratherapeutic doses of elinzanetant, ranging from 240 mg to 600 mg, were evaluated, and elinzanetant was safe and well tolerated up to the maximum tested dose of 600 mg in this study.</td></tr>
<tr><td>Dose proportionality</td><td>In healthy volunteers (Study 21678), elinzanetant C_{max} and AUC increased in greater than dose-proportional manner (20% to 50%) over the dose ranges from 40 to 160 mg once daily (0.33 to 1.33 times the recommended dose)</td></tr>
<tr><td>Accumulation</td><td>PopPK estimates (geometric mean and CV%) for the accumulation ratios of elinzanetant are 1.7 (16.9%) for AUC and 1.13 (6.2%) for C_{max}.</td></tr>
<tr><td>Time to achieve steady-state</td><td>Steady-state plasma concentrations of elinzanetant were reached 5 to 14 days after once daily dosing</td></tr>
<tr><td>Bridge between to-be-marketed and clinical trial/study formulations</td><td>The to-be-marketed formulation was used in pivotal Phase 3 clinical studies (OASIS 1, OASIS 2, and OASIS 3) submitted in this application to support efficacy and safety.</td></tr>
<tr><td></td><td>Absorption</td></tr>
<tr><td>Bioavailability</td><td>Absolute bioavailability of elinzanetant is 52%</td></tr>
<tr><td>T_{max}</td><td>The median T_{max} is 1.0 (1.00 – 2.50) hours</td></tr>
<tr><td>Food effect (fed/fasted) Geometric least squares mean and 90% CI</td><td>Under fed conditions (high-fat breakfast containing 800 to 1000 kcal, with 500 to 600 kcal from fat and 250 kcal from carbohydrate), C_{max} was reduced by ~70% and $AUC_{(0\text{-}24)}$ by 42% compared to fasted state (Study 21678).</td></tr>
</table>

Characteristic	Drug Information
	Table 11. Assessment of Food Effect on Elinzanetant Source: CSR for Study 21678, table 11-2 Abbreviations: $AUC_{(0-24)}$, area under the concentration-time curve from time 0 to 24 h; C_{max}, maximum plasma concentration; CSR, clinical study report; PK, pharmacokinetic Elinzanetant 120 mg was administered once daily before bedtime, regardless of food intake, in pivotal Phase 3 clinical studies (OASIS 1, OASIS 2, and OASIS 3) and the Phase 2b (SWITCH-1) study and demonstrated to reduce both the frequency and severity of hot flushes (refer to clinical review of efficacy findings). Therefore, the food effect observed in Study 21678 were deemed clinically insignificant and elinzanetant can be administered once daily at bedtime with or without food.
	Distribution
Volume of distribution	The volume of distribution after intravenous administration at steady state (V_{ss}) of elinzanetant is 137 L.
Plasma protein binding	Elinzanetant: 99.7%; metabolites M18/21, M27 and M30/34: ≥99.5%.
Drug as substrate of transporters	In vitro drug transporter assessment (R-13687) showed that elinzanetant is a substrate of P-gp.
	Elimination
Mass balance results	Following a single oral administration of 120 mg [^{14}C]elinzanetant suspension to healthy male subjects, on average, 90.8% of the radioactivity administered was recovered, with 90.4% in feces and 0.44% in urine.
Clearance	The clearance of elinzanetant after single intravenous administration is 8.77 L/h
Half-life	The half-life of elinzanetant is approximately 45 hours following once daily oral dosing of elinzanetant 120 mg. The half-lives of metabolite M18/21, M27, and M30/34 are 30 hours, 29 hours, and 37 hours, respectively.
Metabolic pathway(s)	Elinzanetant is primarily metabolized by CYP3A4, producing three principal metabolites M18/21, M27, and M30/34. Metabolite M30/34 is a major metabolite of elinzanetant in human plasma representing 13.7% of total drug-related exposure, whereas M27 and M18/21 each represents 7.6% and 4.9%, respectively.
Primary excretion pathways (% dose)	Following oral administration of elinzanetant, approximately 90% of the dose is excreted in feces (50% unchanged) and less than 1% in urine.
	Intrinsic Factors and Specific Populations
Body weight	Population PK analysis demonstrated that body mass (BMI 21.9 kg/m2 to 34.1 kg/m^2) is unlikely to have a clinically meaningful impact on the exposure of elinzanetant and its metabolites. No dosage adjustments are recommended based on body mass or weight.
Age	Population PK analyses based on the PK data from eleven Phase 1 studies, one Phase 2 study, and three Phase 3 studies demonstrated that age (range: 22 to 75 years) is unlikely to have a clinically meaningful impact on the exposure of elinzanetant and its metabolites. No dosage adjustments are recommended in patients based on age.
Renal impairment	Population pharmacokinetic analysis demonstrated that among subjects enrolled in Phase 3 studies, subjects with mild (eGFR 60-90 mL/min, n=402) or moderate (eGFR 30-60 mL/min, n=23) renal impairment did not have significantly higher exposure of elinzanetant compared to those with normal renal function (n=586) and no additional safety concerns were identified in subjects with mild or moderate

PK Parameter	Adjusted Geometric Mean: Fed Condition	Adjusted Geometric Mean: Fasted Condition	Geometric Mean Ratio (90% CI) of Fed/Fasted
C_{max} (ng/mL)	768	2540	0.30 (0.323, 0.394)
$AUC_{(0-24)}$ (ng*h/mL)	4250	7390	0.58 (0.497, 0.665)

Characteristic	Drug Information
	renal impairment. The dedicated renal impairment Study 21669 suggested that severe renal impairment (eGFR <30 mL/min) did not result in a larger extent of increase in elinzanetant exposure than mild or moderate renal impairment. Also, renal clearance plays a minor role in elimination of elinzanetant. Consequently, no dose adjustment is necessary for patients with mild, moderate, or severe renal impairment. However, since the impact of end-stage renal disease on the PK of elinzanetant has not been evaluated, elinzanetant is not recommended for patients with end-stage renal disease.
Hepatic impairment	Population pharmacokinetic analysis demonstrated that mild hepatic impairment does not significantly affect the drug exposure (AUC) of elinzanetant in the Phase 3 study population. The effect of moderate hepatic impairment on the drug exposure was not evaluated in the population pharmacokinetic analysis due to the limited number of subjects with moderate hepatic impairment in the analysis (N=1). The dedicated hepatic impairment study (Study 21668) indicated that individuals with moderate hepatic impairment exhibited 2.3-fold increase in AUC compared to healthy subjects. Consequently, no dose adjustment is necessary for patients with mild hepatic impairment but elinzanetant is not recommended for patients with moderate to severe hepatic impairment.
	Drug Interaction Liability (Drug as Object)
Inhibition/induction of metabolism	Elinzanetant is primarily metabolized by CYP3A4. <u>Clinical DDI studies</u> Elinzanetant C_{max} increased approximately 3.3-fold and AUC increased 6.3-fold following concomitant use with itraconazole 200 mg (strong CYP3A4 and P-gp inhibitor). Elinzanetant C_{max} increased 2.0-fold and AUC increased 3.0-fold following concomitant use with erythromycin (moderate CYP3A4 inhibitor) as shown by PBPK modeling predictions. Elinzanetant C_{max} reduced by 44% and AUC reduced by 64% following concomitant use with carbamazepine (moderate to strong CYP3A4 and P-gp inducer) 600 mg administered twice daily.
Inhibition/induction of transporter systems	Elinzanetant is a substrate for P-gp.

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Precipitant)
Inhibition/induction of metabolism	In vitro studies Elinzanetant and its metabolites M18/21, M27, and M30/M34 showed inhibitory potency on CYP3A4 but did not inhibit CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 2J2. Elinzanetant and its metabolites M18/21, M27, and M30/M34 did not induce CYP1A2, CYP2B6, CYP2C19 and CYP3A4 at clinically relevant concentrations. Clinical DDI studies Elinzanetant is a weak inhibitor of CYP3A4. Elinzanetant increased midazolam (sensitive CYP3A4 substrate) C_{max} 1.5-fold and AUC1.8-fold.
Inhibition/induction of transporter systems	Elinzanetant and its metabolites M18/21, M27, and M30/M34 inhibit P-gp, BCRP, and BSEP in vitro. In clinical DDI studies, no clinically relevant interaction potential with transporters were identified.

Source: Reviewer generated summary from the Applicant's summary of clinical pharmacology, and Pharmacokinetics Tabulated Summary
Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; BMI, body mass index; BSEP, bile salt export pump; C_{max}, maximum plasma concentration; DDI, drug-drug interaction; eGFR, estimated glomerular filtration rate; EPC, established pharmacologic class; N, number of subjects; n, number of subjects with given characteristic; PBPK, physiologically based pharmacokinetic; P-gp, P-glycoprotein; PK, pharmacokinetic; popPK, population pharmacokinetic; T_{max}, time to maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The clinical development program evaluated doses ranging from 1.5 mg to 300 mg. The free base form of elinzanetant in a soft-gel capsule formulation was evaluated at doses between 25 mg and 160 mg once daily. The Applicant conducted a Phase 2 study, SWITCH-1 (also known as Study 814-PM-02), to evaluate a four-fold range of elinzanetant doses – 40, 80, 120, and 160 mg once daily over 12 weeks. SWITCH-1 was a Phase 2b, international, randomized, double-blind, placebo-controlled, dose-finding study. Subjects were postmenopausal women aged 40 to 65 years who were in good general health and reported an average of at least 8 moderate or severe hot flashes per day (including nighttime) over the last 5 days of recording in the paper diary during screening. The primary efficacy outcomes were mean change in the frequency and severity of moderate and severe hot flashes from baseline at Week 4 and Week 12, respectively.

Following randomization, 47 subjects received placebo and 152 received elinzanetant. The number of subjects randomized to different doses was not evenly distributed due to the adaptive design of the study. After reviewing emerging efficacy and safety data during interim reviews, a blinded data review committee decided to discontinue first the 80 mg group then the 40 mg group, resulting in changes to the randomization ratio. Ultimately, of those randomized to elinzanetant, 31 received the 40 mg dose, 17 received 80 mg, 52 received 120 mg, and 52 received 160 mg. Of the randomized subjects, 43 (91.5%) completed the treatment with placebo; 29 (93.5%), 14 (82.4%), 51 (98.1%) and 43 (82.7%) completed treatment with 40 mg, 80 mg, 120 mg and 160 mg elinzanetant, respectively.

Results of SWITCH-1 are shown in Table 12 and Table 13 below. For the coprimary endpoint of daily frequency of moderate and severe hot flashes at Weeks 4 and 12, the reduction from baseline was significantly greater in those receiving elinzanetant at both time points for the 120 mg group (Week 4, p=0.0002; Week 12, p=0.0116) and at Week 4 for the 160 mg group (p=0.0115) based on the mixed-effect model for repeated measures (MMRM) analysis. For the coprimary endpoint of weekly severity of moderate and severe hot flashes at Weeks 4 and 12, the reduction from baseline was significantly greater in subjects taking elinzanetant than those receiving placebo for the 160 mg group at Week 12 only using MMRM analysis (p=0.0479), and for the 120 mg group at Week 4 only using nonparametric analyses (p=0.0436).

Table 12. Average Daily Frequency of Moderate and Severe Hot Flashes and Change From Baseline at Week 4 and Week 12, SWITCH-1 (FAS)

			NT-814			
		Placebo (N=47)	40 mg (N=31)	80 mg (N=17)	120 mg (N=52)	160 mg (N=52)
Daily Frequency and Change from Baseline of Moderate and Severe Hot Flashes by Week						
Baseline	Mean (SD)	11.82 (4.42)	12.13 (8.81)	14.55 (5.87)	13.54 (7.17)	12.92 (6.90)
	Median (range)	10.14 (7.0, 29.1)	10.14 (7.0, 55.0)	13.43 (7.7, 29.0)	10.29 (7.0, 34.4)	9.93 (7.0, 39.6)
Week 4	Mean (SD)	9.33 (6.20)	7.94 (5.85)	10.24 (8.91)	6.78 (5.98)	7.63 (8.81)
	Median (range)	8.14 (0.1, 32.7)	6.57 (0.0, 27.7)	8.57 (0.0, 35.6)	5.29 (0.0, 27.1)	4.86 (0.0, 37.0)
Week 12	Mean (SD)	7.36 (5.80)	5.64 (4.77)	9.08 (8.44)	5.75 (5.66)	6.67 (8.92)
	Median (range)	6.00 (0.0, 24.3)	4.21 (0.0, 18.4)	7.57 (1.7, 39.1)	4.57 (0.0, 29.1)	2.43 (0.0, 33.0)
Change from baseline to Week 4	Mean (SD)	-2.45 (3.65)	-4.19 (5.78)	-4.30 (6.45)	-6.76 (5.85)	-5.42 (5.36)
	Median (range)	-2.29 (-13.9, 3.6)	-3.57 (-27.3, 5.3)	-5.00 (-14.3, 16.4)	-5.79 (-24.0, 2.6)	-6.57 (-17.6, 17.6)
Change from baseline to Week 12	Mean (SD)	-4.49 (4.29)	-6.48 (7.82)	-5.49 (5.31)	-7.91 (6.66)	-6.57 (5.83)
	Median (range)	-4.43 (-16.4, 2.6)	-5.07 (-41.6, 3.1)	-5.64 (-16.9, 10.1)	-6.43 (-31.0, 4.3)	-6.86 (-19.7, 18.7)

		Placebo (N=47)	NT-814 40 mg (N=31)	NT-814 80 mg (N=17)	NT-814 120 mg (N=52)	NT-814 160 mg (N=52)
Percentage Change from Baseline of Moderate and Severe Hot Flashes by Week						
Week 4	Mean (SD)	-24.16 (34.22)	-32.43 (34.19)	-34.97 (41.32)	-49.46 (32.69)	-47.52 (50.10)
	Median (range)	-21.05 (-98.1, 36.0)	-36.11 (-100.0, 48.7)	-34.31 (-100.0, 85.8)	-48.22 (-100.0, 28.6)	-56.34 (-100.0, 186.4)
Week 12	Mean (SD)	-41.00 (36.59)	-50.85 (35.81)	-42.62 (25.28)	-57.92 (32.95)	-56.66 (53.11)
	Median (range)	-37.54 (-100.0, 29.0)	-55.76 (-100.0, 28.9)	-43.49 (-78.4, 35.0)	-63.49 (-100.0, 47.6)	-70.69 (-100.0, 198.5)
Statistical Analysis of Change from Baseline versus Placebo (MMRM)						
Change from Baseline to Week 4						
LS mean (95% CI)		-2.80 (-4.26, -1.34)	-4.32 (-6.10, -2.54)	-4.09 (-6.50, -1.68)	-6.73 (-8.11, -5.35)	-5.43 (-6.83, -4.02)
Difference in LS means (95% CI)		NA	-1.52 (-3.83, 0.78)	-1.29 (-4.11, 1.53)	-3.93 (-5.94, -1.92)	-2.63 (-4.66, -0.60)
p-value		NA	0.1946	0.3682	0.0002	0.0115
Wilcoxon p-value		NA	0.1677	0.0164	<0.0001	<0.0001
Change from Baseline to Week 12						
LS mean (95% CI)		-4.81 (-6.48, -3.15)	-6.48 (-8.49, -4.46)	-5.58 (-8.32, -2.85)	-7.76 (-9.31, -6.21)	-6.59 (-8.24, -4.95)
Difference in LS means (95% CI)		NA	-1.67 (-4.28, -0.95)	-0.77 (-3.97, 2.44)	-2.95 (-5.22, -0.67)	-1.78 (-4.12, 0.56)
p-value		NA	0.2097	0.6369	0.0116	0.1346
Wilcoxon p-value		NA	0.3084	0.1756	0.0043	0.0023

Source: Table 11-1, page 73-74, Final Study Report, SWITCH-1
Abbreviations: FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of randomized subjects; NA, not applicable; SD, standard deviation

Table 13. Average Weekly Severity of Moderate and Severe Hot Flashes and Change From Baseline at Week 4 and Week 12, SWITCH-1 (FAS)

			NT-814			
		Placebo (N=47)	40 mg (N=31)	80 mg (N=17)	120 mg (N=52)	160 mg (N=52)
Weekly Severity and Change from Baseline of Moderate and Severe Hot Flashes by Week						
Baseline	Mean (SD)	2.54 (0.20)	2.51 (0.26)	2.63 (0.24)	2.54 (0.24)	2.54 (0.26)
	Median (range)	2.54 (2.1, 3.0)	2.51 (2.0, 3.0)	2.68 (2.1, 3.0)	2.52 (2.0, 3.0)	2.52 (2.0, 3.0)
Week 4	Mean (SD)	2.24 (0.50)	2.13 (0.61)	2.19 (0.69)	2.03 (0.66)	2.01 (0.73)
	Median (range)	2.38 (1.0, 3.0)	2.15 (0.0, 3.0)	2.16 (0.0, 3.0)	2.20 (0.0, 3.0)	2.14 (0.0, 3.0)
Week 12	Mean (SD)	2.13 (0.57)	1.97 (0.69)	2.37 (0.52)	1.99 (0.71)	1.80 (0.81)
	Median (range)	2.22 (1.0, 3.0)	2.07 (0.0, 3.0)	2.41 (1.3, 3.0)	2.17 (0.0, 3.0)	2.06 (0.0, 3.0)
Change from baseline to Week 4	Mean (SD)	-0.31 (0.41)	-0.38 (0.54)	-0.44 (0.56)	-0.51 (0.57)	-0.54 (0.67)
	Median (range)	-0.15 (-1.5, 0.2)	-0.21 (-2.5, 0.2)	-0.38 (-2.3, 0.1)	-0.36 (-2.5, 0.4)	-0.38 (-2.6, 0.3)
Change from baseline to Week 12	Mean (SD)	-0.41 (0.50)	-0.53 (0.64)	-0.26 (0.45)	-0.56 (0.68)	-0.73 (0.78)
	Median (range)	-0.25 (-1.6, 0.4)	-0.38 (-2.5, 0.4)	-0.07 (-1.1, 0.2)	-0.39 (-2.5, 0.4)	-0.51 (-2.8, 0.2)
Statistical Analysis of Change from Baseline versus Placebo (MMRM)						
Change from Baseline to Week 4						
LS mean (95% CI)		-0.32 (-0.48, -0.17)	-0.37 (-0.57, -0.18)	-0.46 (-0.73, -0.20)	-0.51 (-0.66, -0.36)	-0.51 (-0.67, -0.36)
Difference in LS means (95% CI)		NA	-0.05 (-0.30, 0.20)	-0.14 (-0.45, 0.17)	-0.19 (-0.41, 0.03)	-0.19 (-0.41, 0.03)
p-value		NA	0.7033	0.3724	0.0896	0.0900
Wilcoxon p-value		NA	0.6268	0.3811	0.0436	0.0916
Change from Baseline to Week 12						
LS mean (95% CI)		-0.42 (-0.60, -0.23)	-0.51 (-0.73, -0.28)	-0.25 (-0.57, 0.06)	-0.56 (-0.74, -0.39)	-0.68 (-0.87, -0.50)
Difference in LS means (95% CI)		NA	-0.09 (-0.39, 0.21)	0.16 (-0.20, 0.52)	-0.15 (-0.41, 0.11)	-0.27 (-0.53, -0.00)
p-value		NA	0.5511	0.3822	0.2606	0.0479
Wilcoxon p-value		NA	0.4058	0.2287	0.4074	0.0796

Source: Table 11-2, page 76, Final Study Report, SWITCH-1
Abbreviations: FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of randomized subjects; NA, not applicable; SD, standard deviation

The Applicant concluded that elinzanetant 120 mg once daily was shown to be the lowest effective dose, with no additional benefit observed with the 160 mg once daily dose. In addition, the Applicant also conducted exposure-response (E-R) modeling of Phase 3 data and concluded that doses lower than 120 mg would be associated with reduced efficacy.

The plasma concentrations achieved with the 120 mg dose are associated with full occupancy of central NK1 receptors throughout a dose interval at steady state as demonstrated in a human positron emission tomography (PET) study. Although it is not possible to assess NK3 receptor occupancy directly, as a suitable NK3 PET ligand does not exist, the achieved concentrations are also very likely to fully occupy central NK3 receptors.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

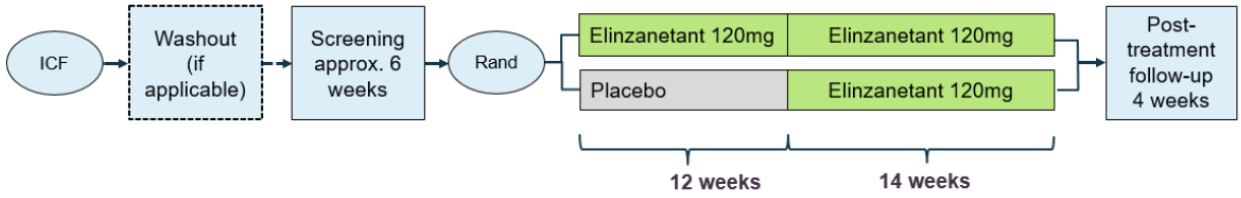
6.2.1. Study Design, OASIS 1, OASIS 2, and OASIS 3

OASIS 1 and OASIS 2 were two randomized, double-blind, placebo-controlled, Phase 3, international studies conducted in postmenopausal women aged 40 to 65 years with moderate to severe VMS. Both studies were designed to evaluate the efficacy and safety of elinzanetant 120 mg for the treatment of moderate to severe VMS associated with menopause.

Both studies had virtually identical designs. In these studies, eligible subjects who met all the enrollment criteria were randomized in a 1:1 ratio to receive either 120 mg of elinzanetant or a matching placebo orally once daily. Randomization was stratified by region (North America and the rest of the world).

Both studies included a wash-out period (if applicable), a screening period, and a 12-week placebo-controlled treatment period where the subjects were randomized to receive either elinzanetant 120 mg or placebo. After completing the first 12 weeks of treatment, subjects in the placebo arm then received elinzanetant 120 mg for 14 weeks, and subjects who were in the active arm continued to receive elinzanetant 120 mg for another 14 weeks. Following completion of the 26-week treatment period (or early discontinuation), subjects were followed by a 4-week safety follow-up period. Figure 2 below shows a schematic of OASIS 1 and OASIS 2 studies.

Figure 2. Schematic, OASIS 1 and OASIS 2



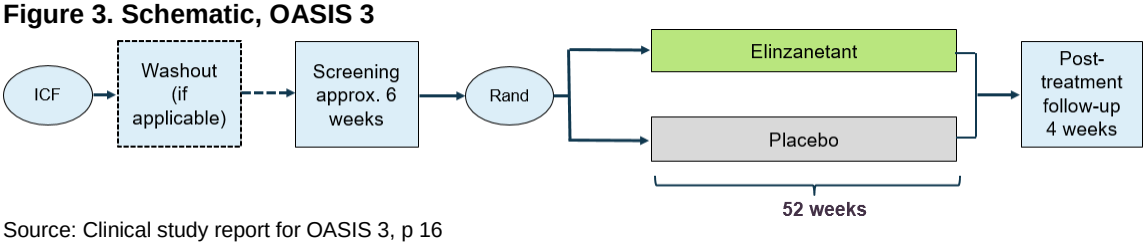
Source: Clinical study report for OASIS 1, p 21; clinical study report for OASIS 2, p19
Abbreviations: approx., approximately; ICF, informed consent form; Rand., randomization

OASIS 3 was a randomized, multi-center, multi-country, double-blind, placebo-controlled, parallel-group, Phase 3 study conducted in postmenopausal women aged 40 to 65 years with VMS. OASIS 3 was designed to provide long-term safety and supportive efficacy data.

Eligible subjects who met all the enrollment criteria in OASIS 3 were randomized in a 1:1 ratio to receive either 120 mg of elinzanetant or a matching placebo orally once daily for 52 weeks. Randomization was stratified by region (North America and the rest of the world).

OASIS 3 included a wash-out period (if applicable), an approximately 6-week screening period, a 52-week placebo-controlled treatment period, and a 4-week safety follow-up period. Unlike OASIS 1 and OASIS 2 in which subjects randomized to the placebo arm switched to the treatment arm after 12-week treatment, subjects randomized to placebo arm in OASIS 3 remained in the placebo arm during the entire 52-week treatment period. Figure 3 below shows a schematic of OASIS 3.

Figure 3. Schematic, OASIS 3



Source: Clinical study report for OASIS 3, p 16
Abbreviations: approx., approximately; ICF, informed consent form; Rand., randomization

6.2.2. Eligibility Criteria, OASIS 1, OASIS 2, and OASIS 3

OASIS 1 and OASIS 2 had identical eligibility criteria, with eligible subjects having a minimum of 50 moderate to severe hot flashes (HFs, including nighttime episodes) per week at baseline. In contrast, OASIS 3 had no required minimum episodes of moderate to severe hot flashes at baseline. Also, unlike in OASIS 1 and OASIS 2, subjects in OASIS 3 were not required to have a negative gynecologic ultrasound, endometrial biopsy, cervical cytology, or Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) at screening. Otherwise, the three studies had the same criteria for eligibility as outlined below.

Inclusion Criteria

(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, in the opinion of the investigator, based on the medical history, physical examination, 12-lead ECG, bone mineral density (BMD), vital signs, gynecological

ultrasound, endometrial biopsy, mammogram, clinical laboratory tests, eC-SSRS, and other assessments completed during screening.

(6) Normal or clinically insignificant cervical cytology not requiring further follow-up:

(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 subjects with ASCUS will be used as an adjunctive test automatically. Subjects with ASCUS can be included if they are negative for high-risk HPV strains.

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

(7) Body mass index (BMI) between 18 and 38 kg/m2 at screening

(8) Subject 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) Subject has completed HFDD for at least 11 days during the 2 weeks preceding baseline visit, and subject 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).

(10) Capable of giving signed informed consent.

Exclusion Criteria

(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 retest 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 tumors). 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.

(a) Treated hyperthyroidism with no abnormal increase of thyroid function laboratory parameters and no relevant clinical signs for >6 months before signing of informed consent is acceptable.

(b) Treated hypothyroidism with normal thyroid function test results during screening and a stable (for >3 months before signing of informed consent) dose of replacement therapy is acceptable.

(7) Any unexplained postmenopausal uterine bleeding.

(8) Clinically relevant abnormal findings on mammogram

(9) Renal impairment greater than moderate (i.e., estimated glomerular filtration rate <30 mL/min/1.73m2) at screening

(11) Abnormal liver parameters (presence of at least one of the following criteria):

(a) Aspartate aminotransferase (AST) >2x upper limit of normal (ULN)

(b) Alanine aminotransferase (ALT) >2xULN

(c) AP >2xULN

(d) TBL > ULN unless explained by Gilbert's syndrome

(e) International Normalized Ratio > ULN unless explained by, e.g., intake of anticoagulants

(f) Diagnosis of hepatitis B infection, i.e., Hepatitis B surface antigen positive at screening

(g) Diagnosis of hepatitis C infection, i.e., hepatitis C-antibodies and HCV-RNA positive at screening.

(12) Disordered proliferative endometrium, endometrial hyperplasia, polyp, or endometrial cancer diagnosed based on endometrial biopsy during screening.

(13) Any other history, condition, therapy, or uncontrolled intercurrent illness which could in the opinion of the investigator affect compliance with study requirements.

(14) Has used and is unwilling to wash-out use of any of the prohibited concomitant medications.

(15) Inability to comply with the use of prohibited medications.

(16) Concurrent (or within 2 months prior to signing of ICF) participation in a clinical study with an investigational medicinal product (including medical devices).

(17) At screening a suicidal ideation in the past 6 months (as indicated by "Yes" on item 4 or item 5 of the suicidal ideation section of the eC-SSRS) or suicidal behavior in the past 6 months (indicated by "Yes" on any item of the suicidal behavior section of the eC-SSRS).

(18) Clinically relevant drug or alcohol abuse within 12 months of signing of informed consent.

(19) Dependent on the investigator, the contract research organization(s) or Sponsor for education or employment (e.g., family members, employees, people who receive grants/education).

(20) Known hypersensitivity to elinzanetant or any of the excipients in the formulation.

(21) Inability to comply with the study procedures for any reason.

6.2.3. Clinical Endpoints, OASIS 1, OASIS 2, and OASIS 3

Primary Efficacy Endpoints, OASIS 1, OASIS 2, and OASIS 3

In OASIS 1 and OASIS 2, the following four coprimary efficacy endpoints were assessed:

- Mean change in the frequency of moderate to severe VMS from baseline to Week 4
- Mean change in the frequency of moderate to severe VMS from baseline to Week 12
- Mean change in the severity of moderate to severe VMS from baseline to Week 4
- Mean change in the severity of moderate to severe VMS from baseline to Week 12

In OASIS 3, the primary endpoint was assessed as the mean change in the frequency of moderate to severe VMS from baseline to Week 12. In this study, this endpoint was assessed to provide supportive efficacy evidence.

Across the three studies, subjects recorded the number (frequency) and severity of each hot flash twice daily (morning and evening) using a HFDD data at baseline, during the entire 26-week treatment, and at the 4-week follow-up periods. See Section 16.5 for more details on the eDiary, HFDD. Hot flash severity was graded as mild (a sensation of heat without sweating), moderate (a sensation of heat with sweating, but able to continue activity), and severe (a sensation of heat with sweating, causing cessation [stopping] of activity). See Section 16.5 for a copy of morning and evening HFDD.

In all three OASIS studies, the calculations of frequency and severity data at baseline and at each postbaseline visit are discussed below.

Baseline Frequency/Severity

The baseline frequency was calculated based on data from all available days during the 14 days prior to start of treatment and is shown in Equation 1.

Equation 1. Calculation of Baseline Frequency, OASIS 1, OASIS 2, and OASIS 3

$$\frac{\text{Total number of moderate to severe HFs}}{\text{Total \# of available days with data}}$$

Source: Section 9.4.2.1 of OASIS 1 and OASIS 2 Protocol Amendment 2
Abbreviations: HFs, hot flashes

The baseline severity was then calculated by averaging the mean daily severity of the available days during the 14 days prior to start of treatment. The mean daily severity at baseline was calculated as shown in Equation 2.

Equation 2. Calculation of Mean Daily Severity at Baseline, OASIS 1, OASIS 2, and OASIS 3

$$\frac{2 * \text{number of moderate HFs} + 3 * \text{number of severe HFs}}{\text{Total \# moderate and severe HFs on that day}}$$

Source: Section 9.4.2.1 of OASIS 1 and OASIS 2 Protocol Amendment 2
Abbreviations: HFs, hot flashes

When no moderate or severe HF were reported for a particular day, the mean severity for that day was set to 0.

Per protocol, at least 11 days need to be available for the derivation of the baseline frequency or severity value. Otherwise, the baseline value was set as missing. Based on this rule, all subjects in OASIS 1 had baseline frequency/severity scores, while one subject each in OASIS 2 and OASIS 3 had missing baseline frequency/severity scores.

Postbaseline Frequency/Severity

At the postbaseline visits, weekly frequency and severity values were calculated using available data during that week. The postbaseline weekly frequency was calculated as shown in Equation 3.

Equation 3. Calculation of Postbaseline Weekly Frequency, OASIS 1, OASIS 2, and OASIS 3

$$\frac{\text{Total number of moderate to severe HFs during that week}}{\text{Total number of available days with data during that week}}$$

Source: Section 9.4.2.1 of OASIS 1 and OASIS 2 Protocol Amendment 2
Abbreviations: HFs, hot flashes

The postbaseline weekly severity was calculated by averaging the mean daily severity of VMS of the available days during that week. The mean daily severity for a particular day was calculated as shown in Equation 4.

Equation 4. Calculation of Mean Daily Severity, OASIS 1, OASIS 2, and OASIS 3

$$\frac{1 * \text{number of mild HFs} + 2 * \text{number of moderate HFs} + 3 * \text{number of severe HFs}}{\text{Total \# of mild, moderate, and severe HFs on that day}}$$

Source: Section 9.4.2.1 of OASIS 1 and OASIS 2 Protocol Amendment 2
Abbreviations: HFs, hot flashes

When no HFs were reported for a particular day, the mean severity for that day was set to 0.

Per protocol, when data were missing for more than 2 days within a week, the frequency or severity value for that week was set to missing.

6.2.3.1. Key Secondary Endpoints, OASIS 1, OASIS 2, and OASIS 3

In OASIS 1 and OASIS 2, the Applicant defined the following three key secondary efficacy endpoints. There was no key secondary endpoint defined in OASIS 3.

- Mean change in frequency of moderate to severe HF from baseline to Week 1
- Mean change in Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b (PROMIS SD SF 8b) total T-score from baseline to Week 12
- Mean change in Menopause Specific Quality of Life Scale (MENQOL) total score from baseline to Week 12

During the 12-week placebo-controlled period, PROMIS SD SF 8b and MENQOL were administered to subjects electronically per the following schedules:

- PROMIS SD SF 8b: baseline, Weeks 1, 2, 3, 4, 8, and 12
- MENQOL: baseline, Weeks 4, 8, and 12

For PROMIS SD SF 8b, subjects' responses to eight items of the instrument (such as restless sleep, satisfaction with sleep, refreshing sleep, difficulties sleeping, difficulties getting to sleep, difficulties staying asleep, amount of sleep, and overall sleep quality) were scored on a 1 to 5 numeric rating scale and aggregated to derive total raw scores ranging from 8 to 40. These total raw scores were then converted into T-scores using a look-up table for comparison with population norms. A higher score indicates a higher level of sleep disturbance.

For MENQOL, subjects' responses to the 29 items were scored individually on a scale indicating whether the subject experienced the symptom (yes/no). If they select yes, they rate how bothered they were by the symptom using a 6-point verbal descriptor scale. The items assess four domains of symptoms and functioning: vasomotor symptoms, psychosocial functioning, physical functioning, and sexual functioning. Domain scores are calculated as mean of single item converted scores. The MENQOL total score was calculated as the mean of four domain mean scores.

It is important to note that, as communicated to the Applicant in the end-of-phase 2 (EOP2) Final Meeting Minutes dated December 17, 2020, results from the key secondary endpoints would not be considered for labeling for the following considerations:

> "Class Labeling" for an approved VMS indication will include efficacy findings for the four primary VMS endpoints and the clinically meaningful reduction in hot flash frequency, and safety findings as appropriate. Outcomes of secondary endpoints (b) (4) are not used to determine the effectiveness of drug product for a VMS indication and are not included in labeling. NT-814 [elinzanetant] will receive labeling consistent with other drugs approved for the same VMS indication.

Therefore, in this review, the analyses of these key secondary endpoints were considered for exploratory use only.

6.2.4. Statistical Analysis Plan for Efficacy, OASIS 1, OASIS 2, and OASIS 3

6.2.4.1. Analysis Populations, OASIS 1, OASIS 2, and OASIS 3

All efficacy analyses were conducted based on the full analysis set (FAS), which consisted of all randomized subjects.

In OASIS 1, the FAS population consisted of 396 subjects (199 in elinzanetant 120 mg arm and 197 in placebo arm). Of these, 393 subjects received study medication (199 received elinzanetant 120 mg and 194 received matching placebo).

In OASIS 2, the FAS population consisted of 400 subjects (200 in elinzanetant 120 mg arm and 200 in placebo arm). All 400 subjects received study medication (201 received elinzanetant 120 mg and 199 received matching placebo).

In OASIS 3, the FAS consisted of 628 subjects (313 in elinzanetant 120 mg arm and 315 in placebo arm). Of these, 627 subjects received study medication (313 received elinzanetant 120 mg arm and 314 received matching placebo).

6.2.4.2. Analysis of Coprimary Efficacy Endpoints, OASIS 1, OASIS 2, and OASIS 3

The primary efficacy objective of OASIS 1 and OASIS 2 studies was to assess the superiority of elinzanetant 120 mg to placebo in the four coprimary endpoints in postmenopausal women 40 to 65 years of age with moderate to severe VMS.

The prespecified primary analysis to evaluate the superiority of elinzanetant 120 mg to placebo in the four coprimary efficacy endpoints was performed using MMRM analysis including all randomized subjects, even if they stopped treatment temporarily or permanently, or took prohibited medications, following a treatment policy strategy. The MMRM model included treatment group, week (Weeks 1, 4, 8, and 12), and region (United States and the rest of the world) as factors, baseline VMS as covariate, and the interaction effects of treatment by week and baseline measurement by week. An unstructured covariance structure shared across treatment groups was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and to adjust standard errors.

Based on the MMRM model, the LS estimates of the mean change from baseline and standard error (SE) for each treatment arm at Weeks 1, 4, 8, and 12 as well as the LS estimates of the treatment differences (elinzanetant-placebo), SE of the differences, associated 95% confidence interval (CI), and p-value (one-sided) were reported.

The primary efficacy endpoint in OASIS 3 was assessed similarly to the primary analysis of the coprimary efficacy endpoints in OASIS 1 and OASIS 2.

Type I Error Control (Plan for Multiplicity Adjustment)

In OASIS 1 and OASIS 2, superiority in each of the four coprimary endpoints were tested at a one-sided significance level of 2.5%. Since superiority in all four coprimary endpoints within each study must be established to claim study success, the study-wise Type I error rate was controlled at a one-sided significance level of 2.5%. Similarly, since superiority in the single primary endpoint in OASIS 3 must be established to claim study success, the study-wise Type I error rate was also controlled at a one-sided significance level of 2.5%.

Handling of Missing Data

In the primary efficacy analyses in OASIS 1, OASIS 2, and OASIS 3, the Applicant imputed nonmonotone (intermittent) and monotone missing data using Monte Carlo Markov Chain multiple imputation (MI) method under a missing at random missing data mechanism.

Within each study, the Applicant created a total of 500 multiply imputed datasets using SEED numbers 21651 in OASIS 1, 21652 in OASIS 2,

and 21653 in OASIS 3, respectively. After the completion of the imputation steps, each imputed dataset was analyzed using the MMRM model as specified for the primary analysis of the four coprimary endpoints. Then, the results from each multiply imputed dataset were combined using the Rubin's rule (Rubin 1987) to obtain an overall estimated treatment effect.

See Section 16.1 for a detailed description of the missing data handling in the statistical analysis plan-specified primary analyses of (co)primary endpoints in OASIS 1, 2, and 3.

Given the minimal dropout rates and limited missing data within each study (Table 14), the Applicant's approach to handling missing data in the primary efficacy analysis appears reasonable.

Sensitivity Analyses

To evaluate the robustness of the primary efficacy results, the Applicant performed the following sensitivity analyses based on the FAS population under the treatment policy strategy.

- Sensitivity analysis 1 (SA1): MMRM analysis without any missing data imputation. The MMRM model used in SA1 was the same as those used in the primary analyses except that SA1 used all data from Weeks 1 to 12 while the primary analyses used data only from Weeks 1, 4, 8, and 12. This sensitivity analysis was conducted by the Applicant post hoc per FDA's request.
- Sensitivity analysis 2 (SA2): A tipping point analysis was used to assess the sensitivity of the main analysis results to violations of missing at random assumptions used in the primary analyses. In the tipping point analysis, delta adjustments were applied only to the MI values in the elinzanetant arm. For the two coprimary endpoints of VMS frequency, the adjustments were applied with delta values from 1 to 10 with an increase of 1 in each successive tipping point iteration. For the endpoints related to severity of hot flashes, the adjustments were applied with delta values of 0.2 to 2 with an increase of 0.2 in each successive tipping point iteration.

To further assess the robustness of the primary efficacy analysis based on the treatment policy strategy, the Applicant reanalyzed the primary analysis using the following two supplementary estimands:

- In the first supplementary estimand, observed data after temporary treatment interruption and permanent treatment discontinuation due to COVID-19, administrative and any other treatment unrelated reasons, and intake of prohibited medications and permanent treatment discontinuation with initiation of alternative VMS treatment, were censored and imputed by the MMRM model.
- In the second supplementary estimand, observed data after temporary treatment interruption and permanent treatment discontinuation due to COVID-19, administrative and any other treatment unrelated reasons were censored and imputed by the MMRM model whereas observed data after intake of prohibited medications and permanent treatment discontinuation

with initiation of alternative VMS treatment were censored and imputed by baseline data (considered as treatment failure).

Subgroup Analyses

In OASIS 1 and OASIS 2, subgroup analyses of the four coprimary efficacy endpoints were performed by geographic region (North America and the rest of the world), age group (40 to 49, 50 to 59, and 60 to 65 years), BMI group (<18.5, ≥18.5 to <25, ≥25 to <30, and ≥30 kg/m^2), race (Black or African American, White, Asian, American Indian or Alaskan Native, and Multiple), ethnicity (Hispanic or Latino and Not Hispanic or Latino), and smoking history (Current, Former, and Never smokers). Analyses within each subgroup were performed similarly to the primary analysis for the coprimary endpoints.

Given that OASIS 3 was a supportive study, subgroup analysis of the primary endpoint was not conducted in this study.

6.2.4.3. Analysis of Key Secondary Endpoints, OASIS 1, OASIS 2, and OASIS 3

Three key secondary endpoints in OASIS 1 and OASIS 2 were analyzed similarly to the primary analysis for the coprimary efficacy endpoints. For PROMIS SD SF 8b, the MMRM model used data from Weeks 1, 4, 8, and 12. For MENQOL, the MMRM model used data from Weeks 4, 8, and 12 since Week 1 data were not collected for MENQOL. In the analysis of PROMIS SD SF 8b total T-score and MENQOL total score, score-level missing data were handled by multiple imputation.

There was no prespecified key secondary endpoints in OASIS 3.

6.2.5. Results of Analyses for Clinical Trials Intended To Demonstrate Benefit, OASIS 1, OASIS 2, and OASIS 3

This section focuses on the results from pivotal studies OASIS 1 and OASIS 2. For OASIS 3, only results of the primary efficacy endpoint were reported as supportive efficacy evidence.

6.2.5.1. Subject Disposition, OASIS 1 and OASIS 2 (Pivotal)

Table 14 and Table 15 below show the summary of subject disposition and the primary reasons for study discontinuation during the 12-week double-blinded treatment period in OASIS 1 and OASIS 2, respectively.

As shown, a total of 396 subjects in OASIS 1 and 400 in OASIS 2 were randomized; these comprise the efficacy population. Of the randomized subjects, 339 (86%) in OASIS 1 and 351 (88%) in OAISIS 2 completed the first 12-week treatment period. The rates of study discontinuation before Week 12 were 10% in OASIS 1 and 8% in OASIS 2. The most common reasons for discontinuation before Week 12 in OASIS 1 were adverse event (AE; 4%) and subject decision (2%). Similarly, the most common reasons for discontinuation in OASIS 2 before Week 12 were subject decision (3%) and AE (2%). In both OASIS 1 and OASIS 2,

around 5% of subjects who discontinued before completing the 12-week treatment remained in the studies and either completed the post-treatment phase or directly entered the follow-up phase.

Table 14. Summary of Subject Disposition and Reasons for Study Discontinuation, OASIS 1

Subject Disposition	Elinzanetant 120 mg	Placebo	Total
Randomized (efficacy population)	199 (100%)	197 (100%)	396 (100%)
Randomized and treated	198 (99.5%)	195 (99.0%)	393 (99.2%)
Completed 12-week treatment period	171 (85.9%)	168 (85.3%)	339 (85.6%)
Completed 26-week treatment period	156 (78.4%)	159 (80.7%)	315 (79.5%)
Permanent discontinuation of study drug before Week 12	27 (13.6%)	27 (13.7%)	54 (13.6%)
Withdrawal from study before Week 12	18 (9.0%)	20 (10.2%)	38 (9.6%)
Adverse event	7 (3.5%)	8 (4.1%)	15 (3.8%)
Lack of efficacy	0	2 (1.0%)	2 (0.5%)
Lost to follow-up	3 (1.5%)	2 (1.0%)	5 (1.3%)
Noncompliance with study drug	2 (1.0%)	3 (1.5%)	5 (1.3%)
Other	0	0	0
Protocol deviation	0	0	0
Physician decision	2 (1.0%)	0	2 (0.5%)
Subject decision	4 (2.0%)	5 (2.5%)	9 (2.3%)
Completed post-treatment phase	1 (0.5%)	1 (0.5%)	2 (0.5%)
Directly entered follow-up	8 (4.0%)	6 (3.0%)	14 (3.5%)

Source: Reviewer's Analysis and Table 8.1.3 / 1 in Clinical Study Report for OASIS 1

Table 15. Summary of Subject Disposition and Reasons for Study Discontinuation, OASIS 2

Subject Disposition	Elinzanetant 120 mg	Placebo	Total
Randomized (efficacy population)	200 (100%)	200 (100%)	400 (100%)
Randomized and treated	200 (100%)	200 (100%)	400 (100%)
Completed 12-week treatment period	170 (85.0%)	181 (90.5%)	351 (87.8%)
Completed 26-week treatment period	160 (80.0%)	170 (85.0%)	330 (82.5%)
Permanent discontinuation of study drug before Week 12	30 (15.0%)	19 (9.5%)	49 (12.3%)
Withdrawal from study before Week 12	20 (10.0%)	12 (6.0%)	32 (8.0%)
Adverse event	6 (3.0%)	3 (1.5%)	9 (2.3%)
Lack of efficacy	1 (0.5%)	0	1 (0.3%)
Lost to follow-up	3 (1.5%)	0	3 (0.8%)
Noncompliance with study drug	1 (0.5%)	2 (1.0%)	3 (0.8%)
Other	1 (0.5%)	1 (0.5%)	2 (0.5%)
Protocol deviation	0	1 (0.5%)	1 (0.3%)
Physician decision	0	0	0
Subject decision	8 (4.0%)	5 (2.5%)	13 (3.3%)
Completed post-treatment phase	4 (2.0%)	4 (2.0%)	8 (2.0%)
Directly entered follow-up	6 (3.0%)	3 (1.5%)	9 (2.3%)

Source: Reviewer's Analysis and Table 8.1.3 / 1 in Clinical Study Report for OASIS 2

6.2.5.2. Demographics and Baseline Clinical Characteristics, OASIS 1 and OASIS 2 (Pivotal)

The summary of demographic and baseline characteristics of randomized subjects in OASIS 1 and OASIS 2 are shown in Table 16 and Table 17, respectively. As shown, in both studies, the mean age of subjects were approximately 49 years (range: 40 to 65 years), with approximately 68% of subjects aged between 50 to 59 years. Most subjects were White (77% in OASIS 1 and

84% in OASIS 2), Not Hispanic or Latino ethnicity (91% in OASIS 1 and 90% in OASIS 2), and never smokers (67% in OASIS 1 and 63% in OASIS 2). Subjects had a mean BMI of 28 kg/m^2, with about 33% being obese (a BMI of ≥30 kg/m^2). Both studies enrolled subjects with prior history of hysterectomy (42% in OASIS 1 and 36% in OASIS 2), oophorectomy (25% in OASIS 1 and 16% in OASIS 2), or hormone replacement treatment use (32% in OASIS 1 and 31% in OASIS 2). More than half of subjects enrolled in both studies were from the United States and Canada (59% in OASIS 1 and 51% in OASIS 2).

All demographic and baseline characteristics were generally balanced across treatment groups in both studies except that OASIS 1 had higher proportion of subjects who were never smokers in the elinzanetant arm compared to in the placebo arm (75% versus 58%).

Table 16. Demographic and Baseline Characteristics, OASIS 1 (FAS)

Demographic Characteristics	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Total (N=396)
Age			
Mean (SD)	54.6 (4.9)	54.5 (4.9)	54.6 (4.9)
Median (min, max)	54.0 (41, 65)	55.0 (40, 65)	55.0 (40, 65)
Age group, n (%)			
40-49 years	29 (14.6)	31 (15.7)	60 (15.2)
50-59 years	135 (67.8)	134 (68.0)	269 (67.9)
60-65 years	35 (17.6)	32 (16.2)	67 (16.9)
BMI (kg/m^2)			
Mean (SD)	27.78 (4.84)	27.65 (4.52)	27.72 (4.68)
Median (min, max)	27.40 (18.3, 39.0)	27.20 (18.3, 37.7)	27.35 (18.3, 39.0)
BMI (kg/m^2), n (%)			
<18.5	1 (0.5)	1 (0.5)	2 (0.5)
≥18.5 to <25	69 (34.7)	58 (29.4)	127 (32.1)
≥25 to <30	64 (32.2)	73 (37.1)	137 (34.6)
≥30	65 (32.7)	65 (33.0%)	130 (32.8)
Race, n (%)			
White	151 (75.9)	154 (78.2)	305 (77.0)
Black or African American	38 (19.1)	38 (19.3)	76 (19.2)
Asian	2 (1.0)	1 (0.5)	3 (0.8)
American Indian or Alaskan Native	1 (0.5)	1 (0.5)	2 (0.5)
Multiple	3 (1.5)	0	3 (0.8)
Not reported	4 (2.0)	3 (1.5)	7 (1.8)
Ethnicity, n (%)			
Not Hispanic or Latino	180 (90.5)	179 (90.9)	359 (90.7)
Hispanic or Latino	17 (8.5)	14 (7.1)	31 (7.8)
Not reported	2 (1.0)	4 (2.0)	6 (1.5)
Geographic region, n (%)			
United States and Canada	118 (59.3)	117 (59.4)	235 (59.3)
Rest of world	81 (40.7)	80 (40.6)	161 (40.7)
Smoking History, n (%)			
Never	150 (75.4)	115 (58.4)	265 (66.9)
Former	26 (13.1)	33 (16.8)	59 (14.9)
Current	23 (11.6)	49 (24.9)	72 (18.2)
Prior hysterectomy[a], n (%)			
No	115 (57.8)	115 (58.4)	230 (58.1)
Yes	84 (42.2)	82 (41.6)	166 (41.9)

Demographic Characteristics	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Total (N=396)
Prior Oophorectomy[b], n (%)			
No	148 (74.4)	148 (75.1)	296 (74.7)
Yes	51 (25.6)	49 (24.9)	100 (25.3)
Prior hormone replacement therapy, n (%)			
No	134 (67.3)	136 (69.0)	270 (68.2)
Yes	65 (32.7)	61 (31.0)	126 (31.8)

Source: Reviewer's Analysis and Table 4-1 and Table 8.1.5/2 in Clinical Study Report for OASIS 1
Abbreviations: BMI, body mass index; FAS, full analysis set; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

Table 17. Demographic and Baseline Characteristics, OASIS 2 (FAS)

Demographic Characteristics	Elinzanetant 120 mg (N=200)	Placebo (N=200)	Total (N=400)
Age			
Mean (SD)	54.8 (5.0)	54.4 (4.5)	54.6 (4.8)
Median (min, max)	55.0 (40, 65)	54.0 (42, 64)	54.0 (40, 65)
Age group, n (%)			
40-49 years	24 (12.0)	29 (14.5)	53 (13.3)
50-59 years	135 (67.5)	139 (69.5)	274 (68.5)
60-65 years	41 (20.5)	32 (16.0)	73 (18.3)
BMI (kg/m^2)			
Mean (SD)	27.78 (4.81)	27.95 (4.74)	27.86 (4.77)
Median (min, max)	27.00 (17.8, 38.5)	27.35 (18.2, 38.0)	27.25 (17.8, 38.5)
BMI (kg/m^2), n (%)			
<18.5	4 (2.0)	1 (0.5)	5 (1.3)
≥18.5 to <25	55 (27.5)	60 (30.0)	115 (28.8)
≥25 to <30	78 (39.0)	70 (35.0)	148 (37.0)
≥30	63 (31.5)	69 (34.5)	132 (33.0)
Weight (kg)			
Mean (SD)	75.15 (13.48)	74.89 (14.33)	75.02 (13.90)
Median (min, max)	74.01 (45.5, 112.2)	72.60 (46.5, 126.9)	73.44 (45.5, 126.9)
Race, n (%)			
White	163 (81.5)	172 (86.0)	335 (83.8)
Black or African American	35 (17.5)	25 (12.5)	60 (15.0)
Asian	0	1 (0.5)	1 (0.3)
American Indian or Alaskan Native	1 (0.5)	1 (0.5)	2 (0.5)
Multiple	0	1 (0.5)	1 (0.3)
Not reported	1 (0.5)	0	1 (0.3)
Ethnicity, n (%)			
Not Hispanic or Latino	186 (93.0%)	175 (87.5%)	361 (90.3%)
Hispanic or Latino	13 (6.5%)	24 (12.0%)	37 (9.3%)
Not reported	1 (0.5%)	1 (0.5%)	2 (0.5%)
Geographic region, n (%)			
United States and Canada	101 (50.5)	101 (50.5)	202 (50.5)
Rest of world	99 (49.5)	99 (49.5)	198 (49.5)
Smoking History, n (%)			
Never	117 (58.5%)	135 (67.5%)	252 (63.0%)
Former	41 (20.5%)	33 (16.5%)	74 (18.5%)
Current	42 (21.0%)	32 (16.0%)	74 (18.5%)

Demographic Characteristics	Elinzanetant 120 mg (N=200)	Placebo (N=200)	Total (N=400)
Prior hysterectomy[a], n (%)			
No	131 (65.5)	126 (63.0)	257 (64.3)
Yes	69 (34.5)	74 (37.0)	143 (35.8)
Prior Oophorectomy[b], n (%)			
No	176 (88.0)	160 (80.0)	336 (84.0)
Yes	24 (12.0)	40 (20.0)	64 (16.0)
Prior hormone replacement therapy, n (%)			
No	134 (67.0)	142 (71.0)	276 (69.0)
Yes	66 (33.0)	58 (29.0)	124 (31.0)

Source: Reviewer's Analysis and Table 4-1 and Table 8.1.5/2 in Clinical Study Report for OASIS 2
% equals the n divided by N multiplied by 100.
[a] Based on Medical History, preferred term (in MedDRA) considered for hysterectomy are: Hysterectomy, Hysterosalpingectomy, Hysterosalpingo-oophorectomy, and Radical hysterectomy
[b] Based on Medical History, preferred term (in MedDRA) considered for oophorectomy were hysterosalpingo-oophorectomy, oophorectomy, oophorectomy bilateral, salpingo-oophorectomy, salpingo-oophorectomy bilateral, salpingo-oophorectomy unilateral.
Abbreviations: BMI, body mass index; FAS, full analysis set; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects randomized to that treatment arm; n, number of subjects contributing to the specific category; SD, standard deviation

6.2.5.3. Results for Analyses, OASIS 1, OASIS 2, and OASIS 3

6.2.5.3.1. Coprimary Endpoints OASIS 1, OASIS 2, and OASIS 3

Primary Analyses of Coprimary Endpoints

The coprimary efficacy endpoints were analyzed using MMRM model. Results are summarized in Table 18 for the frequency and Table 19 for severity of HFs.

Reduction in the Frequency of VSMs at Weeks 4 and 12

The mean frequency of moderate to severe HFs per day were balanced at baseline in both studies (Table 18). In OASIS 1, subjects in the elinzanetant and placebo groups experienced a mean of 13 and 14 episodes of moderate to severe HFs per day. In OASIS 2, subjects in the elinzanetant and placebo groups had a mean of 15 and 16 episodes of moderate to severe HFs, respectively.

The data from both OASIS 1 and OASIS 2 showed that subjects in the elinzanetant group had a statistically significant reduction from baseline in the frequency of moderate to severe HFs per day at Weeks 4 and 12 compared to those in the placebo group (all $p<0.0001$). At Week 4, subjects in the elinzanetant group reported an average reduction from baseline of 8 (OASIS 1) to 9 (OASIS 2) episodes in moderate to severe HFs per day compared to an average reduction of 4 (OASIS 1) to 6 (OASIS 2) reported by subjects in the placebo group. Similarly, at Week 12, subjects in the elinzanetant group reported an average reduction from baseline of 9 (OASIS 1) to 10 (OASIS 2) episodes in moderate to severe HFs per day compared to an average reduction of 5 (OASIS 1) to 6 (OASIS 2) episodes reported by those in the placebo group.

In addition to the statistical significance, both studies met the Division's criteria of a clinically meaningful reduction in the frequency of moderate to severe HFs of at least 2 episodes per day (or 14 per week) above that demonstrated with placebo at Week 4 and maintained through

Week 12. For example, the mean differences between elinzanetant and placebo were -3.3 at Week 4 and -3.2 at Week 12 in OASIS 1, and -3.0 at Week 4 and -3.2 at Week 12 in OASIS 2.

In addition to both OASIS 1 and OASIS 2 meeting the Division's 14/2 criteria for a clinically meaningful reduction in VMS frequency at Weeks 4 and 12, the Applicant also conducted additional exploratory anchor-based analyses to derive clinically meaningful within-patient change thresholds for VMS frequency at Weeks 4 and 12. However, given that the mean frequency reductions at Weeks 4 and 12 in both studies met the Division's 14/2 criteria, the review team did not further evaluate the validity of the exploratory anchor-based analyses submitted by the Applicant.

Table 18. Change From Baseline in Mean Daily Frequency of Moderate to Severe Hot Flashes, MMRM Analysis by Treatment Group, OASIS 1 and OASIS 2 (FAS)

	OASIS 1		OASIS 2	
Visit/Statistics	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Elinzanetant 120 mg (N=200)	Placebo (N=200)
Baseline				
N	199	197	199	200
Mean (SD)	13.38 (6.57)	14.26 (13.94)	14.66 (11.08)	16.16 (11.15)
Change from Baseline to Week 4				
LS-Mean (SE)	-7.60 (0.43)	-4.31 (0.43)	-8.58 (0.49)	-5.54 (0.49)
Difference vs. placebo (95% CI)	-3.29 (-4.47, -2.10)		-3.04 (-4.40, -1.68)	
p-Value (one-sided)	<0.0001		<0.0001	
Change from Baseline to Week 12				
LS-mean (SE)	-8.66 (0.58)	-5.44 (0.59)	-9.72 (0.50)	-6.48 (0.49)
Difference vs. placebo (95% CI)	-3.22 (-4.81, -1.63)		-3.24 (-4.60, -1.88)	
p-Value (one-sided)	<0.0001		<0.0001	

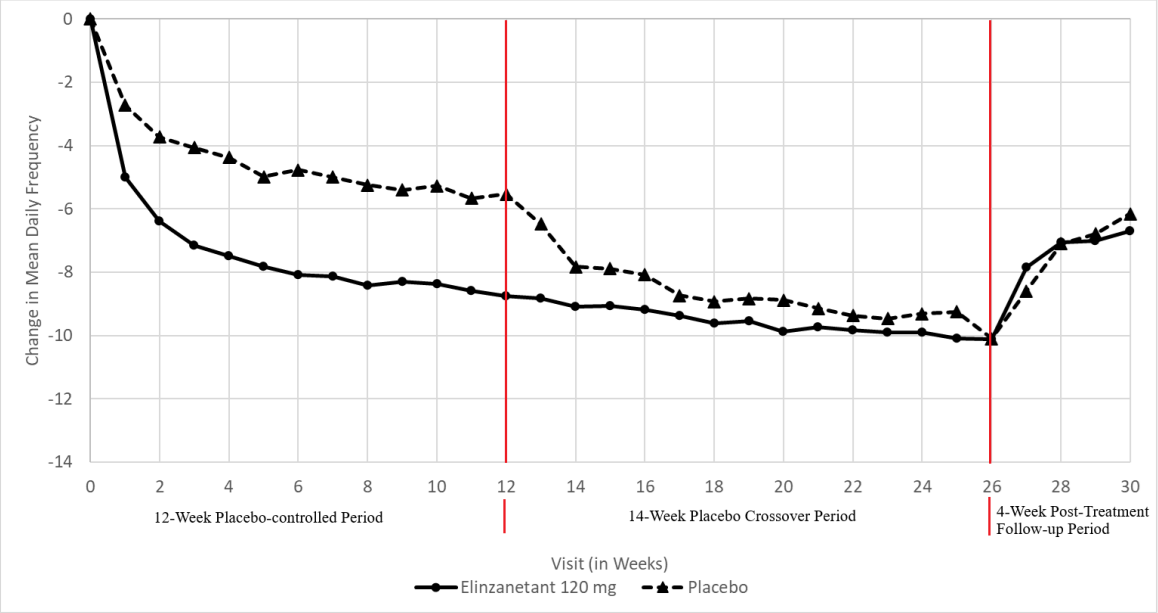
Source: Reviewer's Analysis and Table 5-2 in Clinical Study Reports for OASIS 1 and 2
The LS means, SE, CI, and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week (1, 4, 8, and 12), and region (United States vs. the rest of the world) as factors, with baseline frequency as covariates, as well as an interaction of treatment by week and an interaction of baseline frequency by week.
Abbreviations: FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of subjects in treatment arm; n, subjects with given characteristic; SD, standard deviation; SE, standard error

Figure 4 and Figure 5 below show the mean changes from baseline in the frequencies of moderate to severe HFs episodes over time in OASIS 1 and OASIS 2, respectively.

In both studies, subjects who received elinzanetant 120 mg had greater reductions in the mean frequency of moderate to severe HFs compared to those given placebo during the 12-week placebo-controlled treatment period. The effect was noticed as early as Week 1. During the Week 12 to Week 26 crossover period, continued reduction in VMS frequency in both treatment arms was observed. Subjects who were initially randomized to placebo but switched to elinzanetant 120 mg during this 14-week placebo crossover period reported pronounced improvement, further providing efficacy evidence for elinzanetant 120 mg. Additionally, in both OASIS 1 and OASIS 2, the mean changes in the frequency of moderate to severe HFs increased in both arms during the 4-week follow-up post-treatment period (i.e., during Week 26 to Week 30). By Week 26, subjects who were initially randomized to active study drug had received elinzanetant 120 mg for the full 26 weeks, whereas those originally assigned to placebo had taken elinzanetant 120 mg for 14 consecutive weeks. Upon discontinuation of treatment, both groups exhibited a similar degree of symptom recurrence, which further affirm the

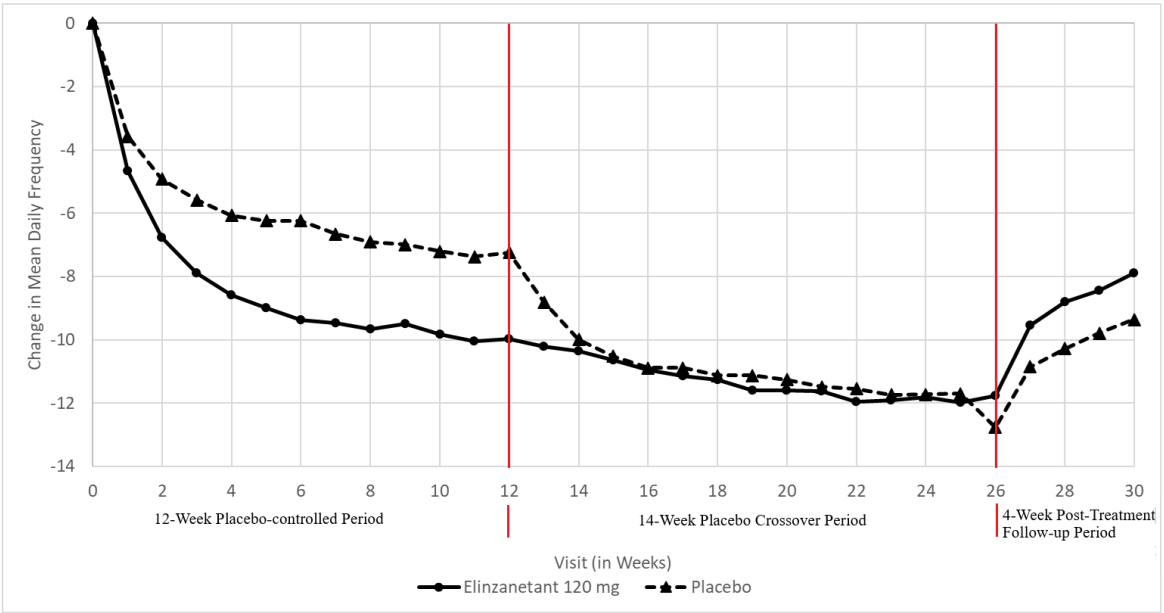
treatment benefit of elinzanetant 120 mg in the reduction of the frequency of moderate to severe HFs.

Figure 4. Change From Baseline in Mean Frequency of Moderate to Severe Vasomotor Symptoms Over Time, OASIS 1



Source: Reviewer's Analysis
Hot flash daily data were collected during the entire study in OASIS 1

Figure 5. Change From Baseline in Mean Frequency of Moderate to Severe Vasomotor Symptoms Over Time, OASIS 2



Source: Reviewer's Analysis
Hot flash daily data were collected during the entire study in OASIS 2

The results from OASIS 3 supported the reduction in the frequency of HFs observed at Weeks 4 and 12 in OASIS 1 and OASIS 2 (Table 19). However, because OASIS 3 did not require subjects to have a minimum number of moderate to severe HFs at baseline, the magnitude of reduction in this study was numerically smaller compared to that seen in OASIS 1 and OASIS 2.

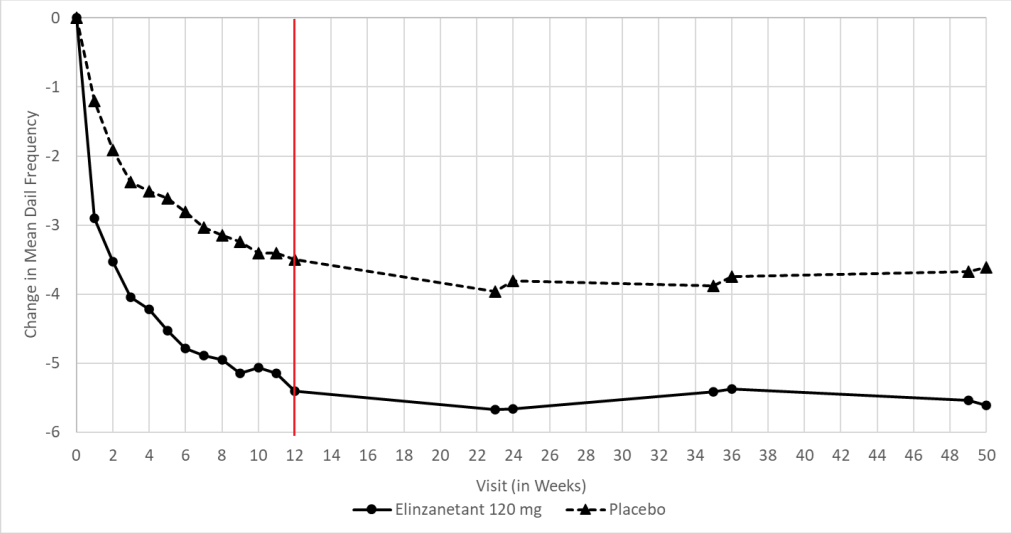
Table 19. Change From Baseline in Mean Daily Frequency of Moderate to Severe Hot Flashes, MMRM Analysis by Treatment Group, OASIS 3 (FAS)

Visit/Statistics	Elinzanetant 120 mg (N=313)	Placebo (N=315)
Baseline		
N	312	315
Mean (SD)	6.71 (7.15)	6.81 (6.15)
Change from Baseline to Week 4*		
LS-Means (SE)	-4.14 (0.18)	-2.45 (0.18)
Difference vs. Placebo (95% CI)	-1.69 (-2.19, -1.18)	
p-Value (one-sided)	<0.0001	
Change from Baseline to Week 12		
LS-means (SE)	-4.89 (0.18)	-3.34 (0.18)
Difference vs. placebo (95% CI)	-1.55 (-2.04, -1.05)	
p-Value (one-sided)	<0.0001	

Source: Reviewer's Analysis and Table 5-1 in Clinical Study Report for OASIS 3
*Analyses performed by the FDA reviewers.
The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week (1, 4, 8, and 12), and region (United States vs. the rest of the world) as factors, with baseline frequency as covariates, as well as an interaction of treatment by week and an interaction of baseline frequency by week.
Abbreviations: FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of subjects in treatment arm; n, subjects with given characteristic; SD, standard deviation; SE, standard error

Figure 6 below shows the mean change in the frequency of moderate to severe HFs from baseline through Week 50 in OASIS 3. As shown, there was a reduction in both treatment arms from baseline though Week 50. Elinzanetant 120 mg treated subjects had greater reduction in HF frequency at all time points compared to placebo treated subjects, confirming the maintenance of the treatment effect through Week 50.

Figure 6. Change From Baseline in Mean Frequency of Moderate to Severe Vasomotor Symptoms Over Time, OASIS 3



Source: Reviewer's Analysis
Hot flash daily data were collected during Weeks 1-12, 23-24, 35-36, and 49-50 in OASIS 3.

Reduction in the Severity of HFs at Weeks 4 and 12

In both OASIS 1 and OASIS 2, severity of HFs was similar between treatment groups at baseline, with the mean severity score about 2.5. In both studies, and at both Weeks 4 and 12 timepoints, subjects in the elinzanetant group had a statistically significant reduction from baseline in the HF severity per day compared to those in the placebo group (all $p<0.001$). Therefore, the coprimary efficacy endpoint of VMS severity was met in both OASIS 1 and OASIS 2.

Table 20. Change From Baseline in Mean Daily Severity of Moderate to Severe Hot Flashes, MMRM Analysis by Treatment Group, OASIS 1 and OASIS 2 (FAS)

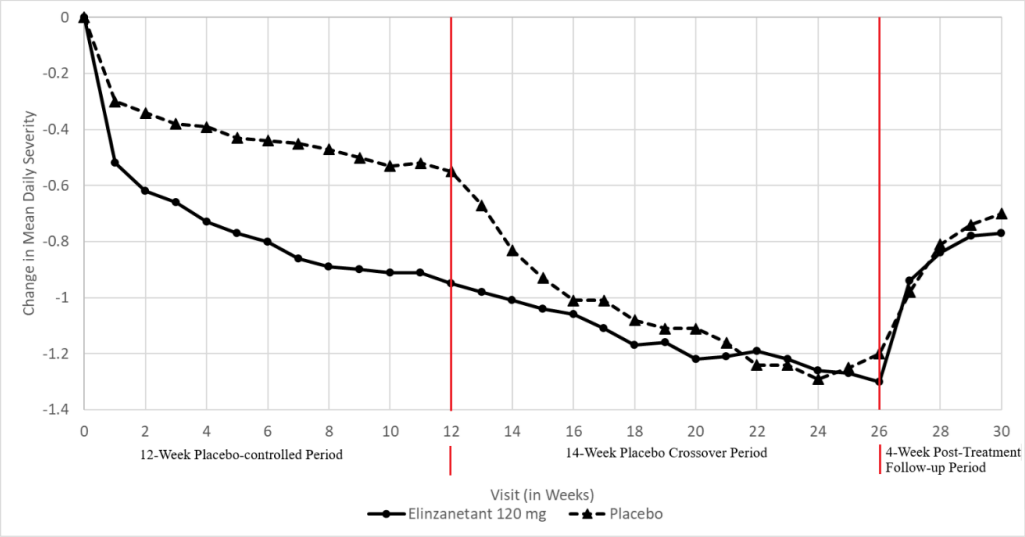
	OASIS 1		OASIS 2	
Visit/Statistics	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Elinzanetant 120 mg (N=200)	Placebo (N=200)
Baseline				
N	199	197	199	200
Mean (SD)	2.56 (0.22)	2.53 (0.23)	2.53 (0.24)	2.54 (0.24)
Change from Baseline to Week 4				
LS-Mean (SE)	-0.73 (0.04)	-0.40 (0.04)	-0.75 (0.04)	-0.53 (0.04)
Difference vs. placebo (95% CI)		-0.33 (-0.44, -0.23)		-0.22 (-0.34, -0.09)
p-Value (one-sided)		<0.0001		0.0003

Visit/Statistics	OASIS 1 Elinzanetant 120 mg (N=199)	OASIS 1 Placebo (N=197)	OASIS 2 Elinzanetant 120 mg (N=200)	OASIS 2 Placebo (N=200)
Change from Baseline to Week 12				
LS-Mean (SE)	-0.92 (0.05)	-0.52 (0.05)	-0.91 (0.06)	-0.62 (0.05)
Difference vs. placebo (95% CI)	-0.40 (-0.54, -0.25)		-0.29 (-0.44, -0.14)	
p-Value (one-sided)	<0.0001		<0.0001	

Source: Reviewer's Analysis and Table 5-3 in Clinical Study Reports for OASIS 1 and 2
The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week (1, 4, 8, and 12), and region (United States vs. the rest of the world) as factors, with baseline frequency as covariates, as well as an interaction of treatment by week and an interaction of baseline frequency by week.
Abbreviations: LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of subjects in treatment arm; n, subjects with given characteristic; SD, standard deviation; SE, standard error

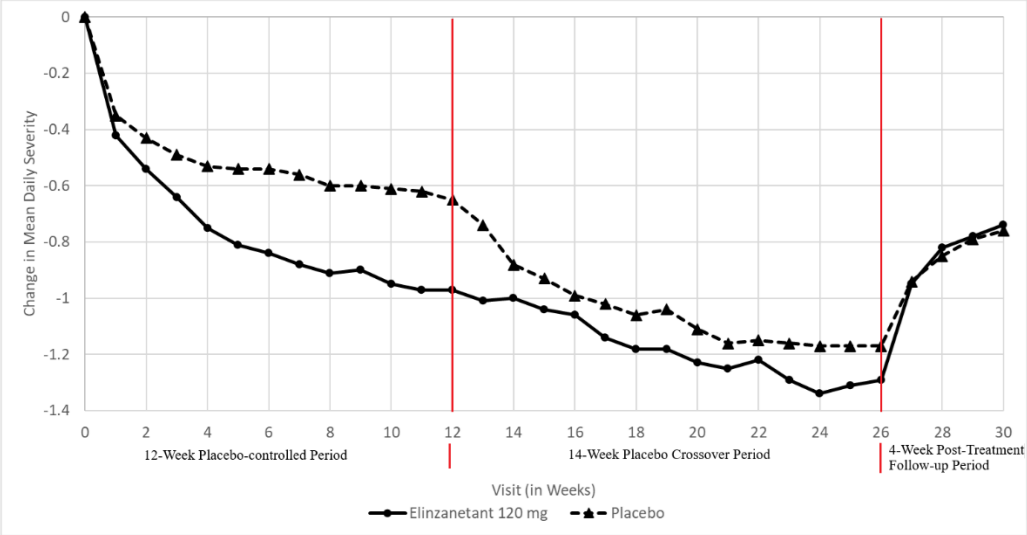
Figure 7 and Figure 8 below show the mean changes from baseline in the severity of moderate to severe HFs over time in OASIS 1 and OASIS 2. The figures showed similar patterns of reduction in HF severity over time as was seen with the reduction in the frequency of HFs.

Figure 7. Change From Baseline in Mean Severity of Moderate to Severe Vasomotor Symptoms Over Time, OASIS 1



Source: Reviewer's Analysis
Hot flash daily data were collected during the entire study in OASIS 1.

Figure 8. Change From Baseline in Mean Severity of Moderate to Severe Vasomotor Symptoms Over Time, OASIS 2



Source: Reviewer's Analysis
Hot flash daily data were collected during the entire study in OASIS 2.

The percentages of subjects who achieved a certain level of reduction in the frequency and severity of HFs at Weeks 4 and 12 were also assessed in both OASIS 1 and OASIS 2. Figure 88, Figure 89, Figure 90, and Figure 91 in Section 16.3 display the cumulative percent of subjects who achieved a certain level of reduction in the frequency and severity of HFs by treatment group. As shown, in both studies, and at both Week 4 and Week 12 timepoints, the cumulative distribution function curves of the two groups clearly separate, indicating that more elinzanetant-treated subjects than placebo-treated subjects achieved a given level of reduction in the frequency and severity of HFs at these timepoints. For example, in OASIS 1, more elinzanetant-treated subjects than placebo-treated subjects reported a mean of at least five fewer episodes of moderate to severe HFs daily at Week 4 (68% versus 40%) and at Week 12 (74% versus 50%), respectively. Corresponding results were seen in elinzanetant subjects compared to placebo subjects in OASIS 2 at Week 4 (68% versus 45%) and at Week 12 (77% versus 55%), respectively. The findings related to reduction in the severity of moderate to severe HFs were similar. More elinzanetant-treated subjects than placebo-treated subjects achieved at least 1-unit reduction per day in severity score at both timepoints in both studies (26% versus 5% at Week 4 and 40% versus 16% at Week 12 in OASIS 1; 30% versus 13% at Week 4 and 44% versus 22% at Week 12 in OASIS 2).

In summary, the primary analyses of the four coprimary endpoints in both OASIS 1 and OASIS 2 studies have shown that subjects treated with elinzanetant 120 mg had a statistically significant reduction in the frequency and severity of VMS from baseline at Week 4 and Week 12.

6.2.5.3.2. Sensitivity Analysis of Coprimary Endpoints OASIS 1, OASIS 2, and OASIS 3

Two sensitivity analyses (SA1 and SA2) described in Section 6.2.4.2 were conducted for the four coprimary efficacy endpoints (Table 216 and Table 217 in Section 16.2). Both sensitivity analyses results showed the robustness of the primary efficacy results under varying model specification (SA1) and missing data assumption (SA2). See Section 16.2 for the results from the sensitivity analyses.

To further evaluate the robustness of the primary analyses results for the four coprimary endpoints, several supporting analyses under different estimand strategies (e.g., composite strategy for ICE of intake of prohibited medications and permanent treatment discontinuation with alternative VMS treatment), different model specifications, and data handling strategies were conducted. The various supporting analyses provided the same conclusion except for minor numerical differences. The consistent findings across these analyses reinforce the reliability of the primary analysis results.

6.2.5.3.3. Subgroup Analysis of Coprimary Endpoints OASIS 1, OASIS 2, and OASIS 3

In OASIS 1 and OASIS 2, subgroup analyses for the four coprimary endpoints were performed based on geographic region, age group, race, ethnicity, BMI, and smoking status. These analyses were consistent with the primary analyses, demonstrating that elinzanetant 120 mg treatment resulted in greater reduction in VMS frequency and severity at both Weeks 4 and 12 compared to placebo within each subgroup category.

The results of subgroup analyses are presented in Figure 92 through Figure 99 in Section 16.4.

6.2.5.3.4. Key Secondary Endpoints OASIS 1, OASIS 2, and OASIS 3

Table 21, Table 22, and Table 23 below show the results of the three key secondary endpoints as described in Section 6.2.4.3. As shown in Table 21, in both studies, the reductions in the mean frequency of moderate to severe HFs from baseline to Week 1 were statistically significantly higher in the elinzanetant group than in the placebo group ($p<0.0001$ in OASIS 1 and $p=0.0013$ in OASIS 2). Similarly, the reductions (improvement) from baseline to Week 12 in the PROMIS SD SF 8b total T-scores (Table 22) and in MENQOL total scores (Table 23) in both OASIS 1 and OASIS 2 were statistically significantly greater in the elinzanetant 120 mg group than in the placebo group (all $p<0.01$). Since there was no multiplicity adjustment plan for testing these secondary endpoints, p-values are intended for descriptive use only.

Table 21. Change in Mean Daily Frequency of Moderate to Severe Hot Flashes From Baseline to Week 1, MMRM Analysis by Treatment Group, OASIS 1 and OASIS 2 (FAS)

	OASIS 1		OASIS 2	
Visit/Statistics	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Elinzanetant 120 mg (N=200)	Placebo (N=200)
Baseline				
n	199	197	199	200
Mean (SD)	13.38 (6.57)	14.26 (13.94)	14.66 (11.08)	16.16 (11.15)
Change from Baseline to Week 1				
LS-Mean (SE)	-5.13 (0.33)	-2.68 (0.33)	-4.93 (0.39)	-3.28 (0.39)
Difference vs. placebo (95% CI)	-2.45 (-3.36, -1.55)		-1.66 (-2.73, -0.58)	
p-Value (one-sided)	<0.0001		0.0013	

Source: Reviewer's Analysis and Table 5-2 in Clinical Study Reports for OASIS 1 and 2
The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week (1, 4, 8, and 12), and region (United States versus the rest of the world) as factors, with baseline frequency as covariates, as well as an interaction of treatment by week and an interaction of baseline frequency by week.
Abbreviations: FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of subjects in treatment arm; n, subjects with given characteristic; SD, standard deviation; SE, standard error

Table 22. PROMIS SD SF 8b Total T-Score Change From Baseline to Week 12, MMRM Analysis by Treatment Group, OASIS 1 and OASIS 2 (FAS)

	OASIS 1		OASIS 2	
Visit/Statistics	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Elinzanetant 120 mg (N=200)	Placebo (N=200)
Baseline				
n	184	179	188	193
Mean (SD)	61.0 (7.7)	60.2 (7.2)	61.7 (6.2)	60.7 (7.2)
Change from Baseline to Week 12				
LS-Mean (SE)	-10.41 (0.60)	-4.83 (0.62)	-10.28 (0.54)	-5.97 (0.53)
Difference vs. placebo (95% CI)	-5.58 (-7.18, -3.98)		-4.32 (-5.77, -2.86)	
p-Value (one-sided)	<0.0001		0.0003	

Source: Reviewer's Analysis and Table 5-4 in Clinical Study Reports for OASIS 1 and 2
The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week (1, 4, 8, and 12), and region (United States versus the rest of the world) as factors, with baseline measurement as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Abbreviations: FAS, full analysis set; LS, least squares; MMRM, mixed-effect model for repeated measures; SD, standard deviation; SE, standard error

Table 23. MENQOL Total Score Change From Baseline to Week 12, MMRM Analysis by Treatment Group, OASIS 1 and OASIS 2 (FAS)

	OASIS 1		OASIS 2	
Visit/Statistics	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Elinzanetant 120 mg (N=200)	Placebo (N=200)
Baseline				
n	179	173	186	189
Mean (SD)	4.56 (1.27)	4.49 (1.31)	4.48 (1.14)	4.49 (1.17)
Change from Baseline to Week 12				
LS-Mean (SE)	-1.36 (0.08)	-0.94 (0.08)	-1.29 (0.09)	-1.00 (0.08)
Difference vs. placebo (95% CI)	-0.42 (-0.64, -0.20)		-0.30 (-0.53, -0.07)	
p-Value (one-sided)	<0.0001		0.0003	

Source: Reviewer's Analysis and Table 5-5 in Clinical Study Reports for OASIS 1 and 2
The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week (4, 8, and 12), and region (United States versus the rest of the world) as factors, with baseline measurement as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Abbreviations: LS, least squares; MMRM, mixed-effect model for repeated measures; SD, standard deviation; SE, standard error

6.3. Key Efficacy Review Issues

The review team did not identify any substantive review issues related to efficacy. Substantial evidence of efficacy was established based on OASIS 1 and OASIS 2. See Section 6.2.5.3.1 above for additional discussion.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The Applicant completed a comprehensive nonclinical program with elinzanetant and its major metabolites to inform safety considerations for the clinical use of elinzanetant. The program included pivotal, good laboratory practice (GLP)-compliant general toxicology studies in rats and monkeys, reproductive and developmental toxicology studies in rats and rabbits, in vitro and in vivo genotoxicity studies, and carcinogenicity studies in rats and transgenic mice. The main clinically relevant nonclinical safety signals include: (i) central nervous system (CNS)-related signals, including tremors and convulsions, (ii) skeletal muscle degeneration, (iii) malignant adenocarcinoma of the uterus, the combination of malignant and benign endometrial tumors and squamous cell carcinoma of the uterus, and lymphomas of the hematolymphoid system, (iv) phototoxic signals, (v) gastrointestinal (GI)-related signals, and (vi) reproductive and developmental toxicity signals. The potential for hepatotoxicity with elinzanetant, based on the integrated assessment of liver-related signals detected in the nonclinical studies and a comparative quantitative structure-activity relationship analysis of elinzanetant and the NK3R inhibitor fezolinetant, is discussed at the end of this section.

A brief overview of the nonclinical pharmacology and pharmacokinetic (PK) data on elinzanetant is described below. This is followed by integrated summary sections of all pertinent findings and studies that identified potential risks or safety concerns. Biological plausibility of certain findings, for example the CNS-related findings, is included. However, the underlying

plausible mechanism could not be determined for all findings based on the known pharmacology and pharmacodynamics of elinzanetant and its metabolites. Full reviews of all the studies are in Section 13.2 and in the nonclinical review in DARRTS (DARRTS°ID:°5623053 2025).

7.1.1. Pharmacology

Elinzanetant is an NK1R/NK3R antagonist. Inhibition of NK1R/NK3R on KNDy neurons can decrease neuronal activity involved in thermoregulation, which is thought to contribute to the VMS associated with menopause.

Elinzanetant has ~10-fold higher affinity to NK1R compared to NK3R, with mean pKi values of 9.43 and 8.42 for NK1R and NK3R, respectively. Elinzanetant has three principal metabolites, M27, M30/34, and M18/21, which also act as noncompetitive antagonists at NK1R and NK3R.

In vitro selectivity assays including a wide range of receptors, ions channels, transporters, and enzymes to identify potential off-target effects of elinzanetant yielded only a few notable findings. Elinzanetant and its three principal metabolites may have the potential to inhibit estrogen and progesterone receptors (ER and PR, respectively). Radioligand binding and functional assays with elinzanetant produced equivocal results. In Study R-13674, elinzanetant had no effect on radioligand binding to ER and PR, and in Study R-14344, elinzanetant (up to 30μM) had no effect on the activity of recombinant human PR-B. However, in Study 14343, elinzanetant inhibited radiolabeled estradiol and progesterone binding to recombinant human ERβ and to recombinant human PR-B, respectively; the half maximal inhibitory concentrations (IC_{50}s) were 22.5μM and 0.64μM, respectively. The metabolites M27, M30/M34 (major metabolite), and M18/21 inhibited radiolabeled progesterone binding to recombinant human PR-B with IC_{50}s of 1.34μM, 1.20μM, and 1.69μM, respectively.

Elinzanetant did not generate major safety signals in a complete battery of safety pharmacology studies (cardiovascular, respiratory, and CNS). Elinzanetant inhibited the activity of hERG channels with an IC_{50} of approximately 31μM that provides multiples of exposure of 14X and 4,820X, based on the maximum plasma concentration (C_{max}) and $C_{max, unbound}$ at the maximal recommended human dose, respectively. Elinzanetant metabolites M27, M30/34, and M18/21 had no effect on hERG channel activity. In a cardiovascular study in Cynomolgus monkeys at a single oral dose of 60 mg/kg, there was an increase in heart rate (by ~15%) and a decrease in body temperature (by ~0.6°C), which were both reversible. At the no-observed-adverse-effect level (NOAEL) of 20 mg/kg, there is a safety margin of ~4X (based on the $C_{max, unbound}$ at the maximal recommended human dose). There were no remarkable findings in respiratory function and CNS assessments in Sprague-Dawley rats up to the highest single-dose tested (100 mg/kg), with a safety margin of ~23X (based on the $C_{max, unbound}$ at the maximal recommended human dose).

7.1.2. Pharmacokinetics

PK studies in rats, monkeys, and dogs demonstrated that elinzanetant is absorbed following oral administration, with its oral bioavailability being moderate in male and female rats (77% and 47%, respectively), and low in monkeys and dogs (19%).

Autoradiographic studies revealed that, following the oral administration of radiolabeled elinzanetant to different species, radioactivity distributed to major organs, including the liver and pigmented tissues (e.g., the uveal tract and the retina). In typical PK studies, elinzanetant was also found to cross the blood brain barrier. In pregnant rats, the organ distribution of elinzanetant was similar to that in nonpregnant rats. In addition, elinzanetant crossed the placenta, and elinzanetant and its metabolites were detected in different fetal organs, including the brain. Collectively, these findings suggest that the brain, the liver, pigmented tissues, and the developing fetus can be important targets for elinzanetant-related effects.

Plasma protein binding was high across all preclinical species tested (99.5 to 99.9%) and higher in humans (>99.9%) for elinzanetant and its principal metabolites (M27, M30/34 and M18/21). As such, whenever appropriate for the nonclinical safety assessments, the extent of protein binding is included in the calculations of safety and exposure margins. The nonclinical safety assessment further considers the finding that in animals, as in humans, elinzanetant is metabolized primarily by oxidation at the methyl-phenyl moiety and the morpholine ring mainly to metabolites M27, M30/34 (a major human metabolite), and M18/21.

7.1.3. Integrated Summary of Potential Safety Concern Based on Nonclinical Findings

CNS-Related Safety Signals

Convulsions were noted in two nonclinical studies – a 2-year carcinogenicity study (Study B003186) conducted in female Sprague-Dawley rats (Envigo [formerly Harlan], United States) and a 13-week repeat-dose toxicity study (Study R-13628) conducted in male and female SD rats (Envigo, Netherlands). Table 24 summarizes the CNS-related findings from these studies. The substrain of SD rats from Envigo is referred to as Harlan Sprague-Dawley (SD:Hsd). The sources of the SD:Hsd rats are noted here for context as the discrepant findings between the different studies could potentially be linked to the substrain of rats and their origins.

The CNS-related findings from Studies B003186 and R-13628 are summarized in Table 24 and elaborated in the subsequent paragraphs.

Table 24. Summary of CNS-Related Findings in Rat Studies and Safety Margins

Rat Study	CNS-Related Effects of Elinzanetant	NOAEL/LOAEL	Safety Margin[a]	MOE[b]
13-week study (R-13628 [RH17GJ]) Female (F) and male (M) SD:Hsd rats (Envigo, Netherlands) F: 0, 10, 25, or 50 mg/kg BID, 13 weeks M: 0, 25, 60, or 150 mg/kg (highest dose decreased to 87.5 after Day 9) BID, 13 weeks	<u>Females</u> • At all doses − Spasms (up to 3 min) − Tremors (starting ~Day 24) − Convulsions (starting ~Day 34): − 2/16 @ 20 mg/kg/day; – 3/16 @ 50 mg/kg/day; − 3/21 @ 100 mg/kg/day [3 more F @ 100 mg/kg with decreased activity, hunched posture, and piloerection were euthanized by day 12] <u>Males</u> • 50 and 120 mg/kg/day − Tremors: 1/16 @ each dose , whole body rigidity, spasms (1-3 min), involuntary muscle contractions (convulsions first noted around Day 34), and stiff tail • 300 mg/kg/day − 5 found dead (Days 9-11); 6 euthanized for severe clinical signs (Days 9-12): decreased activity, hunched posture, abnormal gait, piloerection, prostration <u>Females and Males</u> • There were no brain histopathological findings associated with the convulsions. • CNS-unrelated finding: Skeletal muscle degeneration and necrosis in the highest dose groups (discussed below).	No NOAEL	ND	N/A
		LOAELs: F: 20 mg/kg/day Estimated day 34 $AUC_{(0-24)}$ ~35111 µg•h/L M: 50 mg/kg/day Estimated day 34 $AUC_{(0-24)}$ ~31930 µg•h/L	N/A	4X[b]

Rat Study	CNS-Related Effects of Elinzanetant	NOAEL/LOAEL	Safety Margin[a]	MOE[b]
Carcinogenicity study (B003186 [T105128-7]) Female SD:Hsd rats (Envigo, IN, USA) 0, 3.5, 10, 30, or 40 mg/kg, BID, 104 weeks	At ≥60 mg/kg/day: • Increased incidence of whole-body convulsions (first noted around treatment days 162 at 60 mg/kg/day and 106 at 80 mg/kg/day). • Increased incidence of hunched posture • Increased sensitivity to touch. • Decreased general activity. • Increased salivation. At ≥7 mg/kg/day: • Irregular respiration	NOAEL: 20 mg/kg/day $AUC_{(0-24)}$= 64000 µg•h/L	7.5X	N/A
		LOAEL: 60 mg/kg/day Estimated day 162 $AUC_{(0-24)}$ ~149399 µg•h/L	N/A	17X[c]

Source: Reviewer-generated table
[a] Safety margins are ratios of the $AUC_{(0-24)}$ at NOAEL to the clinical $AUC_{(0-24)}$ of 8572 ng•h/mL at the MRHD (clinical study B002427).
[b]MOE estimated using extrapolated $AUC_{(0-24)}$ values for treatment Day 34, when convulsions were first observed in male and female rats treated with the LOAELs for convulsions in the 13-week study [For details, refer to Section 13]. [c]MOE estimated using the extrapolated $AUC_{(0-24)}$ for treatment Day 162, when convulsions were first observed in female rats treated with the LOAEL for convulsions in the carcinogenicity study [For details, refer to Section 13].
Abbreviations: BID, twice daily; CNS, central nervous system; LOAEL, lowest observed adverse effect level; MOE, multiple of exposure; NOAEL, no observed adverse effect level; N/A, not applicable; ND, not determined (since a NOAEL was not established)

In the 13-week repeat-dose toxicity study, male SD:Hsd rats (Netherlands) were treated with the doses of 0, 25, 60, or 150 mg/kg (highest dose decreased to 87.5 after Day 9), BID (twice daily), and female SD:Hsd rats (Netherlands) were treated with the dose of 0, 10, 25, or 50 mg/kg, BID. Treatments were delivered by oral gavage for 13 weeks. Muscle spasms (lasting up to 3 minutes) and tremors were noted around Day 24 after start of treatment and were followed by convulsions (starting around treatment Day 34) in 2 out 16 females at 20 mg/kg/day, 3 out of 16 females at 50 mg/kg/day, and 3 out of 21 females at 100 mg/kg/day. Likewise, 1 out of 16 males in the groups that received the low and mid doses (50 and 120 mg/kg/day, respectively) had tremors, whole-body rigidity, spasm (lasting up to 1 to 3 minutes), stiff tail, and involuntary muscle contractions (convulsions). Male rats treated with the highest tested dose (300/175 mg/kg/day) died prematurely after presenting with reduced activity, hunched posture, abnormal gait, piloerection, and prostration.

In the 2-year carcinogenicity study, female SD:Hsd rats (United States) were treated with the oral doses of 0, 3.5, 10, 30, or 40 mg/kg, BID, for total doses of 0, 7, 20, 60, or 80 mg/kg/day, over the course of 104 weeks. At doses ≥7 mg/kg/day, there was an increased incidence of irregular respiration. At doses ≥60 mg/kg/day, there was an increased incidence of reduced general activity, increased sensitivity to touch, vocalization, hunched posture, and convulsions (Table 25). At doses ≥60 mg/kg/day, prodromal signs of convulsions (e.g., increased sensitivity to touch and decreased activity) generally preceded detection of convulsions, which were first noted around Days 162 and 106 after start of treatment with the doses of 60 mg/kg/day and 80 mg/kg/day, respectively.

Table 25. Incidence of Clinical Signs per Treatment Group in 2-Year Carcinogenicity Study

	Vehicle	Elinzanetant Doses (mg/kg/day)			
Clinical Signs	**Control**	**7**	**20**	**60**	**80**
Total number of rats/group	101	100	100	102	100
Involuntary movements					
Convulsions, whole body <1 minute	7	7	9	27	26
Convulsions, whole body >1 minute	2	0	5	11	9
All convulsions (# associated deaths)	8 (1)	7 (1)	9 (5)	30 (20)	28 (11)
Hunched posture	7	6	2	13	10
Decreased activity	3	5	4	10	16
Increased sensitivity to touch	4	6	2	18	12
Respiration					
Irregular	1	4	3	8	10
Audible	1	1	2	3	4
Fast	1	2	2	6	4
Excessive salivation					
Clear	1	2	2	8	5
Colorless	0	0	0	0	3

Source: Reviewer-generated table using data from the Applicant's study report B003186
Numbers in each row represent the number of animals presenting the listed clinical sign.

Convulsions were not reported in another 13-week repeat-dose toxicity study (Study R-13596) and a 26-week repeat-dose toxicity study (Study R-13894) conducted with male and female SD rats. In the 13-week Study R-13596, SD rats were from Charles River (Canada) and were treated with the oral doses of 0, 5, 25, or 100 mg/kg, once daily. The substrain of SD rats from Charles River is referred to as SD:Crl. In the 26-week study, SD:Hsd rats were from Envigo (United

Kingdom); in this study, female rats were treated with the oral dose of 0, 10, 25, or 40 mg/kg, BID, and male rats were treated with the oral dose of 0, 25, 60, or 90 mg/kg, BID. In both studies, the treatments were delivered by oral gavage. As further discussed in Section 13, the absence of convulsions in these studies could not be explained by insufficient systemic exposure of the animals to elinzanetant.

It is unclear why convulsions were inconsistently observed across the different studies. It is possible that the differential seizure susceptibility of different SD rat substrains (SD:Crl versus SD:Hsd) and of SD:Hsd rats from different sources (United Kingdom, Netherlands, and the United States) could have accounted for, or contributed to, the discrepant findings from the toxicity studies in SD rats treated with elinzanetant. According to a study published by Langer and collaborators, SD:Crl rats are less susceptible than SD:Hsd rats to developing seizures in response to electrical stimulation of the basolateral amygdala (BLA). In addition, SD:Hsd rats from the Netherlands are less susceptible than SD:Hsd rats from Germany to developing seizures in response to BLA electrical stimulation (Langer et al. 2011).

Biological Plausibility of Elinzanetant-Induced Seizures in Rats

Considering the current knowledge that NK1R/NK3R activation increases neuronal excitability (Stacey et al. 2002; Gallopin et al. 2006), it is unlikely that elinzanetant-induced inhibition of NK1R/NK3R would lead to the development of convulsions.

The Applicant has reported that, at 10µM, the elinzanetant metabolite BAY 3462933 (M30/34) inhibits by ~55% [^{3}H]tert-butylbicycloorthobenzoate ([^{3}H]TBOB) binding to gamma-amino butyric acid type A ($GABA_A$) receptors in Wistar rat brain membrane preparations (Study R-14018). $GABA_A$ receptor antagonists (e.g., picrotoxin and bicuculline) are well known for their proconvulsant effects (Sigel and Steinmann 2012). Considering that, in female rats treated with the elinzanetant dose of 60 mg/kg/day, C_{max} and $AUC_{(0-24)}$ of BAY 3462933 (M30/34) were 2.09µM and 46.8µM•h, respectively, on treatment Day 358, BAY 3462933 (M30/34)-induced inhibition of $GABA_A$ receptors may contribute to the proconvulsant effects of elinzanetant in rats.

Additionally, BAY 3462933 (M30/34) inhibits [^{3}H]progesterone binding to PR-B with an inhibition constant of 0.96µM. Two other metabolites of elinzanetant – BAY 3462932 (M27) and BAY 346934 (M18/21) – also inhibit PR-B with Kis of 1.08µM and 1.35µM, respectively. According to binding studies, interactions of elinzanetant with PR-B are equivocal (see Secondary Pharmacology above). However, in one study, elinzanetant inhibited binding of [^{3}H]progesterone to PR-B ectopically expressed in insect Sf9 cells with an IC_{50} of 0.64µM. PR-B inhibition by the elinzanetant metabolites (and, possibly, elinzanetant itself) may contribute to the proconvulsant properties of elinzanetant because PR antagonists and null mutations of the genes that encode PR-A and PR-B reportedly suppress the anticonvulsant effects of progesterone (Lonsdale et al. 2006; Shiono et al. 2021).

Summary and Conclusion

Based on the totality of evidence, the CNS-related findings in the rat were determined to be related to elinzanetant treatment. The mechanism of the CNS-related findings in elinzanetant-treated rats has not been determined; however, as discussed above, PR-B inhibition by the elinzanetant metabolites (and, possibly, elinzanetant itself) and $GABA_A$ receptor inhibition by the metabolite BAY 3462933 could contribute to the convulsions observed in elinzanetant-treated rats. These finding were discussed with internal neurotoxicology experts, and it was determined that additional nonclinical studies were not needed at the time of this review to better define safety margins for this safety signal. For details refer to nonclinical review in DARRTS (DARRTS°ID:°5623053 2025).

Skeletal Muscle Degeneration

In the 13-week repeat-dose toxicity study (Study R-13628 [RH17GJ]) conducted in SD:Hsd rats (Envigo, Netherlands), male rats (11/11) and female rats (3/10) that died prematurely following treatment with the highest test doses of elinzanetant (300 mg/kg/day and 100 mg/kg/day, respectively) presented with moderate to severe degeneration and necrosis of the skeletal muscles in the leg, tongue, and/or larynx (Table 26). Muscle degeneration/necrosis was not noted in elinzanetant-treated rats that presented with convulsions.

Table 26. Incidence of Skeletal Muscle Degeneration in Male and Female Rats Euthanized Due to Overt Toxicity Induced by the Highest Test Doses of Elinzanetant

	Number of Affected Rats/Total Number of Rats	
Findings	**Male Rats (300 mg/kg/day)**	**Female Rats (100 mg/kg/day)**
Skeletal muscle Degeneration/myofiber	11/11	3/6
Larynx Degeneration/necrosis, muscle	9/11	1/6
Tongue Degeneration/necrosis, myofiber	11/11	1/6

Source: Reviewer-generated table using data from study report R-13628 [RH17GJ]

Skeletal muscle degeneration/necrosis correlated with increased transaminases, lactate dehydrogenase, and creatine kinase and was considered the primary cause of death or early termination of rats treated with the highest test doses of elinzanetant. Three additional female rats died prematurely following treatment with the highest test dose (100 mg/kg/day); however, the cause of death was undetermined for these three female rats, which presented no remarkable histopathological findings. As a note, rats with the skeletal muscle degeneration findings were different from the rats that had CNS-related findings (as described above).

The finding of skeletal muscle degeneration was not observed in other repeat-dose toxicity studies conducted in rats and other animal species. In addition, the finding was not reproduced in a separate study that the Applicant designed and conducted specifically to investigate the mechanistic basis of the finding.

Summary and Conclusion

Biological plausibility of elinzanetant to cause skeletal muscle degeneration/necrosis is unclear. A mechanistic study that was conducted in male rats (Study R-13644) to mimic the effects recorded in the 13-week repeat-dose toxicity study (Study R-13628 [RH17GJ]) failed to reproduce the severe skeletal muscle degeneration. The most conservative multiple of exposure for this finding derived from the 13-week repeat-dose study at 100 mg/kg/day in female rats is 16X the human therapeutic exposure on an area under the concentration-time curve (AUC) basis. The clinical relevance of this skeletal muscle finding is unknown.

Genotoxicity and Carcinogenicity

In vitro and in vivo genotoxicity studies with elinzanetant and its three main metabolites (M27, M30/34, and M18/21) showed negative results.

There were no neoplastic findings in the 26-week transgenic mice study (Study B003184).

Positive carcinogenicity findings were present in the 2-year rat study (Study B003186). Female rats were treated orally with elinzanetant doses ranging from 7 to 80 mg/kg/day compared to vehicle for 104 weeks. Elinzanetant dose dependently reduced body weight gain (body weights were 9%, 9%,17%, and 19% lower at 7, 20, 60, 80 mg/kg/day, respectively, compared to control at terminal sacrifice), but had no effect on overall survival. Elinzanetant treatment resulted in neoplastic findings in the uterus and the hematolymphoid system as described in Table 27 below along with safety margins based on clinical exposure.

There were no neoplastic findings in the 26-week transgenic mice study (Study B003184).

Table 27. Summary of Neoplastic Findings in Rat and Transgenic Mouse Studies

Study	Carcinogenic Effects of Elinzanetant	NOAEL/ NOEL	Safety Margin[a]
Rat – 2 years (B003186) @ 7, 20, 60, 80 mg/kg/day in F	Statistically significant increases in the incidence of: • Malignant lymphoma in the hematolymphoid system @ 80 mg/kg/day. • Malignant adenocarcinoma of the uterus @ ≥60 mg/kg/day. • Combined malignant and benign endometrial tumors @ ≥60 mg/kg/day. • Combined malignant and benign endometrial tumors and malignant squamous cell carcinoma of the uterus @ ≥60 mg/kg/day.	NOAEL: 20 mg/kg/day (females)	7.5X

Study	Carcinogenic Effects of Elinzanetant	NOAEL/ NOEL	Safety Margin[a]
Transgenic mouse – 6 months (B003184) @ 10, 30, 85 mg/kg/day in M @ 10, 20, 70 mg/kg/day in F	• No neoplastic findings	NOEL: 70 mg/kg/day (females) 85 mg/kg/day (males)	N/A

Source: Reviewer-generated table
[a]Safety margins are ratios of the $AUC_{(0-24)}$ at the NOAEL or NOEL to the clinical $AUC_{(0-24)}$ of 8572 ng•h/mL for the MRHD of elinzanetant (120 mg/day) obtained from clinical study B002427. Safety margins based on $AUC_{(0-24)}$ are not calculated for transgenic mice.
Abbreviations: F, female; M, male; NOAEL, no observed adverse effect level; NOEL, no observed effect level; N/A, not applicable

Biological Plausibility of Elinzanetant-Induced Endometrial Carcinomas in Rats

The main metabolites of elinzanetant – BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 346934 (M18/21) – inhibit [^{3}H]progesterone binding to PR-B with Kis of 1.08µM, 0.96µM, and 1.35µM, respectively. Considering that C_{max} and $AUC_{(0-24)}$ of BAY 3462933 (M30/34) were 2.09µM and 46.8µM•h, respectively, in female rats treated with the elinzanetant dose of 60 mg/kg/day, it is possible that inhibition of PR-B by BAY 3462933 (M30/34) contributes to the increased incidence of endometrial cancers in rats treated with elinzanetant doses ≥60 mg/kg/day.

As mentioned in the subsections "Secondary Pharmacology" and "CNS-related signals" above, elinzanetant produced equivocal signals in binding studies assessing its interactions with PRs. In one study, elinzanetant inhibited [^{3}H]progesterone binding to PR-B in a concentration dependent manner, with an IC_{50} of ~0.64µM. It is, therefore, plausible that inhibition of PR-B by the parent drug may also contribute to the increased incidence of endometrial cancers in elinzanetant-treated rats.

The primary mechanism of action of elinzanetant as an NK1R/NK3R antagonist may also be an important factor contributing to its carcinogenic potential, particularly if treatment spans ages when sex hormones are regularly cycling as it did in the 2-year carcinogenicity in female rats. In this study, twice daily treatment of female rats with elinzanetant started at adolescence (~2 months of age) and continued through adulthood and reproductive senescence.

NK1R/NK3R inhibition in the hypothalamus can reduce the activity of KNDy neurons, which, in turn, can reduce activity of GnRH-releasing neurons and, thereby, contribute to suppression of the activity of the hypothalamic-pituitary-gonadal (HPG) axis. Findings consistent with suppression of the HPG axis were reported in healthy premenopausal women treated with elinzanetant in a randomized, single-blinded, placebo-controlled clinical study (Pawsey et al. 2021). According to this clinical study, oral treatment of premenopausal women with elinzanetant (40, 80, or 120 mg) dose dependently reduced serum levels of luteinizing hormone and induced a hormonal imbalance with relative estrogen dominance. While levels of estradiol were reduced by the elinzanetant treatment, they remained within the therapeutic window of 30

to 50 pg/mL thought to be important to minimize vasomotor symptoms and bone loss. However, levels of progesterone were sufficiently reduced to increase the duration of the luteal phase of the cycle and prolong bleeding during the menstrual cycle (Pawsey et al. 2021).

Considering the findings of the clinical study by Pawsey et al., it is plausible that, in the 2-year carcinogenicity study, the life-long elinzanetant treatment covering ages when sex hormones were regularly cycling in the female rats caused a hormonal imbalance with relative estrogen dominance. This could, in turn, have contributed to a reduction of the potential protective effect of progesterone against development of endometrial adenocarcinomas in the rats.

Summary and Conclusion

In the 2-year carcinogenicity study in female rats, the highest noncarcinogenic dose of elinzanetant was 20 mg/kg/day (7.5X the human therapeutic exposure on an AUC basis) and the lowest dose found to be carcinogenic was 60 mg/kg/day (~29X the human therapeutic exposure on an AUC basis). The neoplastic findings were observed in the uterus and the hematolymphoid system of the female rat.

Phototoxicity

Elinzanetant has several characteristics that, per the FDA guidance for industry *S10 Photosafety Evaluation of Pharmaceuticals* (January 2015), make it a potential phototoxicant. The following nonclinical studies are documented in the nonclinical review in DARRTS (DARRTS°ID:°5623053 2025) and in Section 13.2 of this review.

- Elinzanetant absorbs photons in the UV spectrum (290 to 700 nm).
  - One peak was detected at 321.4 nm with a calculated molar extinction coefficient of 3762.3 $L \cdot mol^{-1}$, which exceeds the threshold of 1000 $L \cdot mol^{-1}$ for phototoxicity (Study R-13578).
- Elinzanetant distributes to and accumulates in melanin-rich tissues (Study R-13624; Study R-14368).
- Elinzanetant is cytotoxic in the in vitro Balb/c 3T3 neutral red uptake phototoxicity assay, with an IC_{50} of 0.845 µg/mL in presence of UV-A (Study R-13578).

Summary and Conclusion

Based on the in vitro phototoxicity assay, the most conservative multiple of exposure (MOE) for phototoxicity was approximately 7-fold. The MOE should be interpreted with caution because elinzanetant concentrations in human pigmented tissues are derived based on the distribution of elinzanetant to rat pigmented tissues (eyes and skin) and no additional in vivo animal photosensitivity studies have been conducted.

GI-Related Signals

GI-related signals were noted with elinzanetant treatment in repeat-dose toxicity studies in rats and monkeys.

In rats treated orally with elinzanetant for 7 days (Study R-13586), histopathological findings of mucosa degeneration along with regeneration of the gastric mucosa, isthmus regenerative hypertrophy, and/or hyperplasia of the isthmus epithelium were observed at 300 mg/kg/day in both male and female rats. Minimal multifocal degeneration/regeneration was also noted at 100 mg/kg/day in female rats. In a 13-week repeat-dose toxicity study with 4-week recovery (Study R-13628), rats with decreased food consumption died prematurely (three males at 300 mg/kg/day and two females at 100 mg/kg/day) and had alterations in the large intestine consisting of distended colon or cecum and/or hard content in the colon.

In monkeys, GI-related adverse effects consisted of findings of loose feces, decrease food consumption, and excessive salivation starting at 60 mg/kg/day (10-fold the human therapeutic exposure on an AUC basis) in a 7-day oral repeat dose study (Study R-13627). Ulceration in the pyloric region of the stomach was seen in females at 100 mg/kg/day (2.4-fold the human therapeutic exposure on an AUC basis). In a 4-week oral repeat-dose toxicity study (Study R-13639), 2 monkeys (one male and one female) that were prematurely sacrificed treated with 60 mg/kg/day (4-fold the human therapeutic exposure on an AUC basis) had abnormal fecal consistency (loose/watery) and reduction in food intake along with histopathological findings of hemorrhage in the adventitia and in mucosa of multiple regions in the GI tract.

Similar findings were noted in the 13-week studies (Study R-13629 and Study R-13612) and the 39-week study (Study R-13895), with abnormal feces (liquid/soft) and/or diarrhea observed in many animals across all dose groups (highest dose tested was 80 mg/kg/day) at various points throughout the study. In the 13-week study, monkeys treated with once daily oral elinzanetant doses ≥20 mg/kg/day (≥0.5-fold the human therapeutic exposure on an AUC basis) presented with increased incidence of thin appearance and dehydration; these findings are indicative of GI disturbances. In the 13-week study, monkeys treated with twice daily oral elinzanetant doses ≥30 mg/kg/day (≥0.2-fold the human therapeutic exposure on an AUC basis) presented with diarrhea and doses ≥80 mg/kg/day (≥2.3-fold the human therapeutic exposure on an AUC basis) presented with thin appearance. In the 39-week study, two female monkeys treated twice daily with oral doses ≥60 mg/kg/day (2-fold the human therapeutic exposure on an AUC basis) and male monkeys treated twice daily oral administration at ≥30 mg/kg/day (0.7-fold the human therapeutic exposure on an AUC basis) had diarrhea that led to dehydration, weight loss, and general ill-health.

Summary and Conclusion

The multiples of exposure for the GI effects in monkey is low, with observed findings starting at the oral elinzanetant doses equivalent to 0.2-fold the human therapeutic exposure at the maximum recommended human dose (MRHD).

Reproductive and Developmental Toxicity

In reproductive and developmental toxicity studies, elinzanetant administration prior to or during pregnancy caused fetal harm in rats in the form of pre- and postimplantation loss, reduced litter size or total litter loss, decrease in fetal body weight, and decrease in neonatal pup viability. A summary of relevant findings is provided below; for additional details refer to Section 8.4 and Section 13 of this review. In a fertility and early embryonic development study in rats, there was

an increase in the percentage of pre- and postimplantation embryo loss and decrease in fetal body weights at 14-fold the human therapeutic exposure when rat dams were treated orally prior to mating and through the early embryonic period.

In a pre- and postnatal developmental study in rats, a higher incidence of still born pups, an increase in total litter loss, a decrease in pup viability between postnatal Days 0 and 4, and an increase in the number of neonatal pups without milk in the stomach were observed in the mid- and high-dose groups, with maternal systemic exposures that were within the range of human therapeutic exposure. Decreased maternal care was also a clinical observation in these treatment groups. Whether the neonatal effects were due to decreased maternal care or other potential elinzanetant-related effects on the offspring could not be definitively concluded from this study.

In an embryofetal development study in rabbits, maternal toxicity was noted in the form of marked body weight loss and decreased food consumption at systemic exposures that were within the range of human therapeutic exposure.

No teratogenicity was observed in the reproductive and developmental studies with elinzanetant in rats or rabbits.

Biological Plausibility of Pregnancy Loss and Stillbirths in Elinzanetant-Treated Rats

The pregnancy losses and stillbirths noted in rats exposed to elinzanetant during gestation may be related, at least in part, to NK1R/NK3R inhibition. As discussed in an earlier section, NK1R/NK3R inhibition can reduce the activity of GnRH-releasing neurons in the hypothalamus and, consequently, suppress the HPG axis. It is plausible that suppression of the HPG axis leads to an imbalance of the sex hormones needed to sustain pregnancy. In fact, drugs that act as GnRH receptor inhibitors (e.g., relugolix) are known to cause pregnancy loss and stillbirth in rats (Sumitomo°Pharma 2021).

Summary and Conclusion

Based on findings from animal reproduction studies, elinzanetant may cause pregnancy loss or stillbirth when administered during pregnancy. Fetal malformations were not observed in these animal studies.

Potential for Liver Toxicity

In the pivotal chronic toxicity studies conducted by the Applicant, including a 26-week study in SD rats (Study R-13894) and a 39-week study in monkeys (Study R-13895), elinzanetant increased levels of the liver-associated enzymes ALT, AST, and ALP. Specifically, in male rats treated orally with the dose of 180 mg/kg/day (90 mg/kg, BID), ALT increased by ~2 fold, and in female rats treated orally with ≥50 mg/kg/day (≥25 mg/kg, BID), AST increased by ~2 fold. In male and female monkeys treated orally with the dose of 40 and 30 mg/kg, BID, respectively, ALT increased by ~1.8 fold (male monkeys) to ~3.6 fold (female monkeys). In these studies, the increased enzyme activity was not associated with histopathological findings that are typically indicative of adverse liver tissue damage.

Liver damage was reported in nonpivotal short-term studies in rats and monkeys. Specifically, following a 7-day oral treatment with elinzanetant tosylate doses of 100 and 300 mg/kg/day, SD rats presented with hepatocellular necrosis and lobular hepatocellular hypertrophy (Study 13586). In addition, following a 4-day oral treatment with the elinzanetant dose of 300 mg/kg/day, monkeys (n=2; one male and one female) presented with hepatocellular vacuolation and/or single-cell necrosis (Study 13580).

The discrepancy in the liver-associated histopathology findings between the chronic and short-term studies is unclear. However, upregulation of certain cytochrome P450 (CYP) enzymes is thought to contribute to drug-induced liver injury (Jaeschke et al. 2002) and the Applicant reports that elinzanetant and its metabolites can cause concentration-dependent CYP induction. Thus, the initial injury that develops following short-term treatment with elinzanetant could result at least in part from upregulation of CYPs and could be subsequently resolved by adaptative responses. In this context, hepatic adaptation to an initial drug-induced liver injury has been reported with other drugs (Eakins et al. 2015).

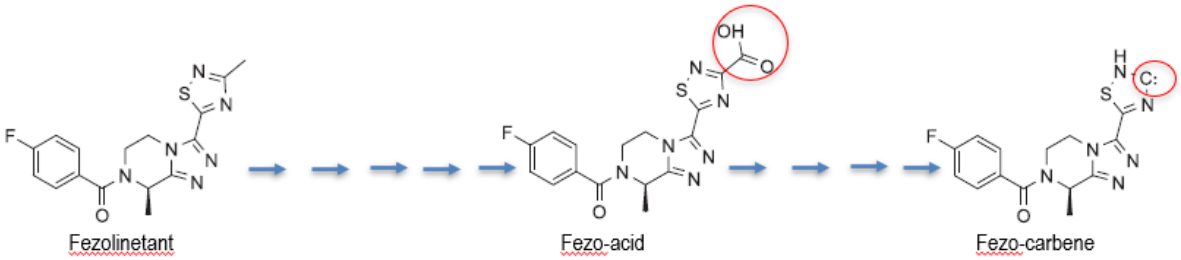
Following a consult request from the OND/Drug-Induced Liver Injury (DILI) Team, the Center for Drug Evaluation and Research (CDER) Computational Toxicology Consultation Service (CTCS) team conducted a quantitative structure-activity relationship [(Q)SAR] analysis to assess whether the chemical structure of elinzanetant has structural features that could predict its hepatotoxic potential. The team concluded that, based on their (Q)SAR analysis, elinzanetant is predicted to be equivocal for the endpoints of liver damage and cholestasis, negative for liver enzyme abnormalities, and positive for bile duct disorders and gall bladder disorders. Refer to nonclinical review in DARRTS for details and internal memo from the CTCS team appended in the review (DARRTS°ID:°5623053 2025).

Hypothetical Hepatotoxicity Predictions for Elinzanetant Considering Findings From Fezolinetant

Fezolinetant is an NK3R antagonist approved under the brand name Veozah (NDA 216578; approval date: May 12, 2023) for the treatment of moderate to severe VMS due to menopause (see Section 7.2 below). In the preapproval clinical study database, elevations of hepatic enzymes were seen but there were no cases meeting Hy's law criteria or with elevated bilirubin levels. The approved fezolinetant labeling thus included a warning for its potential to elevate liver enzymes, and FDA recommended monitoring and follow-up of hepatic function and injury in patients taking fezolinetant. After receiving postmarketing reports of serious hepatotoxicity in patients taking fezolinetant, FDA revised labeling in 2024 to add a Boxed Warning for serious hepatotoxicity that occurred within 40 days of starting treatment and recommended monthly testing of hepatic function for the first three months of treatment and additional follow up testing at 6 and 9 months after initiation of treatment.

In February 2025, Nuthi et al. published an article reporting that a reactive carbene metabolite could contribute to the hepatotoxicity of fezolinetant. The authors hypothesized that the high electrophilicity of a carbene metabolite that can be generated from the fezolinetant metabolite referred to as fezo-acid, as illustrated in Figure 9, is likely to favor the carbene reaction with thiol groups in the liver to produce thiol adducts that can be hepatotoxic (Nuthi et al. 2025).

Figure 9. Generation of the Fezo-Carbene Metabolite by Decarboxylation of the Fezolinetant Metabolite Fezo-Acid

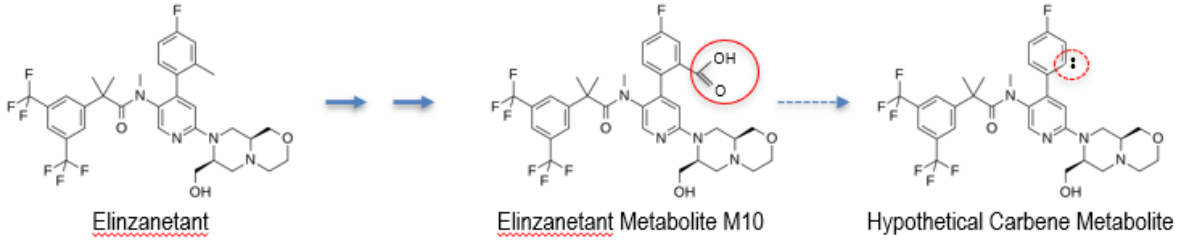


Source: Reviewer-generated figure based on Nuthi et al. (2025)
The red circles highlight the carboxylic acid group in the fezo-acid structure and the neutral carbon atom with a valence of two and two unshared valence electrons in the fezo-carbene structure.

The Nonclinical Team consulted with the CTCS team to determine if the mechanism hypothesized in this paper could help further inform the (Q)SAR assessment to predict the hepatotoxic potential for elinzanetant and its metabolites. The CTCS team's overall conclusion indicated that elinzanetant is unlikely to be converted into a carbene metabolite and is not predicted to have a hepatotoxic potential comparable to that of fezolinetant. The following is a summary of the CTCS assessment:

- The elinzanetant acid metabolite M10 could hypothetically undergo decarboxylation to form a carbene metabolite (Figure 10). However, per Nuthi et al. (2025), in part due to stabilization of charges by resonance, decarboxylation would be more likely for heteroaromatic rings (as the thiadiazole ring that has the -COOH group in fezo-acid) than for a benzene ring (as the ring that has the -COOH group in the elinzanetant metabolite M10). Without empirical evidence, it is difficult to predict whether decarboxylation of the benzene group in the M10 metabolite can happen in vivo.

Figure 10. Hypothetical Carbene Metabolite Generated by Decarboxylation of the Elinzanetant Metabolite M10

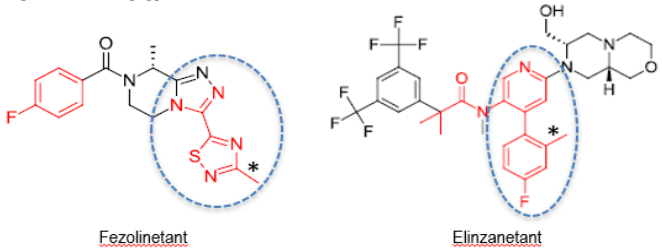


Source: Reviewer-generated figure
The red circles highlight the carboxylic acid group in the elinzanetant M10 metabolite and the neutral carbon atom with a valence of two and two unshared valence electrons in the hypothetical carbene metabolite.

- Both elinzanetant and fezolinetant have bi-aryl structural alerts (Figure 11). However, in part because the dissimilar aromatic ring types between the two compounds cause the alerts to be weighed differently for each molecule, the (Q)SAR models predict elinzanetant to be negative and fezolinetant to be positive for liver enzyme abnormalities.
- The presence of a methyl substituent (that could undergo enzymatic oxidative hydrolysis) in the bi-aryl alert is not a requirement for a bi-aryl substructure to be identified as an alert by

the hepatotox (Q)SAR models. Thus, the possibility of carbene generation is not a requirement for bi-aryl substructures to be identified as structural alerts for hepatotoxicity.

Figure 11. (Q)SAR-Identified Structural Alerts in Fezolinetant and Elinzanetant



Source: figure modified by reviewer from the CTCS consult report issued on December 19, 2024
The blue circles highlight the bi-aryl substructures in the structural alerts (substructures in red font) in fezolinetant and elinzanetant.
The stars mark the methyl groups that could undergo enzymatic oxidative hydrolysis to carboxylic acids.
Abbreviation: (Q)SAR, quantitative structure-activity relationship

- Additional (Q)SAR analysis on M10 or any other metabolites is unlikely to yield additional useful information because the liver tox model training sets are largely populated with drug substances with information from postmarket reporting and do not include many metabolites or impurities.

Summary and Conclusion

There were no histopathological findings indicating hepatotoxicity in the pivotal, long-term repeat-dose toxicity studies in rats and monkeys. The findings of hepatocellular necrosis and lobular hepatocellular hypertrophy, hepatocellular vacuolation, and/or single-cell necrosis seen in short-term toxicity studies at high doses have multiples of exposure of 21X (average of males and females) in rats, 13X in male monkeys, and 2.7X in female monkeys as compared to the human therapeutic exposure on an AUC basis. Considering the comparative (Q)SAR analysis by the CTCS team, the likelihood of generation of a reactive carbene metabolite that can form hepatotoxic thiol adducts is low for elinzanetant compared to fezolinetant due to their dissimilar structures. Therefore, from the nonclinical perspective, the potential for hepatotoxicity with the maximal recommended human dose of elinzanetant appears lower than with fezolinetant.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Elinzanetant is a combined NK3/NK1 receptor antagonist. To date, there are no FDA-approved products with a combined NK3/NK1 receptor antagonism profile. Fezolinetant (Veozah, NDA 216578), an NK3 receptor antagonist only, is approved for the treatment of moderate to severe VMS due to menopause and is known to cause rare but serious hepatotoxicity with a relatively short latency period (within 2 months).

FDA has approved several NK1 related products, e.g., substance P/NK1 receptor antagonists, for the prevention of chemotherapy-induced nausea and vomiting, including aprepitant (proprietary name Emend, NDAs 021549 and 207865), fosaprepitant, Focinvez, and rolapitant (proprietary name Varubi, NDS 206500). Additionally, netupitant/palonosetron (proprietary name Akynzeo, NDA 205718) combines netupitant, a substance P/NK1 receptor antagonist and palonosetron, a

5-HT_3 receptor antagonist, for the same indication. Safety issues noted in the labeling for these drugs include drug-drug interactions arising from the inhibition of CYP3A4/CYP2D6, reduced International Normalized Ratio or prothrombin time when coadministered with warfarin, and reduced efficacy of hormonal contraceptives. For aprepitant, labeling recommends exercising caution when administered in patients with severe hepatic impairment. Because these NK1 receptor antagonists are approved for use in cancer patients who are taking chemotherapy, not all the safety concerns identified with these products may be relevant to the target population for elinzanetant due to different risk-benefit considerations.

Of note, due to concerning findings from nonclinical reproductive toxicity studies (see Section 7.1), use of elinzanetant is contraindicated in pregnancy and effective contraception is recommended in perimenopausal women who may want to take elinzanetant to treat their VMS. Hormonal contraceptives are metabolized by CYP enzymes. Because elinzanetant does not have induction potential for any CYP enzymes, reduced efficacy of hormonal contraceptives is not expected to be an issue in the indicated population.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. During this review, elinzanetant was approved for marketing in several countries, including the United Kingdom and Canada. Given the recent approval, there is no postmarket experience to report.

7.4. FDA Approach to the Safety Review

Section 3.2 provides a description and assessment of the clinical studies and whether the studies submitted were fit for purpose.

The Phase 3 studies OASIS 1, OASIS 2, and OASIS 3 provide primary support for safety of elinzanetant for the treatment of moderate to severe VMS due to menopause. Subjects taking elinzanetant 120 mg/day in the SWITCH-1 study (a dose-finding Phase 2 study) also provided 12 weeks of safety information.

The safety data reviewed includes the final study reports submitted by the Applicant for each OASIS study and their corresponding datasets (Study Data Tabulation Model and Analysis Data Model), the 120-day safety update, the Applicant's responses to information requests, and literature references provided by the Applicant. The primary safety assessment examined adverse events of special interest (AESIs), safety findings from each of the three OASIS studies and overall safety profile from the pooled OASIS 1 and OASIS 2 using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. To assess severity, a 3-point grading scale was used (mild, moderate, severe). The Applicant considered the following AEs to be of special interest: events triggering close liver observation, somnolence or fatigue, phototoxicity, and postmenopausal bleeding. Safety assessments included adverse events, including SAEs, AESIs, AEs related to abuse potential, clinical safety laboratory assessments, including liver monitoring, vital signs, and physical examinations (including weight, hip and waist circumference, and waist to hip ratio). Additional assessments included mammograms, transvaginal ultrasound (TVU),

endometrial biopsy, sleepiness scale, suicidal ideation and behavior measured with eC-SSR, and ECGs. Bone mineral density was measured in OASIS 3. In OASIS 1, 2, and 3, treatment-emergent adverse events (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.

The clinical team reviewed the Applicant's mapping of verbatim terms to MedDRA preferred terms (PTs) for the events reported in the relevant clinical studies and found the Applicant's mapping strategy acceptable. The team also reviewed the definitions of TEAEs and AEs in the relevant clinical studies and found them to be acceptable. The review team assessed the narratives of all SAEs and discontinuations due to adverse events.

The clinical team identified the following key safety review issues: number of deaths, SAEs, adverse events leading to discontinuation, TEAEs, and AESIs including abuse potential, bone safety, hepatic safety, cardiac safety, nervous system disorders (including CNS depression [somnolence/fatigue], vertigo/dizziness, syncope/presyncope/hypotension), fractures, driving ability, breast safety, endometrial safety, seizures, and phototoxicity. The safety data will be presented for the placebo-controlled Weeks 1 to 12 (OASIS 1 and 2) and 1 to 52 (OASIS 3). The data from OASIS 1 and 2 is shown from the individual studies and from the pooled studies for Weeks 1 to 12. It is reasonable to pool these studies as they have a very similar study design. Data from OASIS 1 and 2 from Weeks 13 to 26 (when all subjects took elinzanetant) are not presented in tables given limitations to these analyses as there is no control group during this study period. The narratives of SAEs and discontinuations due to AEs were assessed for OASIS 1 and 2 from Weeks 13 to 26, when all subjects were on elinzanetant. The most robust long-term safety data are from OASIS 3, which was placebo-controlled for 52 weeks. The Applicant also provided an integrated analysis of safety, from studies 21686 (SWITCH-1), and OASIS 1, 2, and 3. The safety analysis set (SAF) was defined as all subjects who receive at least one dose of study drug. Safety data, such as narratives from the entire clinical program, including the Phase 1 and 2 studies, are discussed as relevant to specific safety considerations, such as adverse events of special interest.

When evaluating the individual results of OASIS studies, the rates of adverse events in placebo versus treatment were compared with the number (percentage) of subjects who experienced an AE along with the risk difference or the risk ratio (with 95% CI). The evaluation of pooled data that includes variable duration of exposures to placebo and elinzanetant was carried out through the exposure adjusted incidence rate for statistical analysis of adverse events, calculated diving the number of subjects with event X by the total patient years. For OASIS 3, data are shown for number (percentage) and exposure adjusted incidence rate.

The review team's approach to the data presentation and analysis of the three clinical studies consisted of review of the raw data presented by the Applicant in adsl.xpt and adae.xpt files, and tabulation and statistical analysis of the raw data in collaboration with the FDA Clinical Data Science Analysis Scientific Team. The Clinical Data Science Analysis Scientific Team performed standard safety analyses including OND custom medical queries (OCMQs) to determine safety signals, and additional analyses as requested by the clinical team.

7.5. Adequacy of the Clinical Safety Database

The safety database was adequate for sufficient safety analysis of elinzanetant for the proposed indication of treatment of moderate to severe VMS due to menopause. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review. No major issues were identified with respect to coding of adverse events.

The safety population from clinical studies conducted with daily elinzanetant 120 mg versus placebo for the treatment of moderate to severe VMS due to menopause is presented in Table 28. The total number of subjects that were randomized in Phase 2/3 studies was 1,523, and the safety analysis set (which included subjects who received at least one dose of study drug) was comprised of 1,519 in OASIS 1, 2, and 3 and the SWITCH-1 study.

Table 28. Safety Population for Elinzanetant*, Study Sample Sizes by Study (All Enrolled Subjects) From Clinical Studies, OASIS 1 and OASIS 2 (Pooled), OASIS 3, and SWITCH-1

Study	Treatment Group Total (Week 1-12)	Number of Subjects Randomized	Number of Subjects Validated for Safety
OASIS 1 and 2			
	Total	796	793
	Elinzanetant 120 mg	399	398
	Placebo	397	395
OASIS 3			
	Total	628	627
	Elinzanetant 120 mg	313	312
	Placebo	315	315
SWITCH-1	Total	99	99
	Elinzanetant 120 mg	52	52
	Placebo	47	47
Total			1,519

Source: Compiled by reviewer from safety database from module 5.3.3.1. and 5.3.5.3, reports 13559, PH 42782, 42780, and 42784
*Safety population: women who were randomized and received at least one dose of elinzanetant or placebo.
The number of subjects enrolled is the number of subjects who signed informed consent. For SWITCH-1, those randomized to elinzanetant 40 mg, 80 mg, 160 mg are excluded.

Table 29 shows the total number of subjects randomized to elinzanetant versus placebo that had a treatment duration of 12 weeks.

Table 29. Total Number of Subjects (Week 1 to 12) Randomized to Either Elinzanetant 120 mg or Placebo

Clinical Study Groups, Safety Population**	Elinzanetant 120 mg/d (N=713)	Placebo (N=707)
OASIS 1	199	194
OASIS 2	201	199
OASIS 3	313	314

Source: Compiled by reviewer from safety database from module 5.3.3.1 and 5.3.5.3, reports 13559, PH 42782, 42780, and 42784
**Safety population: women who were randomized and received at least one dose of elinzanetant or placebo
Abbreviation: d, day; N, number of subjects in treatment arm

The safety evaluation for elinzanetant comprises 627 women in the long-term safety and efficacy study OASIS 3 and 1,519 women in the pooled analysis from SWITCH-1, and OASIS 1, 2, and 3. Of the 1,113 women who received elinzanetant 120 mg in any of the four studies, 219 were

treated for at least 50 weeks, 575 were treated for at least 23 weeks and 966 were treated for at least 12 weeks.

Analysis of the overall exposure of elinzanetant showed that the duration of elinzanetant treatment varied across the three studies (14 and 26 weeks in OASIS 1 and 2, and 52 weeks in OASIS 3). In OASIS 1 and OASIS 2 combined, 349 women received placebo for the first 12 weeks, and 348 women switched to elinzanetant 120 mg for the next 14 weeks (as one woman did not continue the study after 12 weeks). In addition, there was a subgroup of subjects from the Phase 2 SWITCH-1 study (dose-finding study) who were randomized to elinzanetant 120 mg/day versus placebo (12 weeks). Thus, total exposure of women who received at least one dose of elinzanetant 120 mg daily was 1,113 across the Phase 2/3 studies (SWITCH-1 and OASIS 1, 2, and 3) (Table 30 and Table 31).

Table 30. Variation of the Overall Exposure of Elinzanetant Treatment Across the Clinical Studies

Parameter	N	Elinzanetant (120 mg/d)	Placebo
Duration of exposure to elinzanetant 120 mg/d			
At least 12 weeks	996		
At least 23 weeks	575		
At least 50 weeks	219		
Group			
Randomized		N=764	N=759
Safety analysis (Week 1-12 group)*		N=765	N=754

Source: compiled by reviewer from safety database from module 5.3.3.1. and 5.3.5.3, reports 13559, PH 42782, 42780, and 42784
*Study drug was never taken by 2 women randomized to elinzanetant 120 mg and 2 women randomized to placebo. 3 women who were planned to start with placebo erroneously received elinzanetant 120 mg.
Abbreviation: d, day; N, number of subjects in treatment arm

Table 31. Overall Exposure Data for Elinzanetant 120 mg

Dosage	≥1 Dose	≥3 Months	≥6 Months	≥12 Months
Total elinzanetant daily dose 120 mg				
Phase 2 and 3 studies	765	757	966	966
Phase 1 studies	632			

Source: compiled by reviewer from safety database Module 5.3.5.3, Integrated analysis of safety

The number of subjects exposed is consistent with the parameters established by International Conference on Harmonization (ICH) *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* guidelines (March 1995). To date, the total exposure to elinzanetant is approximately (b) (4) individuals using any formulation and more than (b) (4) using soft gel capsule formulation (approximately (b) (4) for at least 23 weeks, and approximately (b) (4) for at least 50 weeks). The reviewers conclude that the studies submitted in support of application are fit for purpose. The safety database and exposure for the to-be-marketed product elinzanetant are acceptable and the population represents the expected target population.

OASIS 1 and 2

Exposure

Duration of exposure for the safety populations is shown in Table 32. Both studies were performed for treatment of vasomotor symptoms over 26 weeks in postmenopausal women. In OASIS 1, the mean duration of treatment was 22.6 weeks, and the total exposure tabulated was 86 person-years for the elinzanetant group, whereas placebo counterparts had a mean duration of 22.6 weeks and 84 person-years of exposure. In OASIS 2, the mean duration of treatment was 22.4 weeks, and total exposure was 86 person-years for the elinzanetant group, whereas placebo counterparts were mean of 23.1 weeks and 88 person-years. A majority of subjects were exposed between ≥24 and <30 weeks (80.8% and 83.7%, respectively for elinzanetant and placebo groups (pooled data), respectively).

Table 32. Duration of Exposure, Safety Population, OASIS 1 and OASIS 2

	OASIS 1		OASIS 2		Pooled	
Parameter	**Elinzanetant 120 mg (N=199)**	**Placebo (N=194)**	**Elinzanetant 120 mg (N=201)**	**Placebo (N=199)**	**Elinzanetant 120 mg (N=400)**	**Placebo (N=393)**
Duration of treatment, weeks						
Mean (SD)	22.6 (6.6)	22.6 (7.2)	22.4 (7.4)	23.1 (6.5)	22.5 (7)	22.8 (6.8)
Median (Q1, Q3)	25.1 (25, 25.7)	25.3 (25, 25.9)	25.1 (25, 25.9)	25.3 (25, 25.9)	25.1 (25, 25.9)	25.3 (25, 25.9)
Min, max	0.6, 28	0.4, 29	0.3, 34	0.1, 29.3	0.3, 34	0.1, 29.3
Total exposure (person-years)	86	84	86	88	172	172
Subjects treated, by duration, n (%)						
<4 weeks	7 (3.5)	9 (4.6)	12 (6.0)	8 (4.0)	19 (4.8)	17 (4.3)
≥4 to <8 weeks	7 (3.5)	11 (5.7)	9 (4.5)	8 (4.0)	16 (4.0)	19 (4.8)
≥8 to <12 weeks	9 (4.5)	4 (2.1)	4 (2.0)	2 (1.0)	13 (3.2)	6 (1.5)
≥12 to <18 weeks	11 (5.5)	7 (3.6)	9 (4.5)	8 (4.0)	20 (5.0)	15 (3.8)
≥18 to <24 weeks	5 (2.5)	2 (1.0)	3 (1.5)	5 (2.5)	8 (2.0)	7 (1.8)
≥24 to <30 weeks	160 (80.4)	161 (83.0)	163 (81.1)	168 (84.4)	323 (80.8)	329 (83.7)
≥30 to <36 weeks	0	0	1 (0.5)	0	1 (0.2)	0
≥36 weeks	0	0	0	0	0	0

Source: adex.xpt and adsl.xpt; Software: R
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Demographic and Baseline Clinical Characteristics

For the demographics and baseline clinical characteristics of subjects in OASIS 1 and 2, please refer to Section 6.2.5.2.

OASIS 3

Exposure

The duration of exposure for the safety population is shown in Table 33. The mean (SD) duration of treatment was 41.2 (17.8) weeks and total exposure tabulated as person year was 247 for the elinzanetant group, whereas placebo counterparts were mean of 41.8 (16.8) weeks and 252 person-years exposure. The majority of subjects were exposed between >36 and <52 weeks (66.1% and 67.8, respectively for the elinzanetant and placebo groups).

Table 33. Duration of Exposure, Safety Population, OASIS 3

Parameter	Elinzanetant 120 mg (N=313)	Placebo (N=314)
Duration of treatment, weeks		
Mean (SD)	41.2 (17.8)	41.8 (16.8)
Median (Q1, Q3)	50.4 (42.4, 51.3)	50.6 (42.5, 51.1)
Min, max	0.1, 54.1	0.1, 54.9
Total exposure (person-years)	247	252
Subjects treated, by duration, n (%)		
<4 weeks	21 (6.7)	16 (5.1)
≥4 to <8 weeks	17 (5.4)	15 (4.8)
≥8 to <12 weeks	11 (3.5)	5 (1.6)
≥12 to <18 weeks	13 (4.2)	17 (5.4)
≥18 to <24 weeks	3 (1.0)	10 (3.2)
≥24 to <36 weeks	9 (2.9)	11 (3.5)
≥36 to <52 weeks	207 (66.1)	213 (67.8)
≥52 to <56 weeks	32 (10.2)	27 (8.6)
≥56 weeks	0	0

Source: adex.xpt and adsl.xpt; Software: R
Duration is 52 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Demographic and Baseline Clinical Characteristics

The baseline demographic and clinical attributes of the safety population of clinical study OASIS 3 are shown in Table 34. There were noted similarities in mean age of subjects, age groups. race, ethnicity, and country of participation in the study and control groups (elinzanetant and placebo). In OASIS 3, the treatment arms were well-balanced with regards to demographics and other baseline characteristics, with no relevant differences in age, ethnicity, race, weight, height, or BMI. Most women in the safety analysis set were White (77%) or Black or African American (16.0%) and 11.2% of the women were Hispanic or Latino by ethnicity. The overall mean (SD) age was 54.6 (4.6) years and 54.9 (5), for the elinzanetant and placebo groups (respectively) and the overall mean (SD) BMI was 27.59 (4.68) kg/m^2. The majority of women never smoked. The most frequent medical history findings were obesity (28.5%), hypertension (28.7%), and hysterectomy (22.5%).

Table 34. Baseline Demographic and Clinical Characteristics, Safety Population, OASIS 3

Characteristic	Elinzanetant 120 mg (N=313)	Placebo (N=314)
Sex, n (%)		
Female	313 (100)	314 (100)
Age, years		
Mean (SD)	54.6 (4.6)	54.9 (5)
Median (min, max)	54 (43, 65)	55 (41, 65)
Age group, years, n (%)		
40 to 49	46 (14.7)	43 (13.7)
50 to 59	211 (67.4)	212 (67.5)
60 to 65	56 (17.9)	59 (18.8)
Race, n (%)		
Asian	2 (0.6)	2 (0.6)
Black or African American	50 (16.0)	44 (14.0)
Multiple	0	1 (0.3)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0
Not reported	19 (6.1)	15 (4.8)
White	241 (77.0)	252 (80.3)
Ethnicity, n (%)		
Hispanic or Latino	35 (11.2)	33 (10.5)
Not Hispanic or Latino	265 (84.7)	273 (86.9)
Not reported	13 (4.2)	8 (2.5)
Country of participation, n (%)		
Bulgaria	38 (12.1)	32 (10.2)
Poland	36 (11.5)	55 (17.5)
United States	115 (36.7)	129 (41.1)
Others	124 (39.6)	98 (31.2)
Is in United States, n (%)		
United States	115 (36.7)	129 (41.1)
Not United States	198 (63.3)	185 (58.9)

Source: adsl.xpt; Software: R
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Screening and Enrollment

Out of 1,524 screened subjects there were 896 screening failures, resulting in 628 randomized subjects (Table 35). Subjects were randomized to elinzanetant 120 mg/d (n=313) or placebo (n=315). The safety population consisted of 313 and 314 subjects in the elinzanetant and placebo groups, respectively, with 453 individuals completing the study.

Table 35. Subject Screening and Enrollment, OASIS 3

Disposition	OASIS 3
Subjects screened	1524
Screening failures	896
Subjects randomized	628

Source: ds.xpt and Clinical Study Report; Software: R

Disposition

The disposition of subjects in OASIS 3 is highlighted in Table 36. The analysis of the safety population shows that the overall percentage of discontinuation was balanced between the elinzanetant (16%) and placebo (16.8%) arms. The percentage of discontinuation due to adverse events was higher in the elinzanetant group (5.4%) versus the placebo group (0.6%).

Table 36. Subject Disposition, OASIS 3

Disposition Outcome	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=315) n (%)
Subjects randomized	313	315
Safety population	313	314
Discontinued in overall study	50 (16.0)	53 (16.8)
Adverse event	17 (5.4)	2 (0.6)
Lack of efficacy	0	6 (1.9)
Lost to follow-up	5 (1.6)	2 (0.6)
Noncompliance with study drug	2 (0.6)	3 (1.0)
Other	4 (1.3)	3 (1.0)
Physician decision	1 (0.3)	4 (1.3)
Protocol deviation	0	2 (0.6)
Randomized by mistake	0	2 (0.6)
Subject decision	21 (6.7)	28 (8.9)
Technical problems	0	1 (0.3)

Source: adsl.xpt; Software: R
Duration is 52 weeks.
Safety population consists of subjects who received at least one actual dose of the study drug intervention during the study.
Abbreviations: n, number of subjects in specified population or group; N, number of subjects in treatment arm; NA, not applicable

7.6. Safety Results

7.6.1. Safety Results, OASIS 1 and OASIS 2 (Weeks 1 to 12)

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, OASIS 1 and OASIS 2 (Weeks 1 to 12)

The total number and percentages of AEs for the safety population for OASIS 1 and OASIS 2, and pooled data from OASIS 1 and OASIS 2, for Weeks 1 to 12 are presented in Table 37.

In the pooled data, there was a higher percentage of subjects on elinzanetant (1.2%) than placebo (0.8%) with SAEs. Similar trends were seen for AEs leading to discontinuation and AEs leading to dose modification. The percentage of subjects with any AE was similar in the elinzanetant (47.8%) and placebo (43.3%) arms. AEs were mainly mild or moderate.

Table 37. Overview of Adverse Events, Safety Population, OASIS 1 and OASIS 2 (Week 1 to 12)

	OASIS 1		OASIS 2		Pooled		
Event Category	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)	Risk Difference % (95% CI)
SAE	4 (2.0)	2 (1.0)	1 (0.5)	1 (0.5)	5 (1.2)	3 (0.8)	0.5 (-1.1, 2.2)
SAEs with fatal outcome	0	0	0	0	0	0	0.0 (-1.0, 1.0)
Life-threatening SAEs	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
SAEs requiring hospitalization	2 (1.0)	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.8)	2 (0.5)	0.2 (-1.2, 1.7)
SAEs resulting in substantial disruption of normal life functions	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Other	2 (1.0)	1 (0.5)	0	0	2 (0.5)	1 (0.3)	0.2 (-1.0, 1.6)
AE leading to permanent discontinuation of study drug	17 (8.5)	13 (6.7)	13 (6.5)	4 (2.0)	30 (7.5)	17 (4.3)	3.2 (-0.1, 6.6)
AE leading to dose modification of study drug	6 (3.0)	4 (2.1)	10 (5.0)	2 (1.0)	16 (4.0)	6 (1.5)	2.5 (0.2, 5.0)*
AE leading to interruption of study drug	6 (3.0)	4 (2.1)	10 (5.0)	2 (1.0)	16 (4.0)	6 (1.5)	2.5 (0.2, 5.0)*
AE leading to reduction of study drug	0	0	0	0	0	0	0.0 (-1.0, 1.0)
AE leading to dose delay of study drug	0	0	0	0	0	0	0.0 (-1.0, 1.0)
Any AE	102 (51.3)	94 (48.5)	89 (44.3)	76 (38.2)	191 (47.8)	170 (43.3)	4.5 (-2.4, 11.4)
Severe and worse	6 (3.0)	8 (4.1)	7 (3.5)	5 (2.5)	13 (3.2)	13 (3.3)	-0.1 (-2.7, 2.6)
Moderate	28 (14.1)	34 (17.5)	39 (19.4)	26 (13.1)	67 (16.8)	60 (15.3)	1.5 (-3.7, 6.6)
Mild	68 (34.2)	52 (26.8)	43 (21.4)	45 (22.6)	111 (27.8)	97 (24.7)	3.1 (-3.1, 9.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, OASIS 1 and 2 (Weeks 1 to 12)

There were no deaths in OASIS 1 or OASIS 2.

7.6.1.3. Serious Adverse Events, OASIS 1 and 2 (Weeks 1 to 12)

Subjects with SAEs during Weeks 1 to 12 in OASIS 1 and OASIS 2 (and pooled data), are shown in Table 38. In OASIS 1 and the pooled analyses, the percentage of subjects with SAEs was slightly higher in the elinzanetant groups versus the placebo groups. In OASIS 2, the percentage of subjects with SAEs was the same in the elinzanetant and placebo groups (0.5%). The SAEs were spread over various system organ classes, without a clear pattern. Analyses by OND custom medical query (OCMQ) (narrow) (Table 39) were similar to the analysis by PT and did not reveal any other safety concerns.

Table 38. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled		
System Organ Class Preferred Term	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)	Risk Difference % (95% CI)
Any SAE	4 (2.0)	2 (1.0)	1 (0.5)	1 (0.5)	5 (1.2)	3 (0.8)	0.5 (-1.1, 2.2)
Hepatobiliary disorders (SOC)	0	2 (1.0)	0	0	0	2 (0.5)	-0.5 (-1.8, 0.4)
Cholecystitis acute	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Cholelithiasis	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Infections and infestations (SOC)	2 (1.0)	0	0	1 (0.5)	2 (0.5)	1 (0.3)	0.2 (-1.0, 1.6)
Diverticulitis	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Pneumonia	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Pyelonephritis	0	0	0	1 (0.5)	0	1 (0.3)	-0.3 (-1.4, 0.7)
Urosepsis	0	0	0	1 (0.5)	0	1 (0.3)	-0.3 (-1.4, 0.7)
Nervous system disorders (SOC)	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Syncope	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.5)	0	1 (0.5)	0	2 (0.5)	0	0.5 (-0.5, 1.8)
Pulmonary embolism	1 (0.5)	0	1 (0.5)	0	2 (0.5)	0	0.5 (-0.5, 1.8)
Surgical and medical procedures (SOC)	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Arthrodesis	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Vascular disorders (SOC)	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Deep vein thrombosis	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily. in both treatment groups receive elinzanetant 120 mg once daily.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

Table 39. Subjects With Serious Adverse Events by System Organ Class and OCMQ (Narrow), Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled		
System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)	Risk Difference % (95% CI)
Hepatobiliary disorders (SOC)							
Cholecystitis	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Infections and infestations (SOC)							
Pneumonia	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Bacterial infection	1 (0.5)	1 (0.5)	0	1 (0.5)	1 (0.2)	2 (0.5)	-0.3 (-1.6, 0.9)
Nervous system disorders (SOC)							
Syncope	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Renal and urinary disorders (SOC)							
Renal & urinary tract infection	0	0	0	1 (0.5)	0	1 (0.3)	-0.3 (-1.4, 0.7)
Vascular disorders (SOC)							
Thrombosis	1 (0.5)	0	1 (0.5)	0	2 (0.5)	0	0.5 (-0.5, 1.8)
Thrombosis venous	1 (0.5)	0	1 (0.5)	0	2 (0.5)	0	0.5 (-0.5, 1.8)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OCMQ.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query; PT, preferred term; SOC, system organ class

The following subjects in the elinzanetant arm had SAEs during OASIS 1 and OASIS 2 (including the period after 12 weeks when subjects on placebo switched to elinzanetant (the placebo-elinzanetant arm)). SAEs related to AEs of special interest (including seizure and syncope) are also described in this section. Of the 20 subjects with SAEs, the seizure event was probably related to elinzanetant. For the accident and syncope SAEs, it is unclear if they were related to elinzanetant based on limited information or lack of other factors suggesting causality (such as dechallenge/rechallenge information).

OASIS 1

There were 13 subjects with SAEs while taking elinzanetant:

- 4 subjects randomized to elinzanetant during Weeks 1 to 12 (diverticulitis, pulmonary embolism and pneumonia (same subject), syncope, and arthrodesis)
- 9 subjects in the placebo-elinzanetant arm during Weeks 13 to 26 after switching to elinzanetant (pyelonephritis, cholelithiasis (two subjects), otitis externa, bunion operation, abdominal pain, accident, mammoplasty, and tibia fracture).

In addition, one subject had a post-treatment SAE of adenocarcinoma of the colon about 3 weeks after the last dose of elinzanetant.

Descriptions of the SAEs are included below:

(1) Subject (b) (6) was a 46-year-old woman randomized to the placebo-elinzanetant arm who developed an SAE of pyelonephritis 43 days after starting elinzanetant. The investigator considered this event to be severe in intensity and not related to elinzanetant. The subject was treated with antibiotics and recovered. The review team agrees with the assessment that this SAE does not appear related to elinzanetant.

(2) Subject (b) (6) was a 55-year-old woman who was randomized to the placebo-elinzanetant arm. She developed an SAE of cholelithiasis 66 days after starting elinzanetant. The investigator considered this event to be moderate in intensity and not related to study intervention. The subject was hospitalized, drug was interrupted, and she recovered. The review team agrees with the assessment that this SAE does not appear related to elinzanetant.

(3) Subject (b) (6) was a 52-year-old woman randomized to the placebo-elinzanetant arm. She developed an SAE of cholelithiasis 83 days after starting elinzanetant. She received her last dose of elinzanetant 5 days before the onset of the SAE and was then lost to follow-up and did not complete the study. The investigator considered the event to be severe in intensity and not related to elinzanetant. The review team agrees with this assessment that this SAE does appear related to elinzanetant.

(4) Subject (b) (6) was a 53-year-old woman randomized to elinzanetant who developed an SAE of diverticulitis and an AE leading to discontinuation (term: pain). The SAE occurred 6 days after starting elinzanetant, which the investigator considered to be severe in intensity and not related to study intervention. The drug was interrupted, and the SAE was noted to be recovered/resolved. The AE leading to discontinuation (pain)

developed 55 days after starting elinzanetant. The review team agrees with the assessment that this SAE does not appear related to elinzanetant.

(5) Subject (b) (6) was a 53-year-old woman randomized to the placebo-elinzanetant arm who had an SAE of acute malignant otitis externa 7 days after starting elinzanetant. The investigator considered this event to be severe in intensity and not related to study intervention. The subject received antibiotic treatment, and the study drug was interrupted. The last recorded outcome was recovered/resolved. The review team agrees with the assessment that this SAE does not appear related to elinzanetant.

(6) Subject (b) (6) was a 45-year-old woman randomized to the elinzanetant arm who developed SAEs of pneumonia and pulmonary embolism. The pulmonary embolism also led to discontinuation. The subject reported the SAE of pulmonary embolism 68 days after starting elinzanetant. The investigator considered the SAE severe in intensity and not related to elinzanetant. Then, 72 days after starting elinzanetant, the subject was reported with an SAE of pneumonia. The investigator considered this event to be moderate in intensity and not related to elinzanetant. The review team agrees with the assessment that the SAEs do not appear related to elinzanetant.

(7) Subject (b) (6) was a 49-year-old woman randomized to the placebo-elinzanetant arm who developed an SAE of adenocarcinoma of the colon and an AE leading to discontinuation (term: large intestinal ulcer). The subject was reported with a large intestinal ulcer 85 days after starting elinzanetant, which the investigator considered nonserious. Elinzanetant was withdrawn and she underwent endoscopy and biopsy. Then, 110 days after starting elinzanetant, the subject was reported with adenocarcinoma of the colon, which the investigator considered serious. The event was reported 21 days after withdrawal of the study drug. The investigator considered this event to be severe in intensity and not related to elinzanetant. The review team agrees with the assessment that the SAE does not appear related to elinzanetant.

(8) Subject (b) (6) was a 45-year-old who randomized to the placebo-elinzanetant arm who had an SAE of a bunion operation 84 days after starting elinzanetant. The investigator considered this event to be mild in intensity and not related to elinzanetant. The review team agrees that this SAE does not appear related to elinzanetant.

(9) Subject (b) (6) was a 48-year-old woman randomized to the placebo-elinzanetant arm who developed an SAE of abdominal pain 94 days after starting elinzanetant. The SAE required hospitalization. The investigator considered this event to be moderate in intensity and not related to elinzanetant. The subject had stopped elinzanetant one day prior to the SAE. The investigator thought diet or abdominal adhesions might explain the occurrence of the event. The subject had a history of caesarean section, uterine leiomyoma, and hysterosalpingo-oophorectomy. The review team agrees with the assessment that the SAE does not appear related to elinzanetant.

(10) Subject (b) (6) was a 52-year-old woman randomized to elinzanetant who had an SAE of syncope 5 days after starting elinzanetant. The SAE was considered serious as it was classified as other medically important serious event. The investigator considered this event to be severe in intensity and not related to elinzanetant. The workup included ECG, x-ray, laboratory studies, toxicology screen, and brain CT all of which were normal. Vital sign

measurements were not available from the time of the event but were normal (blood pressure: 129/78; heart rate: 73 bpm) four days prior to the event. The subject discontinued due to this SAE. The subject had an AE of weakness 3 days after starting elinzanetant, but it was considered mild and resolved within a day. The review team notes that the etiology of syncope is unclear. See Section 7.6.3.6 for additional discussion of syncope as an AESI.

(11) Subject (b) (6) was a 49-year-old woman randomized to the placebo-elinzanetant arm who had an SAE of an accident 82 days after starting elinzanetant. The investigator considered this event to be unknown in intensity and not related to study intervention. Additional details on the case could not be obtained. The review team assessed that it is unclear whether the SAE was related to elinzanetant given the lack of additional details.

(12) Subject (b) (6) was a 58-year-old woman randomized to the placebo-elinzanetant arm who had an SAE of mammoplasty 70 days after starting elinzanetant. The investigator considered this event to be severe in intensity and not related to elinzanetant, which the review team agrees with.

(13) Subject (b) (6) was a 59-year-old woman randomized to the placebo-elinzanetant arm who developed an SAE of a tibia fracture 15 days after starting elinzanetant. The investigator considered this event to be severe in intensity and not related to elinzanetant. The event tibia fracture was not associated with any other symptom, injury or central nervous system adverse event. The review team agreed with the assessment that the SAE does not appear related to elinzanetant.

(14) Subject (b) (6) was a 54-year-old woman randomized to elinzanetant who developed an SAE of arthrodesis (surgery tarsal fusion) 82 days after starting elinzanetant. The investigator considered this event to be moderate in intensity and not related to elinzanetant. The surgery was planned prior to study initiation of the study. The review team agrees with the assessment that this SAE does not appear related to elinzanetant.

OASIS 2

There were six subjects with SAEs while taking elinzanetant:

- Two subjects randomized to elinzanetant (one DVT/PE during the first 12 weeks, and one urinary tract infection after the first 12-week placebo-controlled period)
- Three subjects in the placebo-elinzanetant arm during Weeks 13 to 26 after switching to elinzanetant (one with device loosening and joint range of motion decreased, one with mechanical ileus, and one with generalized tonic-clonic seizures).

In addition, one subject had a posttreatment SAE of neck injury about 4 months after the last dose of elinzanetant.

Descriptions of the SAEs are included below:

(1) Subject (b) (6) was a 59-year-old woman who was randomized to the placebo-elinzanetant arm. 42 days after starting elinzanetant, the subject was reported with device loosening (reported term: sled prosthesis loosening right knee). The investigator considered

the AE serious because it required hospitalization. The investigator also considered this event to be moderate in intensity and not related to study intervention. In addition, the subject was reported with decreased joint range of motion, which required hospitalization. The event was moderate and considered not related to elinzanetant. The review team agrees with the assessment that the SAEs do not appear related to elinzanetant.

(2) Subject (b) (6) was a 55-year-old woman who was randomized to the placebo-elinzanetant arm who developed an SAE of mechanical ileus 16 days after starting elinzanetant the subject developed mechanical ileus (reported term: small intestine adhesion ileus). The investigator considered the AE serious because it required hospitalization. The event was moderate in intensity and not related to study intervention. Elinzanetant treatment was interrupted. Of note, the subject had a history of Crohn's disease. The review team agrees with the assessment that the SAE does not appear related to elinzanetant.

(3) Subject (b) (6) was a 58-year-old woman who was randomized to the placebo-elinzanetant arm. She had an SAE of a generalized tonic-clonic seizure that is described in Section 7.7.4. The event was considered an SAE as it required hospitalization. It was of moderate intensity and considered related to elinzanetant, which the review team agrees with.

(4) Subject (b) (6) was a 40-year-old woman randomized to the elinzanetant arm who developed SAEs of PE and DVT. The PE was diagnosed 14 days after starting elinzanetant and appeared to be secondary to a DVT in the calf that was diagnosed 21 days after starting elinzanetant. Both SAEs were of severe intensity and considered not related to elinzanetant and the review team agrees with this assessment. Elinzanetant treatment was interrupted, and the outcome was recovered/resolved.

(5) Subject (b) (6) was a 62-year-old woman who was randomized to the elinzanetant arm and had an SAE of neck injury 129 days after starting elinzanetant. The last dose of elinzanetant was about 4 months before the SAE. The neck injury was caused by a boating accident. The investigator considered this event to be severe in intensity and not related to elinzanetant. She received ketorolac and the last recorded outcome was recovering/resolving. The subject was discontinued prematurely from the study as she was found to have been randomized by mistake and should have been a screen failure. The subject's value of TSH and free T4 were abnormal during the screening visit and met exclusion criterion #6. The review team agrees with the assessment that the SAE does not appear related to elinzanetant.

(6) Subject (b) (6) was a 46-year-old woman randomized to elinzanetant who developed an SAE of a urinary tract infection (which also led to discontinuation). The SAE occurred 179 days after starting elinzanetant and was of severe intensity and deemed not related to elinzanetant, which the review team agrees with. The subject discontinued due to the AE.

7.6.1.4. Adverse Events Leading to Discontinuation, OASIS 1 and OASIS 2 (Weeks 1 to 12)

Table 40 displays subjects with adverse events leading to treatment discontinuation by system organ class and PT (Weeks 1 to 12). In the pooled data from OASIS 1 and OASIS 2, discontinuations occurred in more subjects in the elinzanetant group [30 subjects (7.5%)] compared to the placebo group [17 subjects (4.3%]).

For the OASIS 1 and OASIS 2 studies, the largest imbalance of AEs leading to discontinuation was for fatigue. In the pooled analyses, a higher percentage of subjects in the elinzanetant group (2%) compared to the placebo group (0%) discontinued due to fatigue. Refer to Section 7.6.3.6 for further discussion of fatigue as an AESI. AEs leading to discontinuation in the system organ class (SOC) psychiatric disorders occurred in a higher percentage of the elinzanetant group (1.2%) compared to the placebo group (0.5%). However, this imbalance did not appear to be driven by any specific PTs and there was some overlap in similar PTs observed in the placebo group and the elinzanetant group (such as depressed mood, dysphoria, depressive symptoms, and depression). Given similarities in the PTs, the depression OCMQ (narrow) was evaluated (Table 41). In the pooled data, the elinzanetant and placebo groups had the same percentage of subjects with depression OCMQ (narrow) (0.5%). This OCMQ was made up of the following PTs: depressed mood (0.2% elinzanetant versus 0% placebo), dysphoria (0.2% elinzanetant versus 0% placebo), depression (0% elinzanetant versus 0.3% placebo), and depressive symptom (0% elinzanetant versus 0.3% placebo). There were no notable imbalances in AEs leading to discontinuation between the elinzanetant group and the placebo group, other than fatigue in the analyses by PT and OCMQ (narrow).

Table 40. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled		
System Organ Class Preferred Term	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)	Risk Difference % (95% CI)
Any AE leading to discontinuation	17 (8.5)	13 (6.7)	13 (6.5)	4 (2.0)	30 (7.5)	17 (4.3)	3.2 (-0.1, 6.6)
Cardiac disorders (SOC)	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Palpitations	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Ear and labyrinth disorders (SOC)	0	0	1 (0.5)	1 (0.5)	1 (0.2)	1 (0.3)	-0.0 (-1.2, 1.2)
Vertigo	0	0	1 (0.5)	1 (0.5)	1 (0.2)	1 (0.3)	-0.0 (-1.2, 1.2)
Gastrointestinal disorders (SOC)	4 (2.0)	6 (3.1)	4 (2.0)	2 (1.0)	8 (2.0)	8 (2.0)	-0.0 (-2.2, 2.1)
Gastroesophageal reflux disease	0	0	2 (1.0)	0	2 (0.5)	0	0.5 (-0.5, 1.8)
Diarrhea	1 (0.5)	1 (0.5)	2 (1.0)	1 (0.5)	3 (0.8)	2 (0.5)	0.2 (-1.2, 1.7)
Nausea	2 (1.0)	3 (1.5)	2 (1.0)	1 (0.5)	4 (1.0)	4 (1.0)	-0.0 (-1.7, 1.6)
Abdominal discomfort	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Abdominal pain upper	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Dry mouth	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Dyspepsia	1 (0.5)	2 (1.0)	0	0	1 (0.2)	2 (0.5)	-0.3 (-1.6, 0.9)
General disorders and administration site conditions (SOC)	5 (2.5)	0	4 (2.0)	0	9 (2.2)	0	2.2 (1.2, 4.2) *
Fatigue	4 (2.0)	0	4 (2.0)	0	8 (2.0)	0	2.0 (1.0, 3.9) *
Pain	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Infections and infestations (SOC)	0	0	0	1 (0.5)	0	1 (0.3)	-0.3 (-1.4, 0.7)
Urosepsis	0	0	0	1 (0.5)	0	1 (0.3)	-0.3 (-1.4, 0.7)
Investigations (SOC)	1 (0.5)	2 (1.0)	2 (1.0)	0	3 (0.8)	2 (0.5)	0.2 (-1.2, 1.7)
Depression rating scale score increased	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Serum procollagen type I N-terminal propeptide increased	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Estradiol increased	0	1 (0.5)	1 (0.5)	0	1 (0.2)	1 (0.3)	-0.0 (-1.2, 1.2)
Blood follicle stimulating hormone decreased	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Blood glucose increased	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Glycosylated hemoglobin increased	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Progesterone increased	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)

System Organ Class Preferred Term	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)	Pooled Risk Difference % (95% CI)
Musculoskeletal and connective tissue disorders (SOC)	3 (1.5)	5 (2.6)	0	0	3 (0.8)	5 (1.3)	-0.5 (-2.3, 1.1)
Myalgia	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Neck pain	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Pain in extremity	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Arthralgia	3 (1.5)	4 (2.1)	0	0	3 (0.8)	4 (1.0)	-0.3 (-1.9, 1.3)
Nervous system disorders (SOC)	2 (1.0)	5 (2.6)	7 (3.5)	2 (1.0)	9 (2.2)	7 (1.8)	0.5 (-1.7, 2.7)
Headache	1 (0.5)	3 (1.5)	6 (3.0)	1 (0.5)	7 (1.8)	4 (1.0)	0.7 (-1.1, 2.7)
Somnolence	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Syncope	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Clumsiness	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Paresthesia	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Dizziness	1 (0.5)	2 (1.0)	1 (0.5)	1 (0.5)	2 (0.5)	3 (0.8)	-0.3 (-1.8, 1.1)
Psychiatric disorders (SOC)	4 (2.0)	2 (1.0)	1 (0.5)	0	5 (1.2)	2 (0.5)	0.7 (-0.7, 2.4)
Anxiety	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Depressed mood	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Dysphoria	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Irritability	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Mood altered	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Depression	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Depressive symptom	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Sleep terror	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Renal and urinary disorders (SOC)	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Urinary incontinence	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Reproductive system and breast disorders (SOC)	1 (0.5)	1 (0.5)	0	0	1 (0.2)	1 (0.3)	-0.0 (-1.2, 1.2)
Uterine hemorrhage	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Pelvic pain	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Pulmonary embolism	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)

System Organ Class Preferred Term	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)	Pooled Risk Difference % (95% CI)
Vascular disorders (SOC)	1 (0.5)	1 (0.5)	0	0	1 (0.2)	1 (0.3)	-0.0 (-1.2, 1.2)
Hypertension	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Hot flush	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Table 41. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and OCMQ (Narrow), Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

System Organ Class OCMQ (Narrow)	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)	Pooled Risk Difference % (95% CI)
Cardiac disorders (SOC)							
Systemic hypertension	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Palpitations	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Ear and labyrinth disorders (SOC)							
Vertigo	0	0	1 (0.5)	1 (0.5)	1 (0.2)	1 (0.3)	-0.0 (-1.2, 1.2)
Endocrine disorders (SOC)							
Hyperglycemia	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Gastrointestinal disorders (SOC)							
Diarrhea	1 (0.5)	1 (0.5)	2 (1.0)	1 (0.5)	3 (0.8)	2 (0.5)	0.2 (-1.2, 1.7)
Nausea	2 (1.0)	3 (1.5)	2 (1.0)	1 (0.5)	4 (1.0)	4 (1.0)	-0.0 (-1.7, 1.6)
Dry mouth	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Abdominal pain	0	2 (1.0)	0	0	0	2 (0.5)	-0.5 (-1.8, 0.4)
Dyspepsia	1 (0.5)	3 (1.5)	0	0	1 (0.2)	3 (0.8)	-0.5 (-2.0, 0.7)

System Organ Class OCMQ (Narrow)	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)	Pooled Risk Difference % (95% CI)
General disorders and administration site conditions (SOC)							
Fatigue	4 (2.0)	0	4 (2.0)	0	8 (2.0)	0	2.0 (1.0, 3.9) *
Dizziness	1 (0.5)	2 (1.0)	2 (1.0)	2 (1.0)	3 (0.8)	4 (1.0)	-0.3 (-1.9, 1.3)
Infections and infestations (SOC)							
Bacterial infection	0	0	0	1 (0.5)	0	1 (0.3)	-0.3 (-1.4, 0.7)
Musculoskeletal and connective tissue disorders (SOC)							
Myalgia	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Arthralgia	3 (1.5)	4 (2.1)	0	0	3 (0.8)	4 (1.0)	-0.3 (-1.9, 1.3)
Nervous system disorders (SOC)							
Headache	1 (0.5)	3 (1.5)	6 (3.0)	1 (0.5)	7 (1.8)	4 (1.0)	0.7 (-1.1, 2.7)
Somnolence	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Syncope	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Paresthesia	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Psychiatric disorders (SOC)							
Anxiety	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Irritability	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Study agent abuse potential	0	0	1 (0.5)	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Depression	1 (0.5)	2 (1.0)	1 (0.5)	0	2 (0.5)	2 (0.5)	-0.0 (-1.4, 1.3)
Parasomnia	0	1 (0.5)	0	0	0	1 (0.3)	-0.3 (-1.4, 0.7)
Renal and urinary disorders (SOC)							
Renal & urinary tract infection	0	0	0	1 (0.5)	0	1 (0.3)	-0.3 (-1.4, 0.7)
Reproductive system and breast disorders (SOC)							
Abnormal uterine bleeding	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)

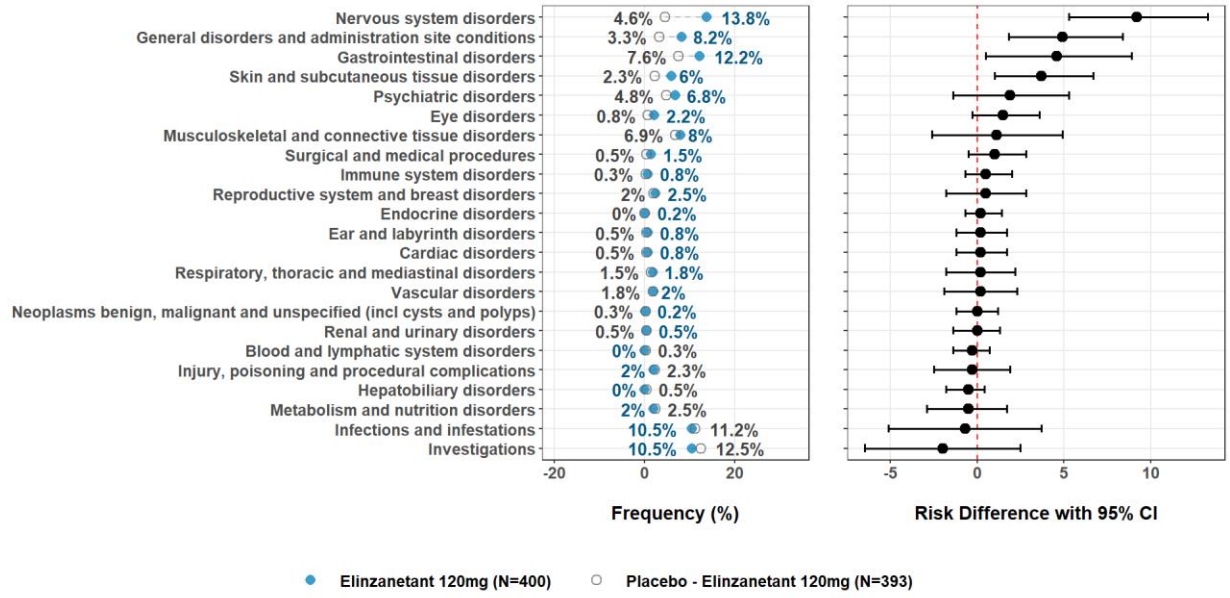
System Organ Class OCMQ (Narrow)	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)	Pooled Risk Difference % (95% CI)
Vascular disorders (SOC)							
Thrombosis	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)
Thrombosis venous	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.7, 1.4)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query; PT, preferred term; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, OASIS 1 and OASIS 2 (Weeks 1 to 12)

By system organ class, for the pooled data, nervous system disorders (e.g., headache, somnolence) represent the AEs with highest frequency and risk difference for elinzanetant versus placebo, followed by general disorders (e.g., fatigue) (Figure 12).

Figure 12. Subjects With Adverse Events by System Organ Class, Safety Population, OASIS 1 and OASIS 2 (Pooled) (Weeks 1 to 12)



Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Abbreviations: incl, including; N, number of subjects in treatment arm

Table 42 displays common adverse events occurring at ≥2% frequency in the safety population, for OASIS 1 and OASIS 2, pooled data, from Week 1 to 12. For the pooled data, headache, fatigue, and arthralgia were observed at the highest frequency in the elinzanetant group. When looking at the individual studies with adverse events occurring in at least 2% of subjects (Table 43), the types and percentages of adverse events were similar. Analyses by OCMQ (narrow) did not reveal any other safety considerations.

Table 42. Subjects With Common Adverse Events Occurring at ≥2% Frequency in Elinzanetant and Greater Than Placebo, OASIS 1 and OASIS 2 (Pooled) (Weeks 1 to 12)

Adverse Reaction	Elinzanetant (N=400) n (%)	Placebo (N=393) n (%)
Headache	32 (8.0)	10 (2.5)
Fatigue	26 (6.5)	7 (1.8)
Arthralgia	15 (3.8)	12 (3.1)
Gastroesophageal reflux disease	12 (3.0)	2 (0.5)
Dizziness	11 (2.8)	4 (1.0)
Nausea	10 (2.5)	7 (1.8)

Adverse Reaction	Elinzanetant (N=400) n (%)	Placebo (N=393) n (%)
Somnolence	9 (2.2)	2 (0.5)

Source: adae.xpt; Software: R
Fatigue contains fatigue and asthenia. Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention. Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily. Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 43. Subjects With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled	
Preferred Term	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)
Any AE	102 (51.3)	94 (48.5)	89 (44.3)	76 (38.2)	191 (47.8)	170 (43.3)
Headache	14 (7.0)	5 (2.6)	18 (9.0)	5 (2.5)	32 (8.0)	10 (2.5)
Fatigue	14 (7.0)	3 (1.5)	11 (5.5)	3 (1.5)	25 (6.2)	6 (1.5)
Gastroesophageal reflux disease	6 (3.0)	2 (1.0)	6 (3.0)	0	12 (3.0)	2 (0.5)
Somnolence	5 (2.5)	0	4 (2.0)	2 (1.0)	9 (2.2)	2 (0.5)
Dizziness	5 (2.5)	2 (1.0)	6 (3.0)	2 (1.0)	11 (2.8)	4 (1.0)
Alopecia	1 (0.5)	2 (1.0)	5 (2.5)	1 (0.5)	6 (1.5)	3 (0.8)
Urinary tract infection	4 (2.0)	1 (0.5)	2 (1.0)	2 (1.0)	6 (1.5)	3 (0.8)
Nausea	5 (2.5)	5 (2.6)	5 (2.5)	2 (1.0)	10 (2.5)	7 (1.8)
Arthralgia	10 (5.0)	10 (5.2)	5 (2.5)	2 (1.0)	15 (3.8)	12 (3.1)
Blood creatine phosphokinase increased	4 (2.0)	1 (0.5)	0	1 (0.5)	4 (1.0)	2 (0.5)
Dyspepsia	4 (2.0)	3 (1.5)	1 (0.5)	2 (1.0)	5 (1.2)	5 (1.3)
Nasopharyngitis	2 (1.0)	3 (1.5)	5 (2.5)	4 (2.0)	7 (1.8)	7 (1.8)
Diarrhea	5 (2.5)	6 (3.1)	4 (2.0)	3 (1.5)	9 (2.2)	9 (2.3)
Hypertension	1 (0.5)	4 (2.1)	2 (1.0)	1 (0.5)	3 (0.8)	5 (1.3)
Upper respiratory tract infection	0	5 (2.6)	3 (1.5)	0	3 (0.8)	5 (1.3)
COVID-19	2 (1.0)	4 (2.1)	8 (4.0)	8 (4.0)	10 (2.5)	12 (3.1)
Influenza	2 (1.0)	4 (2.1)	0	2 (1.0)	2 (0.5)	6 (1.5)
Depression	5 (2.5)	9 (4.6)	1 (0.5)	2 (1.0)	6 (1.5)	11 (2.8)

	OASIS 1		OASIS 2		Pooled	
Preferred Term	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)
Depression rating scale score increased	12 (6.0)	11 (5.7)	9 (4.5)	17 (8.5)	21 (5.2)	28 (7.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

OCMQ Analyses

Additional OCMQ (narrow) analyses were performed for fatigue, headache, gastroesophageal reflux disease, somnolence, and dizziness. See Section 7.6.3.6 for discussion of fatigue, somnolence, and dizziness. Additional safety analyses for headache and gastroesophageal reflux disease are provided below.

Headache

The headache OCMQ (narrow) was made up of the following PTs: headache, migraine, sinus headache, and tension headache, all of which occurred in a higher percentage of subjects in the elinzanetant group compared to the placebo group (Table 44). All the events were mild to moderate severity and none were serious. In the elinzanetant group (pooled data), 1.8% of subjects on elinzanetant compared to 1% of subjects on placebo discontinued due to headache. Headache will be included in the United States Prescribing Information (USPI).

Table 44. Adverse Events Assessment of Headache OCMQ (Narrow), Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled	
OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)
Headache (OCMQ)	15 (7.5)	5 (2.6)	21 (10.4)	5 (2.5)	36 (9.0)	10 (2.5)
Headache	14 (7.0)	5 (2.6)	18 (9.0)	5 (2.5)	32 (8.0)	10 (2.5)
Migraine	1 (0.5)	0	1 (0.5)	0	2 (0.5)	0
Sinus headache	0	0	1 (0.5)	0	1 (0.2)	0
Tension headache	0	0	1 (0.5)	0	1 (0.2)	0
Maximum severity						
Death	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Moderate	3 (1.5)	1 (0.5)	5 (2.5)	3 (1.5)	8 (2.0)	4 (1.0)
Mild	12 (6.0)	4 (2.1)	16 (8.0)	2 (1.0)	28 (7.0)	6 (1.5)
Serious	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	1 (0.5)	3 (1.5)	6 (3.0)	1 (0.5)	7 (1.8)	4 (1.0)

OCMQ (Narrow) Preferred Term	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)
Relatedness	9 (4.5)	4 (2.1)	12 (6.0)	2 (1.0)	21 (5.2)	6 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Relatedness is determined by the investigator.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

Gastroesophageal Reflux Disease

Gastroesophageal reflux was reported by a higher percentage of subjects in the pooled (OASIS 1 and OASIS 2) elinzanetant group (1.2%) compared to the placebo group (0.5%) (Table 45). All the events were mild to moderate severity, except two were severe. None were serious. In the elinzanetant group (pooled data), two subjects (0.5%) on elinzanetant compared to no subjects on placebo discontinued due to gastroesophageal reflux.

Details of the two subjects who discontinued are included below:

- Subject (b) (6) discontinued 1 day after starting elinzanetant due to severe gastroesophageal reflux disease. She had a history of gastroesophageal reflux disease, and the event resolved after discontinuation. The investigator considered the adverse event related to elinzanetant, and the review team agrees with this assessment, but notes the short latency between starting elinzanetant and the AE.
- Subject (b) (6) discontinued 4 days after starting elinzanetant due to gastroesophageal reflux disease that was moderate in intensity. The investigator considered the adverse event related to elinzanetant, and the review team agrees with this assessment.

Table 45. Adverse Events Assessment of Gastroesophageal Reflux Disease Preferred Term, Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

Preferred Term	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)
Gastroesophageal reflux disease	6 (3.0)	2 (1.0)	6 (3.0)	0	12 (3.0)	2 (0.5)
Maximum severity						
Death	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Severe	0	0	2 (1.0)	0	2 (0.5)	0
Moderate	3 (1.5)	0	2 (1.0)	0	5 (1.2)	0
Mild	3 (1.5)	2 (1.0)	2 (1.0)	0	5 (1.2)	2 (0.5)
Serious	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

Preferred Term	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)
Resulting in discontinuation	0	0	2 (1.0)	0	2 (0.5)	0
Relatedness	4 (2.0)	1 (0.5)	4 (2.0)	0	8 (2.0)	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Relatedness is determined by the investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event

As described in Section 7.1.3, there were GI-related findings in the nonclinical studies. In rats there were histopathological findings in rats of mucosa degeneration along with regeneration of the gastric mucosa, isthmus regenerative hypertrophy, and hyperplasia of the isthmus epithelium. In monkeys, there were histopathological findings of hemorrhage in the adventitia and in the mucosa of multiple regions in the GI tract. See Section 7.6.2 for additional discussion of GI-related adverse events in OASIS 3.

7.6.1.6. Laboratory Studies, OASIS 1 and OASIS 2 (Weeks 1 to 12)

In OASIS 1 and OASIS 2, no relevant trend was observed for any laboratory parameter based on descriptive summary statistics. None of the hematology, general chemistry, coagulation, hormone, vitamin, and urinalysis parameters displayed substantial changes over time and no differences between treatment arms were observed (see clinical study report [CSR] PH 42782, Section 8.3.5 and CSR PH 42784, Section 8.3.5). There was a slight increase of sex hormone-binding globulin in the elinzanetant group compared to the placebo group. As noted in Section 7.1.3, there was skeletal muscle degeneration noted in the nonclinical studies, but no elevations in creatine kinase were noted in OASIS 1 or OASIS 2. See Table 46 for selected analytes. See Section 7.6.3.3 for discussion of laboratory studies associated with hepatic safety.

Table 46. Selected Laboratory Data for Comparison Between Treatment Arms, OASIS 1 and OASIS 2

Selected Laboratory Data	Elinzanetant* Change From Baseline to Week 12 (mean ± SD)	Placebo* Change From Baseline to Week 12 (mean ± SD)
OASIS 1		
Leukocytes (%)	0.66 (6.52)	0.66 (7.69)
Lymphocytes (Giga/L)	0.024 (0.389)	0.005 (0.443)
Hematocrit (%)	0.03 (3.04)	-0.37 (2.90)
Hemoglobin (g/dL)	-0.13 (0.63)	-0.17 (0.62)
Sex hormone binding globulin (nmol/L)	4.8 (12.9)	-1.6 (11.3)
Creatine kinase (U/L)	12.5 (313.3)	8.8 (79.6)

Selected Laboratory Data	Elinzanetant* Change From Baseline to Week 12 (mean ± SD)	Placebo* Change From Baseline to Week 12 (mean ± SD)
OASIS 2		
Leukocytes (%)	0.13 (7.32)	1.25 (5.92)
Lymphocytes (Giga/L)	0.017 (0.496)	0.057 (0.397)
Hematocrit (%)	-0.54 (2.75)	-0.39 (2.46)
Hemoglobin (g/dL)	-0.2 (0.64)	-0.03 (0.62)
Sex hormone binding globulin (nmol/L)	4.3 (15.7)	0 (14.5)
Creatine kinase (U/L)	-13 (132.7)	-9.2 (186.9)

Source: compiled by reviewer from section 8.3.5, Clinical study reports for OASIS 1 and 2
*OASIS 1: At baseline, there were 199 subjects in the elinzanetant arm and 194 subjects in the placebo arm. At 12 weeks, there were 170 samples from the elinzanetant group and 162 samples from the placebo group
OASIS 2: At baseline, there were 201 subjects in the elinzanetant arm and 199 subjects in the placebo arm. At 12 weeks, there were 169 samples from the elinzanetant group and 180 samples from the placebo group
Abbreviation: SD, standard deviation

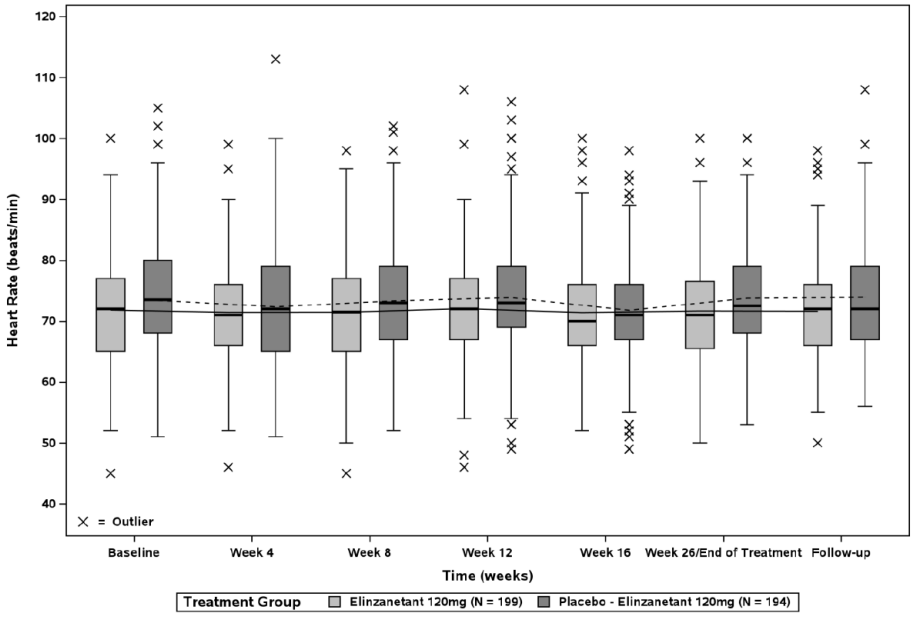
No differences were observed for data of subjects with one or more chemistry analyte levels with elevated or low values. Analytes examined were sodium, potassium, chloride, bicarbonate, glucose, calcium, magnesium, phosphate, protein, albumin, CPK, amylase, lipase, and urea nitrogen. No differences were observed for these values comparing elinzanetant and placebo groups (Source: adlb.xpt; Software: R).

Kidney function (measured as creatinine serum levels), liver function tests, or serum lipids, did not change over time from baseline to end of study when comparing elinzanetant versus placebo groups.

7.6.1.7. Vital Signs, OASIS 1 and OASIS 2 (Weeks 1 to 12)

There were no clinically meaningful changes in vital sign measurements during OASIS 1 and OASIS 2. Median and interquartile range of systolic blood pressure, diastolic blood pressure, and pulse, over time by treatment arm depicted no differences for any parameters over the study. There were no differences between the elinzanetant and placebo groups regarding percentage of subjects with maximum systolic blood pressure, maximum diastolic blood pressure, or hypotension levels. Figure 13 and Figure 14 show heart rate findings according to treatment arm through the duration of treatment for OASIS 1 and OASIS 2, respectively. Similar findings were seen for diastolic blood pressure (Figure 15 and Figure 16) and systolic blood pressure (Figure 17 and Figure 18). See Section 7.6.3.6 for additional discussion of hypotension and syncope.

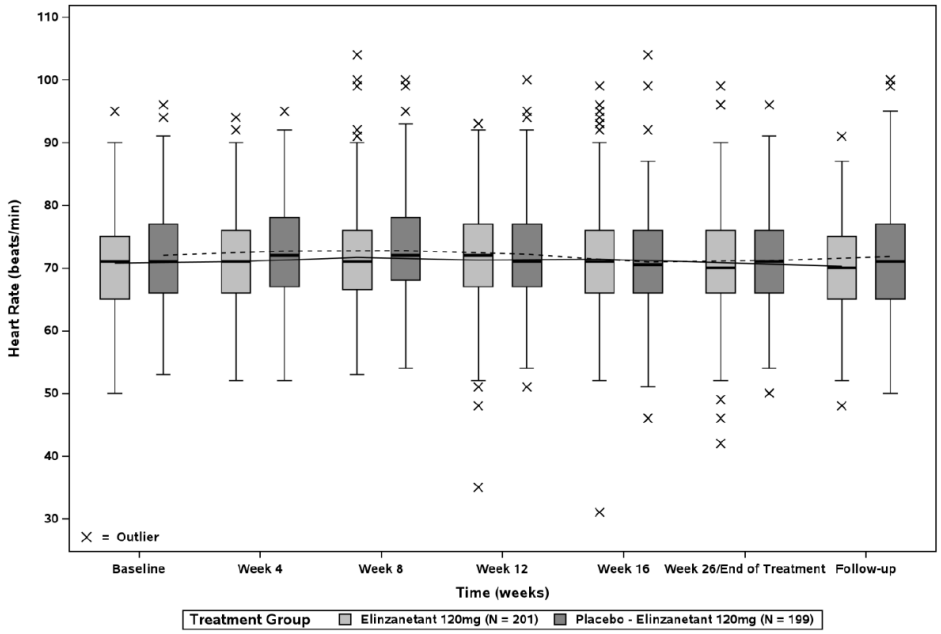
Figure 13. Box Plot of Heart Rate (Beats/Min) by Treatment Group, OASIS 1 (SAF)



Placebo - Elinzanetant 120mg = Placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks
Box: 25th to 75th percentile; horizontal line: median ; vertical lines extend from the box to a distance of at most 1.5 interquartile ranges and any value more extreme is plotted separately;connect lines join arithmetic means by treatment group.
Bayer: /var/swan/root/bhc/3427080/21651/stat/main01/prod/analysis/pgms/f_8_3_4_advs_box.sas 09JAN2024 16:02

Source: Clinical Study Report, OASIS 1, Figure 8.3.4 / 2, page 142
Abbreviations: SAF, safety analysis set

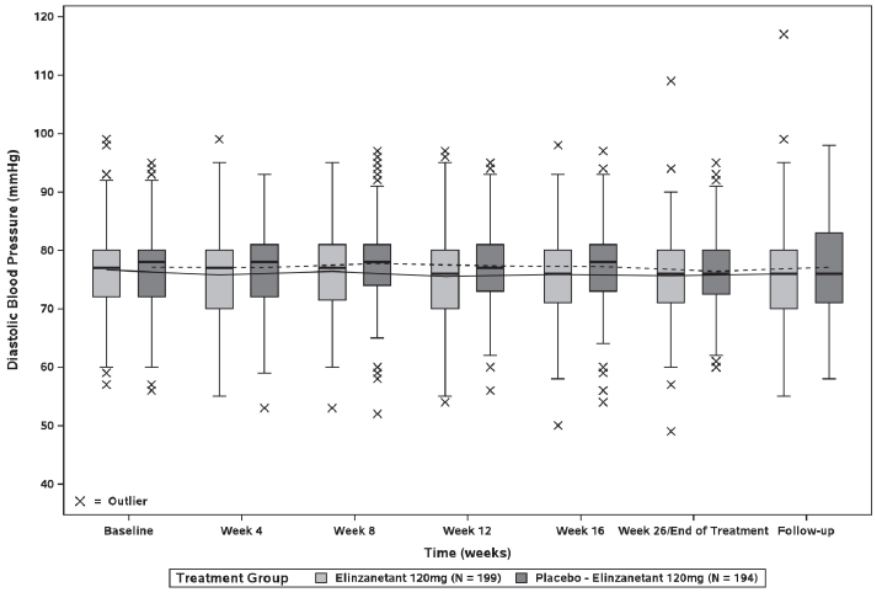
Figure 14. Box Plot of Heart Rate by Treatment Group, OASIS 2 (SAF)



Placebo - Elinzanetant 120mg = Placebo for 12 weeks, followed by Elinzanetant 120 mg for 14 weeks
Box: 25th to 75th percentile; horizontal line: median ; vertical lines extend from the box to a distance of at most 1.5 interquartile ranges and any value more extreme is plotted separately;connect lines join arithmetic means by treatment group.
Bayer: /var/swan/root/bhc/3427080/21652/stat/main01/prod/analysis/pgms/f_8_3_4_advs_box.sas 21NOV2023 18:22

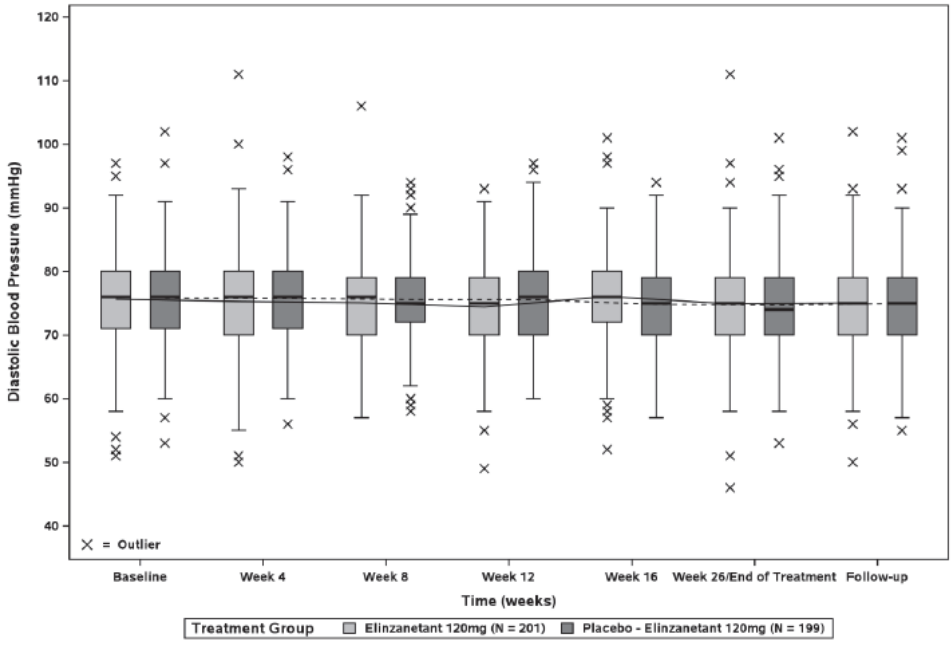
Source: Clinical Study Report, OASIS 2, Figure 8.3.4
Abbreviations: SAF, safety analysis set

Figure 15. Box Plot of Diastolic Blood Pressure by Treatment Group, OASIS 1 (SAF)



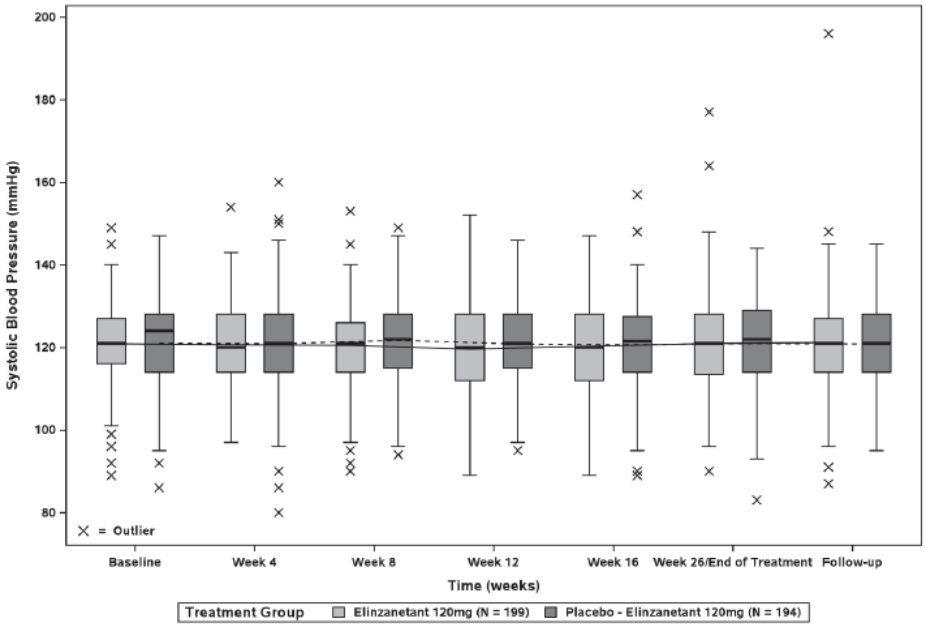
Source: Clinical Study Report, OASIS 1, Figure 8.3.4 / 1, page 146
Abbreviations: SAF, safety analysis set

Figure 16. Box Plot of Diastolic Blood Pressure by Treatment Group, OASIS 2 (SAF)



Source: Clinical Study Report, OASIS 2, Figure 8.3.4 / 3, page 131
Abbreviations: SAF, safety analysis set

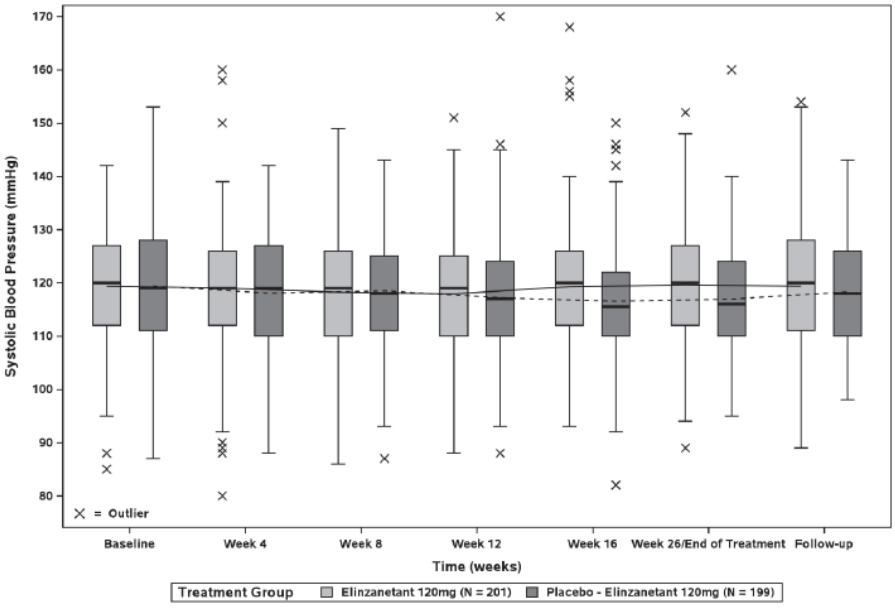
Figure 17. Box Plot of Systolic Blood Pressure by Treatment Group, OASIS 1 (SAF)



Placebo - Elinzanetant 120mg = Placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks
Box: 25th to 75th percentile; horizontal line: median ; vertical lines extend from the box to a distance of at most 1.5 interquartile ranges and any value more extreme is plotted separately;connect lines join arithmetic means by treatment group.

Source: Clinical Study Report, OASIS 1, Figure 8.3.4 / 3, page 148
Abbreviations: SAF, safety analysis set

Figure 18. Box Plot of Systolic Blood Pressure by Treatment Group, OASIS 2 (SAF)



Placebo - Elinzanetant 120mg = Placebo for 12 weeks, followed by Elinzanetant 120 mg for 14 weeks
Box: 25th to 75th percentile; horizontal line: median ; vertical lines extend from the box to a distance of at most 1.5 interquartile ranges and any value more extreme is plotted separately;connect lines join arithmetic means by treatment group.

Source: Clinical Study Report, OASIS 2, Figure 8.3.4 / 2, page 130
Abbreviations: SAF, safety analysis set

7.6.1.8. Assessment of Drug-Induced Liver Injury, OASIS 1 and OASIS 2 (Weeks 1 to 12)

Please refer to Section 7.6.3.3 for a review of this adverse event of special interest.

7.6.1.9. Subgroup Analyses, OASIS 1 and OASIS 2 (Weeks 1 to 12)

The percentage of subjects with adverse events by demographic subgroup was balanced between treatment arms, with no relevant differences in age, ethnicity, race, weight, height, or BMI (Table 47). Notably, adverse events occurred at similar percentages in the various age groups, with no trend towards more adverse events with increasing age.

Table 47. Overview of Adverse Events by Demographic Subgroup, Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled		
Characteristic	Elinzanetant 120 mg (N=199) n/N_s (%)	Placebo (N=194) n/N_s (%)	Elinzanetant 120 mg (N=201) n/N_s (%)	Placebo (N=199) n/N_s (%)	Elinzanetant 120 mg (N=400) n/N_s (%)	Placebo (N=393) n/N_s (%)	Risk Difference % (95% CI)
Sex							
Female	102/199 (51.3)	94/194 (48.5)	89/201 (44.3)	76/199 (38.2)	191/400 (47.8)	170/393 (43.3)	4.5 (-2.4, 11.4)
Age group, years							
40 to 49	11/29 (37.9)	12/29 (41.4)	9/24 (37.5)	10/29 (34.5)	20/53 (37.7)	22/58 (37.9)	-0.2 (-18.0, 17.8)
50 to 59	74/135 (54.8)	65/133 (48.9)	60/135 (44.4)	58/139 (41.7)	134/270 (49.6)	123/272 (45.2)	4.4 (-4.0, 12.8)
60 to 65	17/35 (48.6)	17/32 (53.1)	20/42 (47.6)	8/31 (25.8)	37/77 (48.1)	25/63 (39.7)	8.4 (-8.2, 24.4)
Race							
American Indian or Alaska Native	0/1 (0)	0/1 (0)	1/1 (100)	0/1 (0)	1/2 (50.0)	0/2 (0)	50.0 (-46.8, 92.4)
Asian	1/2 (50.0)	0/0 (NA)	0/0 (NA)	0/1 (0)	1/2 (50.0)	0/1 (0)	50.0 (-64.2, 93.1)
Black or African American	14/38 (36.8)	15/36 (41.7)	11/35 (31.4)	8/25 (32.0)	25/73 (34.2)	23/61 (37.7)	-3.5 (-19.7, 12.7)
Multiple	1/3 (33.3)	0/0 (NA)	0/0 (NA)	1/1 (100)	1/3 (33.3)	1/1 (100)	-66.7 (-95.0, 45.2)
Not reported	3/4 (75.0)	3/3 (100)	0/1 (0)	0/0 (NA)	3/5 (60.0)	3/3 (100)	-40.0 (-78.5, 31.2)
White	83/151 (55.0)	76/154 (49.4)	77/164 (47.0)	67/171 (39.2)	160/315 (50.8)	143/325 (44.0)	6.8 (-0.9, 14.5)
Ethnicity							
Hispanic or Latino	8/17 (47.1)	8/14 (57.1)	2/13 (15.4)	6/24 (25.0)	10/30 (33.3)	14/38 (36.8)	-3.5 (-25.6, 19.5)
Not Hispanic or Latino	93/180 (51.7)	84/176 (47.7)	86/187 (46.0)	69/174 (39.7)	179/367 (48.8)	153/350 (43.7)	5.1 (-2.2, 12.3)
Not reported	1/2 (50.0)	2/4 (50.0)	1/1 (100)	1/1 (100)	2/3 (66.7)	3/5 (60.0)	6.7 (-56.9, 62.1)
Is in United States							
United States	63/118 (53.4)	55/114 (48.2)	29/87 (33.3)	26/88 (29.5)	92/205 (44.9)	81/202 (40.1)	4.8 (-4.8, 14.3)
Not United States	39/81 (48.1)	39/80 (48.8)	60/114 (52.6)	50/111 (45.0)	99/195 (50.8)	89/191 (46.6)	4.2 (-5.8, 14.1)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6.2. Safety Results, OASIS 3

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, OASIS 3

An overview of adverse events in OASIS 3 is shown in Table 48. The percentage of subjects with SAEs was higher in the elinzanetant group (4.2%) compared to the placebo group (1.9%). The overall number of SAEs was relatively low, and none of the events were assessed as related to the study drug by the investigator. There were no reported deaths. The percentage of AEs leading to permanent discontinuation was higher in the elinzanetant group (12.5%) compared to the placebo group (4.1%).

The percentage of any AE was higher in the elinzanetant group (70%) compared to the placebo group (61.1%). In the elinzanetant group, 62.6% of these events were mild or moderate, compared to 54% in the placebo group.

No new trends were found when evaluating the data by exposure adjusted incidence rates (Table 48).

Table 48. Overview of Adverse Events, Safety Population, OASIS 3

Event Category	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
SAE	13 (4.2)	6 (1.9)	2.2 (-0.5, 5.3)	13/254.8 (5.1)	6/261.5 (2.3)	2.8 (-0.6, 6.7)
SAEs with fatal outcome	0	0	0.0 (-1.2, 1.2)	0/259 (0)	0/263.6 (0)	0.0 (-1.5, 1.5)
Life-threatening SAEs	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
SAEs requiring hospitalization	12 (3.8)	5 (1.6)	2.2 (-0.3, 5.2)	12/254.8 (4.7)	5/262 (1.9)	2.8 (-0.4, 6.5)
SAEs resulting in substantial disruption of normal life functions	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Other	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.9 (0.4)	1/263 (0.4)	0.0 (-1.8, 1.8)
AE leading to permanent discontinuation of study drug	39 (12.5)	13 (4.1)	8.3 (4.1, 12.8)*	39/255.4 (15.3)	13/261.5 (5.0)	10.3 (5.0, 16.3)*
AE leading to dose modification of study drug	19 (6.1)	14 (4.5)	1.6 (-2.0, 5.3)	19/248.4 (7.6)	14/253.5 (5.5)	2.1 (-2.5, 7.0)
AE leading to interruption of study drug	19 (6.1)	14 (4.5)	1.6 (-2.0, 5.3)	19/248.4 (7.6)	14/253.5 (5.5)	2.1 (-2.5, 7.0)
AE leading to reduction of study drug	0	0	0.0 (-1.2, 1.2)	0/259 (0)	0/263.6 (0)	0.0 (-1.5, 1.5)
AE leading to dose delay of study drug	0	0	0.0 (-1.2, 1.2)	0/259 (0)	0/263.6 (0)	0.0 (-1.5, 1.5)
Any AE	219 (70.0)	192 (61.1)	8.8 (1.4, 16.2)*	219/118.3 (185.1)	192/131.4 (146.2)	39.0 (7.1, 71.5)*
Severe	23 (7.3)	20 (6.4)	1.0 (-3.1, 5.1)	23/251.7 (9.1)	20/254.7 (7.9)	1.3 (-3.9, 6.6)
Moderate	94 (30.0)	88 (28.0)	2.0 (-5.1, 9.1)	94/214 (43.9)	88/212.5 (41.4)	2.5 (-10.0, 15.0)
Mild	102 (32.6)	84 (26.8)	5.8 (-1.3, 13.0)	102/189.7 (53.8)	84/206.7 (40.6)	13.1 (-0.4, 27.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Severity as assessed by the investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; EAIR, exposure adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of subjects with at least one event; PY, person-years (total exposure); py, person-years (at risk); SAE, serious adverse event

7.6.2.2. Deaths, OASIS 3

There were no deaths in OASIS 3.

7.6.2.3. Serious Adverse Events, OASIS 3

Serious adverse events were analyzed by system organ class and PT (Table 49). The percentage of subjects with SAEs was higher in the elinzanetant group (4.2%) versus the placebo group (1.9%). The overall number of SAEs was relatively low, and none of the events were assessed as related to the study drug by the investigator. All events were reported as single PTs and distributed over several system organ classes without a pattern. Similar trends were seen evaluating the data by exposure adjusted incidence rates.

Table 49. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, OASIS 3

System Organ Class Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Any SAE	13 (4.2)	6 (1.9)	2.2 (-0.5, 5.3)	13/254.8 (5.1)	6/261.5 (2.3)	2.8 (-0.6, 6.7)
Cardiac disorders (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Acute myocardial infarction	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Ear and labyrinth disorders (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.1 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Vertigo	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.1 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Hepatobiliary disorders (SOC)	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/262.7 (0.4)	-0.4 (-2.2, 1.1)
Cholecystitis chronic	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/262.7 (0.4)	-0.4 (-2.2, 1.1)
Infections and infestations (SOC)	3 (1.0)	1 (0.3)	0.6 (-0.9, 2.5)	3/258 (1.2)	1/263.4 (0.4)	0.8 (-1.1, 3.1)
Meningitis meningococcal	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.4 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Fusobacterium infection	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.6 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Epiglottitis	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Infected bite	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.4 (0.4)	-0.4 (-2.2, 1.1)
Injury, poisoning and procedural complications (SOC)	2 (0.6)	1 (0.3)	0.3 (-1.2, 2.0)	2/258.7 (0.8)	1/263.5 (0.4)	0.4 (-1.4, 2.5)
Concussion	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.7 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Injury	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Post procedural hemorrhage	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Investigations (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.5 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Blood glucose increased	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.5 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Musculoskeletal and connective tissue disorders (SOC)	2 (0.6)	1 (0.3)	0.3 (-1.2, 2.0)	2/258.1 (0.8)	1/263.3 (0.4)	0.4 (-1.4, 2.5)
Rotator cuff syndrome	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.4 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Osteoarthritis	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.7 (0.4)	1/263.3 (0.4)	0.0 (-1.8, 1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Invasive ductal breast carcinoma	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)

System Organ Class Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Nervous system disorders (SOC)	3 (1.0)	2 (0.6)	0.3 (-1.4, 2.2)	3/258 (1.2)	2/263 (0.8)	0.4 (-1.7, 2.7)
Syncope	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.1 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Transient ischemic attack	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Multiple sclerosis	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Encephalitis toxic	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.2, 1.1)
Hemiparesthesia	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263 (0.4)	-0.4 (-2.2, 1.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 weeks.
Abbreviations: EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk); SAE, serious adverse event; SOC, system organ class

The numbers and proportions of subjects with SAE by system organ class and OCMQ (narrow) are shown in Table 50. In general, these results were consistent with the analyses by SOC and PT.

Table 50. Subjects With Serious Adverse Events by System Organ Class and OCMQ (Narrow), Safety Population, OASIS 3

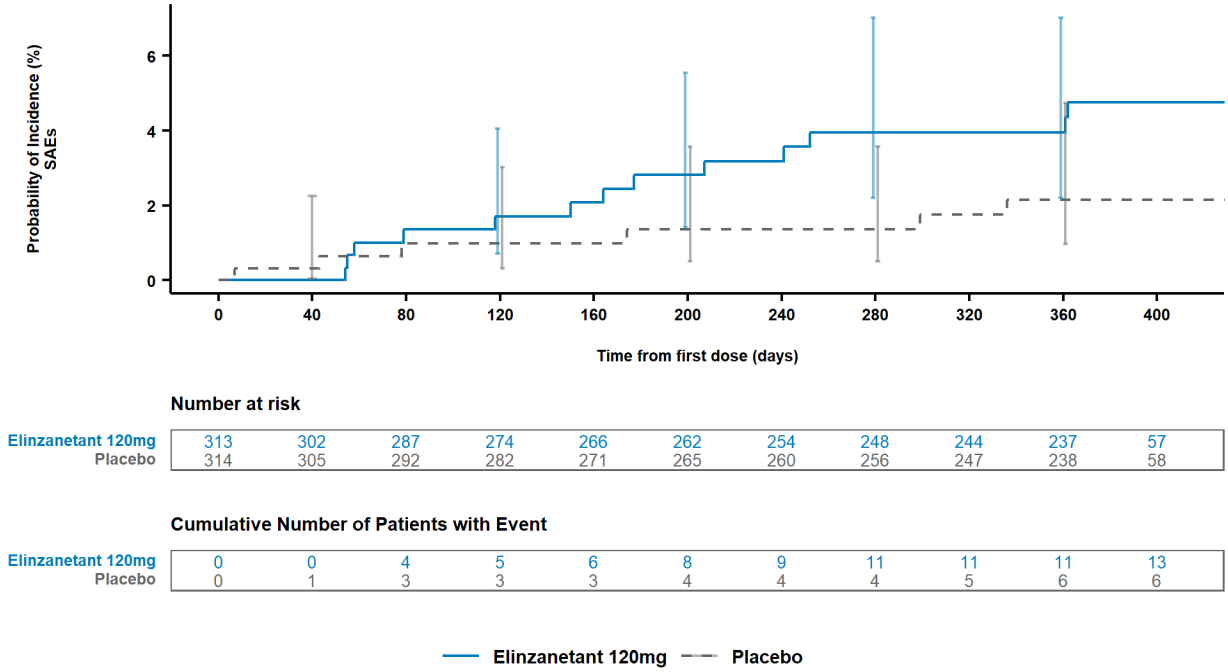
System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Cardiac disorders (SOC)						
Acute coronary syndrome	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Myocardial infarction	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Myocardial ischemia	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Ear and labyrinth disorders (SOC)						
Vertigo	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.1 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Endocrine disorders (SOC)						
Hyperglycemia	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.5 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
General disorders and administration site conditions (SOC)						
Dizziness	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.1 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)

System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Hepatobiliary disorders (SOC)						
Cholecystitis	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/262.7 (0.4)	-0.4 (-2.2, 1.1)
Infections and infestations (SOC)						
Bacterial infection	2 (0.6)	2 (0.6)	0.0 (-1.7, 1.7)	2/258 (0.8)	2/262.5 (0.8)	0.0 (-2.1, 2.1)
Musculoskeletal and connective tissue disorders (SOC)						
Tendinopathy	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.4 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Arthritis	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.7 (0.4)	1/263.3 (0.4)	0.0 (-1.8, 1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)						
Malignancy	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Nervous system disorders (SOC)						
Syncope	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.1 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Stroke and TIA	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Paresthesia	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263 (0.4)	-0.4 (-2.2, 1.1)
Vascular disorders (SOC)						
Thrombosis	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.8 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Thrombosis arterial	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.8 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Hemorrhage	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
For specific preferred terms under each OCMQ, see the table “Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OCMQ.
Abbreviations: EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class; TIA, transient ischemic attack

Figure 19 depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experienced an incident (i.e., first) event by a given time point during the 52-week study period. It is noted that SAEs separation between the elinzanetant group and the placebo group occurs by 120 days, with separation maintained during the study.

Figure 19. Time to Onset of Serious Adverse Events, Safety Population, OASIS 3



Source: adae.xpt; Software: R
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an incident (i.e., first) event by a given time point.
Abbreviations: SAE, serious adverse event

The following 13 subjects in the elinzanetant arm of OASIS 3 had SAEs. Of the 13 subjects with SAEs, it was difficult to assign causality of two of them (syncope and peripheral vertigo); however, there are factors that suggest these SAEs were not secondary to elinzanetant. These SAEs of special interest are also discussed in Section 7.6.3.6 and Section 7.7.5.

(1) Subject [redacted] (b) (6) had an SAE of blood glucose increase of severe intensity that required or prolonged hospitalization. The SAE occurred 207 days after starting elinzanetant. The subject had a history of impaired glucose tolerance and was able to complete participation in the study. The review team agrees with the investigator that the SAE does not appear to be related to elinzanetant.

(2) Subject [redacted] (b) (6) was a 57-year-old woman who was an unrestrained driver in a car and had an injury that was considered serious and led to study discontinuation. The SAE of injury occurred 79 days after starting elinzanetant. The first recorded blood pressure was 105/65 in the trauma bay. No neurological symptoms were reported before the accident. At the time of the accident, concomitant medications included Paxil, Norco (hydrocodone combined with acetaminophen), and gabapentin, all of which could be associated with CNS

effects (such as somnolence, dizziness). The review team agrees with the investigator that the SAE does not appear to be related to elinzanetant.

(3) Subject (b) (6) was a 50-year-old woman who reported a transient ischemic attack that was considered serious as it required or prolonged hospitalization. The SAE occurred 362 days after starting elinzanetant and she was able to complete study participation. The review team agrees with the investigator that the SAE does not appear to be related to elinzanetant.

(4) Subject (b) (6) was a 54-year-old woman with a history of multiple sclerosis who had an adverse event of worsening multiple sclerosis that required or prolonged hospitalization. The SAE occurred 54 days after starting elinzanetant and was considered not related to the study drug. The review team agrees with the investigator that the SAE does not appear to be related to elinzanetant.

(5) Subject (b) (6) was a 54-year-old woman who developed an SAE of meningococcal meningitis requiring or prolonging hospitalization. The SAE occurred 150 days after starting elinzanetant, was considered severe by the investigator, and the drug was interrupted, but the subject was able to complete the study. The SAE was not considered related to elinzanetant. The review team agrees with the investigator that the SAE does not appear to be related to elinzanetant.

(6) Subject (b) (6) was a 56-year-old woman who had an SAE of syncope 55 days after starting elinzanetant. The drug was interrupted and then the subject was able to complete the study per protocol. The cause of the syncope was unclear. She reported that she felt disoriented and passed out while in her car. She was admitted to the hospital and experienced slurred speech, blurred vision, and elevated blood pressure and heart rate. It was noted that she may have had a seizure and would require additional follow-up. Records noted that she had left-sided and facial numbness, tremors, confusion, and hypomagnesemia. Diagnostic evaluations included angiogram, chest X-ray, computerized tomogram of the head, electrocardiogram, and magnetic resonance imaging of the head. The investigator considered the SAE not related to the study medication, which is supported by the observation that the subject was able to restart elinzanetant and complete the study. The review team notes that it is difficult to assign causality to elinzanetant as she was able to restart the study drug. However, this is an adverse event of interest, as discussed further in Section 7.7.4.

(7) Subject (b) (6) was a 53-year-old woman who developed epiglottis 177 days after staring elinzanetant. The subject was treated with antibiotics and withdrew from the study. The SAE was not considered related to elinzanetant, and the review team agrees with this assessment.

(8) Subject (b) (6) was a 57-year-old woman who had an acute myocardial infarction 118 days after starting elinzanetant. A stent was placed, and the subject discontinued the study. The investigator considered the SAE as not related to study intervention, and the review team agrees with this assessment.

(9) Subject (b) (6) was a 60-year-old woman who developed peripheral vertigo 58 days after starting elinzanetant. The SAE required or prolonged hospitalization and was of severe intensity. The subject was able to complete the study, and the dose of elinzanetant was

not changed. The event lasted 5 days. The subject was treated with dimenhydrinate, metoclopramide hydrocholoride, and ondansetron for the event. The investigator considered the SAE not related to study intervention. Given that the subject was able to continue elinzanetant and complete the study, this does suggest that the SAE was not secondary to elinzanetant. However, dizziness/vertigo is an AE of special interest. The review team notes that it is difficult to assign causality to elinzanetant (as she was able to continue elinzanetant). See Section 7.6.3.6 for additional discussion of AESI.

(10) Subject (b) (6) was a 59-year-old woman with two SAEs (concussion and rotator cuff syndrome). The SAE of rotator cuff syndrome occurred 164 days after starting elinzanetant and did not require a change in study interventions. The SAE of concussion occurred 292 days after starting elinzanetant and required or prolonged hospitalization. The subject did not report dizziness, sleepiness, or fatigue prior to the event. She fell off her bicycle at a speed of about 25 km/h and developed the concussion and craniofacial fracture. She was unconscious for a few minutes after the accident. Vital signs are not available from the time of the event, but her heart rate, systolic blood pressure, and diastolic blood pressure measurements were normal at all study visits. She was also diagnosed with a subdural hematoma based on a CT scan of the skull on an unknown date. Given that the subject was able to continue elinzanetant and finish the study and lack of other features suggesting causality, the review team agrees with the investigator's assessment that the concussion was not related to study medication.

(11) Subject (b) (6) was a 56-year-old woman who developed an SAE of osteoarthritis 252 days after starting elinzanetant. The event was considered serious as it required or prolonged hospitalization. The subject completed the study, and the SAE was not considered related to elinzanetant. This review team agrees with this assessment.

(12) Subject (b) (6) was a 52-year-old woman with an SAE of invasive ductal breast carcinoma. The subject completed study interventions prior to the diagnosis. The review team agrees with the assessment that the SAE was not related to study intervention.

(13) Subject (b) (6) was a 61-year-old woman with an SAE of fusobacterium infection that occurred 241 days after staring elinzanetant. It was considered serious as it required or prolonged hospitalization. She was treated with antibiotics and treatment with elinzanetant was interrupted, but she was able to resume medication. The investigator considered this SAE of severe intensity and not related to elinzanetant. The review team agrees with this assessment.

7.6.2.4. Adverse Events Leading to Discontinuation, OASIS 3

The percentage of subjects with AEs leading to permanent study discontinuation was higher in the elinzanetant group (12.5%) compared to the placebo group (4.1%) (risk difference 8.3%, CI: 4.1, 12.8).

Notable imbalances included:

(1) Gastrointestinal disorders SOC occurred in a higher percentage of subjects in the elinzanetant group (2.9%) compared to placebo (1.6%). A variety of PTs occurred at a higher percentage in the elinzanetant group, including abdominal pain upper, gastroesophageal reflux disease, abdominal pain, abdominal pain lower, and diarrhea.

(2) General disorders SOC occurred in a higher percentage of subjects in the elinzanetant group (1.6%) compared to placebo (0%) based on an imbalance in fatigue.

(3) Nervous system disorders SOC (including headache, dizziness, amnesia, lethargy, multiple sclerosis, and somnolence) occurred in a higher percentage of subjects in the elinzanetant arm (2.9%) compared to placebo (0.3%).

(4) Psychiatric disorders SOC occurred in a higher percentage of subjects in the elinzanetant group (2.9%) versus placebo (0.3%). A variety of PTs were included in this category, such as depressed mood, depression, anxiety, apathy, nervousness, suicidal ideation, and insomnia, albeit in small numbers.

(5) Skin and subcutaneous tissue disorders SOC occurred in a higher percentage of subjects in the elinzanetant group (1.3%) compared to placebo (0%). A variety of PTs were included in this category, such as rash, alopecia, dry skin, and photosensitivity reaction.

By PT, the most frequently reported AEs leading to discontinuation were fatigue, headache, abdominal pain upper, and depressed mood, which occurred in 1.6%, 1.3%, 1%, and 1% of the elinzanetant group, respectively, compared to 0% of the placebo group.

Refer to Section 7.6.3.6 for further discussion of nervous system disorders (fatigue, somnolence, dizziness/vertigo) as adverse events of special interest.

Table 51. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, OASIS 3

System Organ Class Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Any AE leading to discontinuation	39 (12.5)	13 (4.1)	8.3 (4.1, 12.8) *	39/255.4 (15.3)	13/261.5 (5.0)	10.3 (5.0, 16.3) *
Ear and labyrinth disorders (SOC)	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.7 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Tinnitus	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.8 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Vertigo	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Endocrine disorders (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Hyperprolactinemia	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Eye disorders (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Vision blurred	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Gastrointestinal disorders (SOC)	9 (2.9)	5 (1.6)	1.3 (-1.2, 4.0)	9/258.2 (3.5)	5/262.4 (1.9)	1.6 (-1.4, 4.9)
Abdominal pain upper	3 (1.0)	0	1.0 (-0.3, 2.8)	3/258.7 (1.2)	0/263.6 (0)	1.2 (-0.3, 3.4)
Gastroesophageal reflux disease	2 (0.6)	1 (0.3)	0.3 (-1.2, 2.0)	2/258.8 (0.8)	1/263.5 (0.4)	0.4 (-1.4, 2.5)
Abdominal pain	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.8 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Diarrhea	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Abdominal pain lower	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Nausea	2 (0.6)	2 (0.6)	0.0 (-1.7, 1.7)	2/258.8 (0.8)	2/263.4 (0.8)	0.0 (-2.1, 2.1)
Dyspepsia	1 (0.3)	2 (0.6)	-0.3 (-2.0, 1.2)	1/258.9 (0.4)	2/262.6 (0.8)	-0.4 (-2.4, 1.5)
General disorders and administration site conditions (SOC)	5 (1.6)	0	1.6 (0.4, 3.7) *	5/258.5 (1.9)	0/263.6 (0)	1.9 (0.5, 4.5) *
Fatigue	5 (1.6)	0	1.6 (0.4, 3.7) *	5/258.5 (1.9)	0/263.6 (0)	1.9 (0.5, 4.5) *
Infections and infestations (SOC)	3 (1.0)	1 (0.3)	0.6 (-0.9, 2.5)	3/258.8 (1.2)	1/263.5 (0.4)	0.8 (-1.1, 3.1)
Herpes zoster	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Sinusitis	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Epiglottitis	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Bronchitis	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Injury, poisoning and procedural complications (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Injury	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)

System Organ Class Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Investigations (SOC)	3 (1.0)	3 (1.0)	0.0 (-1.9, 1.9)	3/258.3 (1.2)	3/263.4 (1.1)	0.0 (-2.3, 2.4)
Weight increased	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.4 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Liver function test abnormal	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Blood follicle stimulating hormone decreased	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Estradiol increased	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Eosinophil count increased	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Gamma-glutamyltransferase increased	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Aspartate aminotransferase increased	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.2, 1.1)
Alanine aminotransferase increased	0	2 (0.6)	-0.6 (-2.3, 0.6)	0/259 (0)	2/263.5 (0.8)	-0.8 (-2.8, 0.7)
Metabolism and nutrition disorders (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Hyperkaliemia	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Musculoskeletal and connective tissue disorders (SOC)	3 (1.0)	1 (0.3)	0.6 (-0.9, 2.5)	3/258.8 (1.2)	1/263.5 (0.4)	0.8 (-1.1, 3.1)
Bone pain	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Muscle spasms	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Myalgia	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.9 (0.4)	1/263.5 (0.4)	0.0 (-1.8, 1.8)
Arthralgia	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Nervous system disorders (SOC)	9 (2.9)	1 (0.3)	2.6 (0.8, 5.1) *	9/258.3 (3.5)	1/263.5 (0.4)	3.1 (0.9, 6.3) *
Headache	4 (1.3)	0	1.3 (0.1, 3.2) *	4/258.8 (1.5)	0/263.6 (0)	1.5 (0.1, 4.0) *
Dizziness	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.7 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Lethargy	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Somnolence	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Amnesia	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Multiple sclerosis	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Dysgeusia	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)

System Organ Class Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Psychiatric disorders (SOC)	8 (2.6)	1 (0.3)	2.2 (0.5, 4.7) *	8/258.4 (3.1)	1/263.2 (0.4)	2.7 (0.6, 5.8) *
Depressed mood	3 (1.0)	0	1.0 (-0.3, 2.8)	3/258.8 (1.2)	0/263.6 (0)	1.2 (-0.3, 3.4)
Depression	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.8 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Anxiety	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.8 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Nervousness	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Suicidal ideation	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Apathy	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Insomnia	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.2 (0.4)	-0.4 (-2.2, 1.1)
Reproductive system and breast disorders (SOC)	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.9 (0.4)	1/263.3 (0.4)	0.0 (-1.8, 1.8)
Vaginal haemorrhage	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Vulvovaginal dryness	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.3 (0.4)	-0.4 (-2.2, 1.1)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Asthma	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Skin and subcutaneous tissue disorders (SOC)	4 (1.3)	0	1.3 (0.1, 3.2) *	4/258.4 (1.5)	0/263.6 (0)	1.5 (0.1, 4.0) *
Rash	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.9 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Alopecia	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.6 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Dry skin	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Photosensitivity reaction	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Vascular disorders (SOC)	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Hypertension	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

Table 52 presents data for subjects with adverse events leading to treatment discontinuation by system organ class and OCMQ (narrow). The results were similar to those seen analyzed by PTs. The most frequent events by OCMQ comparing elinzanetant versus placebo were:

(1) Abdominal pain (gastrointestinal disorder SOC), five subjects (1.6%) versus zero;

(2) Fatigue (general disorders SOC), six subjects (1.9%) versus zero;

(3) Headache (nervous system SOC), four subjects (1.3%) versus zero; and

(4) Depression (psychiatric disorders SOC), five subjects (1.6%) versus zero.

For further discussion of fatigue, please see Section 7.6.3.6. The results for abdominal pain, fatigue, headache, and depression are discussed below.

Abdominal Pain

The gastrointestinal disorder OCMQ (narrow) was made up of the following preferred terms: abdominal pain, dyspepsia, diarrhea, and nausea. All these AEs were more common in the elinzanetant arm than the placebo arm, except for nausea (which occurred in the same percentage of subjects in the elinzanetant and placebo arms). Abdominal pain will be included in the USPI.

Depression

The depression OCMQ was made up of the following PTs: depressed mood and depression, both of which occurred in a higher percentage of subjects in the elinzanetant arm. AEs in the depression OCMQ leading to discontinuation were reported by a higher percentage of subjects in the elinzanetant group (1.6%) compared to the placebo group (0.0%) (Table 51). Of the five subjects with AEs related to depression, two were moderate, two were severe, and one was mild. None were serious.

Details of the subjects who discontinued due to depression are included below:

(1) Subject (b) (6) was a 53-year-old woman who developed two AEs leading to discontinuation: depression and weight increased. The increased weight occurred 96 days after starting elinzanetant. The investigator considered this event to be moderate in intensity and related to study intervention. Then, 165 days after starting elinzanetant, the subject developed severe depression and stopped elinzanetant. The investigator considered this event to be severe in intensity and related to study intervention.

(2) Subject (b) (6) was a 57-year-old woman who developed an AE of depression leading to discontinuation 98 days after starting elinzanetant. The investigator considered this event to be mild in intensity and not related to study intervention. The subject received medications for her depression.

(3) Subject (b) (6) was a 62-year-old woman who developed an AE of depressed mood 6 days after starting elinzanetant and leading to treatment discontinuation. The subject had a history of depression. The investigator considered the AE to be moderate in intensity and related to elinzanetant.

(4) Subject (b) (6) was a 59-year-old woman who developed AEs of apathy and depressed mood 189 days after starting elinzanetant. The investigator considered these events to be severe in intensity and related to elinzanetant.

(5) Subject (b) (6) was a 61-year-old woman who developed two AEs leading to discontinuation: depressed mood and myalgia. 6 days after starting elinzanetant, she developed depressed mood. The investigator considered this AE to be of moderate intensity and related to elinzanetant. Then, 11 days after starting elinzanetant, she developed myalgias. The investigator considered this AE to be of moderate intensity and related to elinzanetant. She discontinued elinzanetant due to the AEs.

There was also one discontinuation related to suicidal ideation.

(1) Subject (b) (6) was a 49-year-old woman with a history of depression who reported suicidal ideation 40 days after starting elinzanetant. The event was moderate in intensity and considered related to study intervention. She discontinued elinzanetant and the AE resolved. The review team agrees with the investigator's assessment of causality, however notes that the subject had a history of depression.

In OASIS 1, OASIS 2, and OASIS 3, suicidal ideation and behavior was monitored by the eC-SSRS, In OASIS 3, 47 subjects (15%) in the elinzanetant arm and 40 subjects (12.7%) in the placebo arm reported a history of previous suicidal ideation or behavior at baseline. Four subjects, all of whom were in the elinzanetant arm, had experienced suicidal ideation within the past 6 months before the baseline visit. During treatment, the number of subjects reporting suicidal ideation was low in both treatment arms (ranged from 2 to 5 subjects per arm at all timepoints measured). No suicidal behavior was reported by any subject during treatment.

Table 52. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and OCMQ (Narrow), Safety Population, OASIS 3

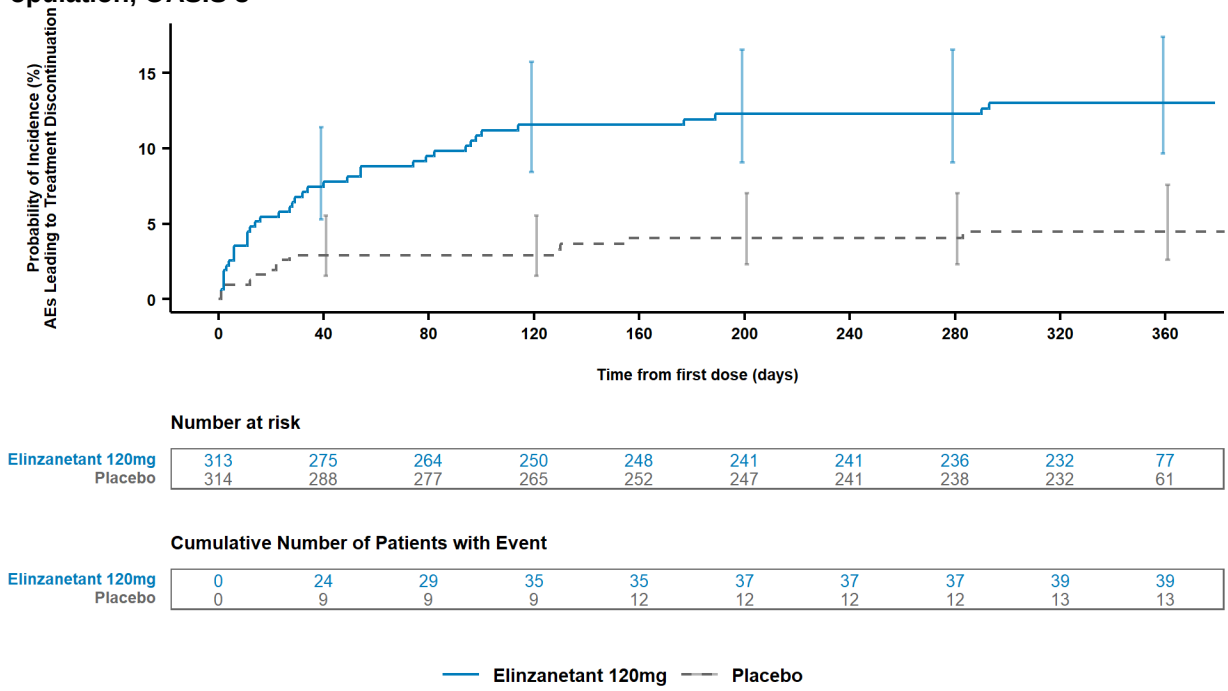
System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)
Cardiac disorders (SOC)		
Systemic hypertension	0	1 (0.3)
Ear and labyrinth disorders (SOC)		
Vertigo	1 (0.3)	0
Endocrine disorders (SOC)		
Hyperprolactinemia	1 (0.3)	0
Gastrointestinal disorders (SOC)		
Abdominal pain	5 (1.6)	0
Dyspepsia	4 (1.3)	2 (0.6)
Diarrhea	1 (0.3)	0
Nausea	2 (0.6)	2 (0.6)
General disorders and administration site conditions (SOC)		
Fatigue	6 (1.9)	0
Dizziness	3 (1.0)	0
Hepatobiliary disorders (SOC)		
Hepatic injury	0	2 (0.6)

System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)
Infections and infestations (SOC)		
Viral infection	1 (0.3)	0
Musculoskeletal and connective tissue disorders (SOC)		
Myalgia	1 (0.3)	1 (0.3)
Arthralgia	0	1 (0.3)
Nervous system disorders (SOC)		
Headache	4 (1.3)	0
Somnolence	2 (0.6)	0
Dysgeusia	0	1 (0.3)
Psychiatric disorders (SOC)		
Depression	5 (1.6)	0
Anxiety	2 (0.6)	0
Self-harm	1 (0.3)	0
Study agent abuse potential	1 (0.3)	0
Insomnia	0	1 (0.3)
Reproductive system and breast disorders (SOC)		
Abnormal uterine bleeding	1 (0.3)	0
Sexual dysfunction	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders (SOC)		
Bronchospasm	1 (0.3)	0
Skin and subcutaneous tissue disorders (SOC)		
Rash	2 (0.6)	0
Alopecia	1 (0.3)	0
Vascular disorders (SOC)		
Hemorrhage	1 (0.3)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
For specific preferred terms under each OCMQ, see the table “Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OCMQ.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query; PT, preferred term; SOC, system organ class

Figure 20 depicts Kaplan-Meier estimates of the cumulative incidence of subjects that experienced AEs leading to discontinuation of treatment during the 52-week study period. AEs leading to discontinuation were increased in elinzanetant from the onset of the study, with relative stability after 120 days of treatment.

Figure 20. Time to Onset of Adverse Events Leading to Treatment Discontinuation, Safety Population, OASIS 3

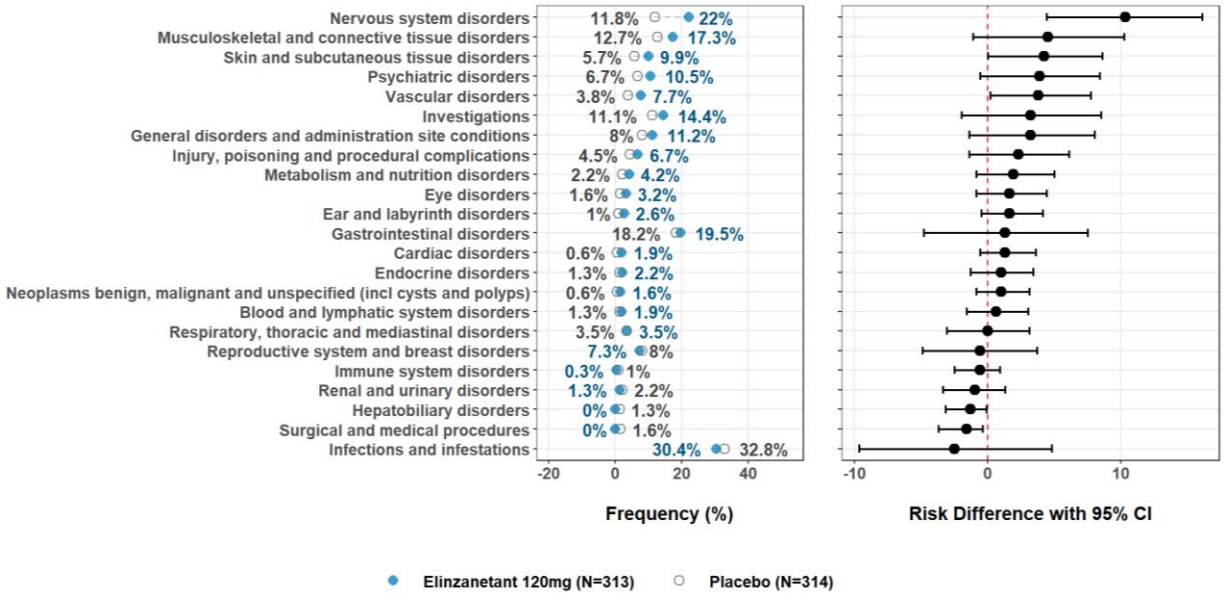


Source: adae.xpt; Software: R
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects that experience an incident (i.e., first) event by a given time point
Abbreviations: AE, adverse event

7.6.2.5. Treatment-Emergent Adverse Events, OASIS 3

The data for AEs are summarized by system organ class according to their frequency in Figure 21. Nervous system disorders showed the highest percentage in the elinzanetant group, followed by musculoskeletal and connective tissue disorders, skin and subcutaneous tissue disorders, and psychiatric disorders.

Figure 21. Subjects With Adverse Events by System Organ Class, Safety Population, OASIS 3



Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention
Abbreviations: incl, including; N, number of subjects in treatment arm

Common AEs (52 weeks) occurring at ≥3% frequency in the elinzanetant arm and greater than the placebo arm are presented in Table 53. The most commonly occurring AEs included headache, fatigue, somnolence, abdominal pain, diarrhea, and dizziness.

Table 53. Subjects With Common Adverse Events Occurring at ≥3% Frequency in Elinzanetant and Greater Than Placebo, OASIS 3

Adverse Reaction	Elinzanetant (N=313) n (%)	Placebo (N=314) n (%)
Headache	30 (9.6)	22 (7.0)
Fatigue	23 (7.3)	9 (2.9)
Somnolence	16 (5.1)	4 (1.3)
Abdominal pain	14 (4.5)	8 (2.5)
Diarrhea	12 (3.8)	3 (1.0)
Dizziness	12 (3.8)	5 (1.6)
Influenza	12 (3.8)	10 (3.2)
Arthralgia	12 (3.8)	11 (3.5)
Hypertension	11 (3.5)	9 (2.9)
Rash	10 (3.2)	4 (1.3)
Muscle spasms	10 (3.2)	2 (0.6)

Source: adae.xpt; Software: R
Fatigue contains fatigue and asthenia
Abdominal pain contains abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper.
Muscle spasms contains Muscle spasms and muscle tightness.
Confidence interval for risk difference is calculated by Miettinen and Nurminen method.
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Analysis of AE by system organ class and OCMQ (narrow) identified the following events that occurred in a higher percentage of the elinzanetant compared to the placebo group (Table 54):

- Palpitations (cardiac disorders SOC), 5 cases (1.6%) versus 0;
- Vertigo (ear and labyrinth disorders SOC), 7 cases (2.2%) versus 1 (0.3%);
- Diarrhea (GI disorders SOC), 12 cases (3.8%) versus 4 (1.3%);
- Fatigue (general disorders SOC), 24 cases (7.7%) versus 9 (2.9%);
- Dizziness (general disorders SOC), 19 (6.1%) versus 6 (1.9%);
- Somnolence (Nervous system disorders SOC), 17 cases (5.4%) versus 4 (1.3%);
- Study agent abuse potential (psychiatric disorders SOC), 16 cases (5.1%) versus 4 (1.3%); and
- Rash (skin and connective tissue disorders SOC), 14 cases (4.5%) versus 5 (1.6%).

Table 54. Subjects With Adverse Events by System Organ Class and OCMQ (Narrow), Safety Population, OASIS 3

System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Blood and lymphatic system disorders (SOC)						
Anemia	3 (1.0)	2 (0.6)	0.3 (-1.4, 2.2)	3/257.7 (1.2)	2/262 (0.8)	0.4 (-1.7, 2.7)
Leukopenia	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/262.8 (0.4)	-0.4 (-2.2, 1.1)
Cardiac disorders (SOC)						
Palpitations	5 (1.6)	0	1.6 (0.4, 3.7) *	5/256.5 (1.9)	0/263.6 (0)	1.9 (0.5, 4.6)*
Systemic hypertension	13 (4.2)	11 (3.5)	0.7 (-2.5, 3.9)	13/251.2 (5.2)	11/255.2 (4.3)	0.9 (-3.2, 5.0)
Acute coronary syndrome	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Myocardial infarction	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Myocardial ischemia	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Arrhythmia	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.2 (0.4)	1/262.8 (0.4)	0.0 (-1.8, 1.8)
Tachycardia	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.2 (0.4)	1/262.8 (0.4)	0.0 (-1.8, 1.8)
Ear and labyrinth disorders (SOC)						
Vertigo	7 (2.2)	1 (0.3)	1.9 (0.2, 4.3) *	7/255 (2.7)	1/263.1 (0.4)	2.4 (0.3, 5.3)*
Endocrine disorders (SOC)						
Hyperglycemia	5 (1.6)	3 (1.0)	0.6 (-1.4, 2.8)	5/255.9 (2.0)	3/261 (1.1)	0.8 (-1.7, 3.6)
Hyperprolactinemia	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.9 (0.4)	1/262.7 (0.4)	0.0 (-1.8, 1.8)
Gastrointestinal disorders (SOC)						
Diarrhea	12 (3.8)	4 (1.3)	2.6 (0.1, 5.5) *	12/252.5 (4.8)	4/261.7 (1.5)	3.2 (0.2, 6.9)*
Abdominal pain	14 (4.5)	8 (2.5)	1.9 (-1.0, 5.1)	14/252.9 (5.5)	8/259.9 (3.1)	2.5 (-1.2, 6.5)
Dry mouth	6 (1.9)	2 (0.6)	1.3 (-0.6, 3.6)	6/254.8 (2.4)	2/261.7 (0.8)	1.6 (-0.7, 4.5)
Dyspepsia	17 (5.4)	14 (4.5)	1.0 (-2.5, 4.6)	17/250.1 (6.8)	14/256.2 (5.5)	1.3 (-3.2, 6.0)
Pancreatitis	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.8 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Constipation	7 (2.2)	7 (2.2)	0.0 (-2.6, 2.6)	7/254.6 (2.7)	7/258.9 (2.7)	0.0 (-3.2, 3.3)
Vomiting	1 (0.3)	2 (0.6)	-0.3 (-2.0, 1.2)	1/258.4 (0.4)	2/263 (0.8)	-0.4 (-2.4, 1.5)
Nausea	9 (2.9)	11 (3.5)	-0.6 (-3.6, 2.3)	9/253.7 (3.5)	11/258.7 (4.3)	-0.7 (-4.5, 3.0)

System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
General disorders and administration site conditions (SOC)						
Fatigue	24 (7.7)	9 (2.9)	4.8 (1.4, 8.6) *	24/246.4 (9.7)	9/258.7 (3.5)	6.3 (1.9, 11.3) *
Dizziness	19 (6.1)	6 (1.9)	4.2 (1.2, 7.6) *	19/249.3 (7.6)	6/259.7 (2.3)	5.3 (1.6, 9.8) *
Peripheral edema	6 (1.9)	3 (1.0)	1.0 (-1.1, 3.3)	6/255.5 (2.3)	3/261.9 (1.1)	1.2 (-1.3, 4.1)
Pyrexia	2 (0.6)	2 (0.6)	0.0 (-1.7, 1.7)	2/257.3 (0.8)	2/263.4 (0.8)	0.0 (-2.1, 2.1)
Decreased appetite	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/262.7 (0.4)	-0.4 (-2.2, 1.1)
Hepatobiliary disorders (SOC)						
Hepatic injury	5 (1.6)	6 (1.9)	-0.3 (-2.7, 2.0)	5/257.7 (1.9)	6/259.7 (2.3)	-0.4 (-3.3, 2.5)
Cholecystitis	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/262.7 (0.4)	-0.4 (-2.2, 1.1)
Immune system disorders (SOC)						
Hypersensitivity	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.8 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Infections and infestations (SOC)						
Fungal infection	8 (2.6)	3 (1.0)	1.6 (-0.5, 4.1)	8/255.4 (3.1)	3/261.3 (1.1)	2.0 (-0.6, 5.2)
Pneumonia	1 (0.3)	2 (0.6)	-0.3 (-2.0, 1.2)	1/258.2 (0.4)	2/262.1 (0.8)	-0.4 (-2.4, 1.5)
Purulent material	0	3 (1.0)	-1.0 (-2.8, 0.3)	0/259 (0)	3/261.8 (1.1)	-1.1 (-3.4, 0.3)
Bacterial infection	21 (6.7)	26 (8.3)	-1.6 (-5.8, 2.6)	21/249.7 (8.4)	26/246.5 (10.5)	-2.1 (-7.9, 3.4)
Viral infection	42 (13.4)	48 (15.3)	-1.9 (-7.4, 3.7)	42/235.2 (17.9)	48/236.4 (20.3)	-2.5 (-10.5, 5.6)
Nasopharyngitis	23 (7.3)	39 (12.4)	-5.1 (-9.9, -0.4)*	23/248.3 (9.3)	39/241.9 (16.1)	-6.9 (-13.6, -0.6)*
Metabolism and nutrition disorders (SOC)						
Lipid disorder	2 (0.6)	3 (1.0)	-0.3 (-2.2, 1.4)	2/257.7 (0.8)	3/261.2 (1.1)	-0.4 (-2.7, 1.8)
Musculoskeletal and connective tissue disorders (SOC)						
Tendinopathy	7 (2.2)	2 (0.6)	1.6 (-0.3, 4.0)	7/254.7 (2.7)	2/262.2 (0.8)	2.0 (-0.4, 5.0)
Fracture	7 (2.2)	5 (1.6)	0.6 (-1.7, 3.1)	7/257.3 (2.7)	5/260.8 (1.9)	0.8 (-2.1, 3.9)
Myalgia	4 (1.3)	2 (0.6)	0.6 (-1.2, 2.7)	4/258.1 (1.5)	2/262.9 (0.8)	0.8 (-1.4, 3.3)
Arthralgia	12 (3.8)	11 (3.5)	0.3 (-2.8, 3.5)	12/251.5 (4.8)	11/258.6 (4.3)	0.5 (-3.4, 4.6)
Osteoporosis	3 (1.0)	2 (0.6)	0.3 (-1.4, 2.2)	3/258.3 (1.2)	2/262.2 (0.8)	0.4 (-1.7, 2.7)
Arthritis	7 (2.2)	8 (2.5)	-0.3 (-3.0, 2.3)	7/255.7 (2.7)	8/260.3 (3.1)	-0.3 (-3.7, 2.9)
Back pain	10 (3.2)	12 (3.8)	-0.6 (-3.7, 2.4)	10/253.4 (3.9)	12/257 (4.7)	-0.7 (-4.7, 3.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)						
Malignancy	2 (0.6)	2 (0.6)	0.0 (-1.7, 1.7)	2/258.9 (0.8)	2/262.4 (0.8)	0.0 (-2.1, 2.1)

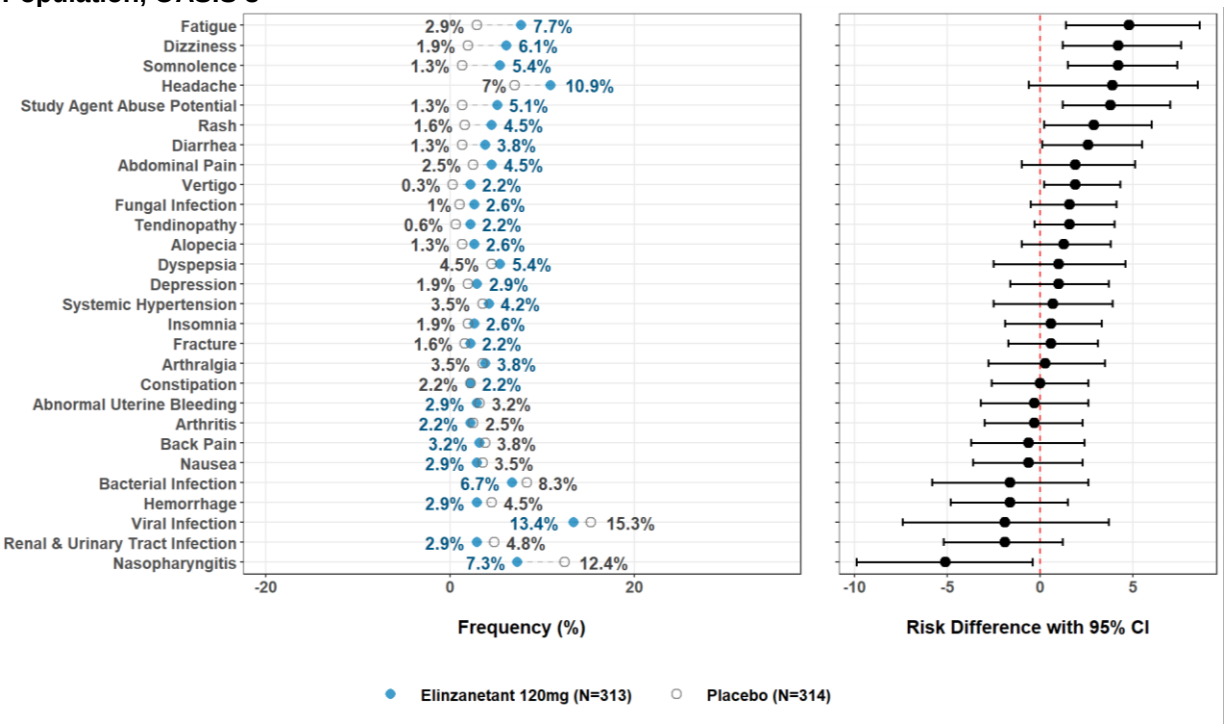
System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Nervous system disorders (SOC)						
Somnolence	17 (5.4)	4 (1.3)	4.2 (1.5, 7.4)*	17/247.7 (6.9)	4/261.2 (1.5)	5.3 (2.0, 9.6)*
Headache	34 (10.9)	22 (7.0)	3.9 (-0.6, 8.5)	34/242.2 (14.0)	22/247.4 (8.9)	5.1 (-0.9, 11.5)
Paresthesia	5 (1.6)	2 (0.6)	1.0 (-0.9, 3.1)	5/256.8 (1.9)	2/262.2 (0.8)	1.2 (-1.0, 3.9)
Syncope	2 (0.6)	0	0.6 (-0.6, 2.3)	2/257.9 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Confusional state	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Stroke and TIA	1 (0.3)	0	0.3 (-0.9, 1.8)	1/258.9 (0.4)	0/263.6 (0)	0.4 (-1.1, 2.2)
Dysgeusia	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Psychiatric disorders (SOC)						
Study agent abuse potential	16 (5.1)	4 (1.3)	3.8 (1.2, 7.0)*	16/247.7 (6.5)	4/261.2 (1.5)	4.9 (1.6, 9.1)*
Depression	9 (2.9)	6 (1.9)	1.0 (-1.6, 3.7)	9/256.3 (3.5)	6/259.7 (2.3)	1.2 (-2.0, 4.6)
Insomnia	8 (2.6)	6 (1.9)	0.6 (-1.9, 3.3)	8/253.7 (3.2)	6/260.9 (2.3)	0.9 (-2.3, 4.2)
Self-harm	2 (0.6)	1 (0.3)	0.3 (-1.2, 2.0)	2/258.6 (0.8)	1/262.7 (0.4)	0.4 (-1.4, 2.5)
Anxiety	6 (1.9)	6 (1.9)	0.0 (-2.4, 2.4)	6/256.2 (2.3)	6/260.8 (2.3)	0.0 (-3.0, 3.1)
Irritability	2 (0.6)	2 (0.6)	0.0 (-1.7, 1.7)	2/257.5 (0.8)	2/261.9 (0.8)	0.0 (-2.1, 2.1)
Renal and urinary disorders (SOC)						
Urinary retention	1 (0.3)	1 (0.3)	0.0 (-1.5, 1.5)	1/258.8 (0.4)	1/262.9 (0.4)	0.0 (-1.8, 1.8)
Renal & urinary tract infection	9 (2.9)	15 (4.8)	-1.9 (-5.2, 1.2)	9/254.7 (3.5)	15/255 (5.9)	-2.3 (-6.6, 1.5)
Reproductive system and breast disorders (SOC)						
Sexual dysfunction	6 (1.9)	2 (0.6)	1.3 (-0.6, 3.6)	6/255.3 (2.4)	2/262.5 (0.8)	1.6 (-0.7, 4.5)
Bacterial vaginosis	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.4 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Abnormal uterine bleeding	9 (2.9)	10 (3.2)	-0.3 (-3.2, 2.6)	9/252.7 (3.6)	10/258.1 (3.9)	-0.3 (-4.0, 3.3)
Respiratory, thoracic and mediastinal disorders (SOC)						
Cough	5 (1.6)	3 (1.0)	0.6 (-1.4, 2.8)	5/256 (2.0)	3/262.2 (1.1)	0.8 (-1.6, 3.6)
Dyspnea	2 (0.6)	0	0.6 (-0.6, 2.3)	2/257.8 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Bronchospasm	2 (0.6)	3 (1.0)	-0.3 (-2.2, 1.4)	2/258.7 (0.8)	3/262.5 (1.1)	-0.4 (-2.7, 1.8)
Respiratory failure	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)

System Organ Class OCMQ (Narrow)	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)	Elinzanetant 120 mg PY =259 (N=313) n/py (EAIR)	Placebo PY =263.6 (N=314) n/py (EAIR)	EAIR Difference (95% CI)
Skin and subcutaneous tissue disorders (SOC)						
Rash	14 (4.5)	5 (1.6)	2.9 (0.2, 6.0)*	14/252.3 (5.5)	5/260.9 (1.9)	3.6 (0.3, 7.6)*
Alopecia	8 (2.6)	4 (1.3)	1.3 (-1.0, 3.8)	8/253.5 (3.2)	4/260.4 (1.5)	1.6 (-1.2, 4.9)
Pruritus	3 (1.0)	2 (0.6)	0.3 (-1.4, 2.2)	3/256.5 (1.2)	2/261.6 (0.8)	0.4 (-1.7, 2.8)
Urticaria	2 (0.6)	2 (0.6)	0.0 (-1.7, 1.7)	2/257.5 (0.8)	2/262.1 (0.8)	0.0 (-2.1, 2.1)
Erythema	0	1 (0.3)	-0.3 (-1.8, 0.9)	0/259 (0)	1/263.5 (0.4)	-0.4 (-2.1, 1.1)
Vascular disorders (SOC)						
Thrombosis	3 (1.0)	0	1.0 (-0.3, 2.8)	3/258.8 (1.2)	0/263.6 (0)	1.2 (-0.3, 3.4)
Hypotension	2 (0.6)	0	0.6 (-0.6, 2.3)	2/257.7 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Thrombosis arterial	2 (0.6)	0	0.6 (-0.6, 2.3)	2/258.8 (0.8)	0/263.6 (0)	0.8 (-0.7, 2.8)
Hemorrhage	9 (2.9)	14 (4.5)	-1.6 (-4.8, 1.5)	9/253.1 (3.6)	14/257.4 (5.4)	-1.9 (-6.0, 2.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks
For specific preferred terms under each OCMQ, see the table “Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OCMQ.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query; PT, preferred term; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class; TIA, transient ischemic attack

The data (frequency and risk difference with 95% CI) for AE occurrence in ≥2% of exposed cases in any treatment arm by OCMQ (narrow) are shown in Figure 22. The results highlight the highest risk difference for fatigue, dizziness, somnolence, headache, study agent drug abuse potential, rash, and diarrhea.

Figure 22. Subjects With Adverse Events ≥2% in Any Treatment Arm by OCMQ (Narrow), Safety Population, OASIS 3



Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Abbreviations: N, number of subjects in treatment arm; OCMQ, OND custom medical query

Additional OCMQ (narrow) analyses were performed for fatigue, dizziness, somnolence, study agent abuse potential, rash, and diarrhea. An assessment of fatigue, dizziness, and somnolence is included in Section 7.6.3. The results for study agent abuse potential, rash, and diarrhea are discussed below.

Study Agent Abuse Potential

The study agent abuse potential OCMQ (narrow) was made up of only one PT: somnolence, which occurred in a higher percentage of subjects in the elinzanetant group (5.1%) compared to the placebo group (1.3%). See Section 7.6.3.6 for further discussion of somnolence.

Rash

The rash OCMQ (narrow) was made up of the following PTs: acne, dermatitis, rash, and urticaria, all of which occurred in a higher percentage of subjects in the elinzanetant group compared to the placebo group, except for urticaria, which occurred in an equal percentage of subjects in both groups (0.6%) (Table 55). There was one AE of rash that was not initially

reported by the investigator. The event occurred on Day 92 of treatment with elinzanetant and was mild in intensity and was considered related to study intervention by the investigator. No action was taken with study drug.

All of the events were mild to moderate severity. In the elinzanetant group, 0.6% of subjects discontinued due to rash OCMQ adverse events compared to 0% of subjects in the placebo group.

Two subjects discontinued due to an adverse event with a PT of rash.

(1) Subject (b) (6) was a 53-year-old woman who developed a mild rash 21 days after starting elinzanetant, for which she discontinued the drug. She also had AEs of dry skin and gastroesophageal reflux disease. The rash did not itch and was from the lower legs to the knees and was felt to be related to study intervention.

(2) Subject (b) (6) was a 51-year-old woman who developed a mild rash 74 days after starting elinzanetant. The AE was not felt to be related to study intervention.

Table 55. Adverse Events Assessment of Rash OCMQ (Narrow), Safety Population, OASIS 3

OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)
Rash (OCMQ)	14 (4.5)	5 (1.6)
Acne	1 (0.3)	0
Dermatitis	1 (0.3)	0
Rash	10 (3.2)	4 (1.3)
Urticaria	2 (0.6)	2 (0.6)
Maximum severity		
Death	0	0
Life-threatening	0	0
Severe	0	0
Moderate	1 (0.3)	1 (0.3)
Mild	13 (4.2)	4 (1.3)
Serious	0	0
Deaths	0	0
Resulting in discontinuation	2 (0.6)	0
Relatedness	5 (1.6)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Relatedness is determined by the investigator.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

Diarrhea

The diarrhea OCMQ (narrow) was made up of the following PTs: diarrhea and norovirus infection (one case in a subject in the placebo group). The imbalance for the diarrhea OCMQ was similar to what was seen when evaluating the diarrhea PTs (3.8% for the elinzanetant group versus 1% for the placebo group). All of the events in the elinzanetant group were mild to

moderate severity. As noted in Section 7.1.3, there were GI-related signals in the nonclinical studies, including diarrhea. Information regarding diarrhea will be included in the USPI.

Additional Analyses

The safety results were evaluated for AEs by system organ class and OCMQ (broad approach). In general, these analyses were consistent with other safety analyses. Imbalances were reviewed in the OCMQs (broad) for arrythmia, palpitations, vertigo, diarrhea, fatigue, fall, dizziness, opportunistic infection, opportunistic infection, myalgia, somnolence, confusional state, syncope, and study agent abuse potential. Review of PTs and OCMQs (narrow) did not show any new safety considerations not previously identified. The reviewers performed an in-depth analysis of potential cases of syncope which is further discussed in Section 7.6.3.

Labeling Considerations

For the label, the Applicant agreed to display adverse event information combining similar preferred terms to clarify the safety information given that there was some splitting of similar preferred terms. An overview of common adverse reactions in OASIS 3 (with similar preferred terms combined) reported in at least 2% of subjects treated with elinzanetant and greater than placebo is shown in Table 56.

Table 56. Common Adverse Reactions Reported in ≥2% in Elinzanetant and Greater than Placebo, Weeks 1-52 (OASIS 3)

Adverse Reaction	Elinzanetant (N=313) n (%)	Placebo (N=314) n (%)
Headache	30 (9.6)	22 (7.0)
Fatigue*	23 (7.3)	9 (2.9)
Dizziness†	19 (6.1)	6 (1.9)
Somnolence‡	16 (5.1)	4 (1.3)
Abdominal pain§	14 (4.5)	8 (2.5)
Rash¶	13 (4.2)	5 (1.6)
Diarrhea	12 (3.8)	3 (1.0)
Muscle spasms#	10 (3.2)	2 (0.6)

Source: Applicant's proposed USPI, submitted October 15, 2025
*Includes asthenia.
†Includes balance disorder, presyncope, vertigo, vertigo CNS origin, vertigo positional, and vestibular neuronitis.
‡Includes lethargy.
§Includes abdominal discomfort, abdominal pain lower/upper.
¶Includes dermatitis, urticaria.
#Includes muscle tightness.

7.6.2.6. Laboratory Studies, OASIS 3

In OASIS 3, no relevant trends were observed for any laboratory parameter based on descriptive summary statistics. None of the hematology, general chemistry, coagulation, hormone, vitamin, and urinalysis parameters displayed substantial changes over time or differences between treatment arms were observed (see CSR PH42784, Section 8.3.5). Similar to OASIS 1 and OASIS 2, a slight increase in the mean value of sex hormone-binding globulin was observed in the elinzanetant 120 mg arm.

Mean change from baseline for serum leukocytes, hemoglobin, platelets, eosinophils, lymphocytes, neutrophils, red blood cells, coagulation parameters (i.e., prothrombin time, and activated partial thromboplastin) showed no differences throughout the study period (52 weeks) comparing elinzanetant versus placebo groups. See Table 57 for selected analytes. See Section 7.6.3.3 for discussion of laboratory studies associated with hepatic safety.

Table 57. Selected Laboratory Data for Comparison Between Treatment Arms, OASIS 3

	Change From Baseline to Week 52 (Mean ± SD)	
Selected Laboratory Data	**Elinzanetant (N=313)***	**Placebo (N=313)***
Leukocytes (%)	-0.95 (6.92)	0.44 (7.30)
Lymphocytes (Giga/L)	-0.028 (0.396)	0.004 (0.429)
Hematocrit (%)	-0.37 (2.96)	-0.24 (3.38)
Hemoglobin (g/dL)	-0.07 (0.74)	0.01 (0.93)
Creatine kinase (U/L)	12.2 (100.5)	17.2 (218.1)

Source: compiled by reviewer from Section 8.3.5, Clinical study report for OASIS 3
*There were 313 subjects at baseline in each treatment group. At 52 weeks, there were 238 samples from the elinzanetant group and 235 samples from the placebo group
Abbreviations: N, number of subjects in treatment arm; SD, standard deviation

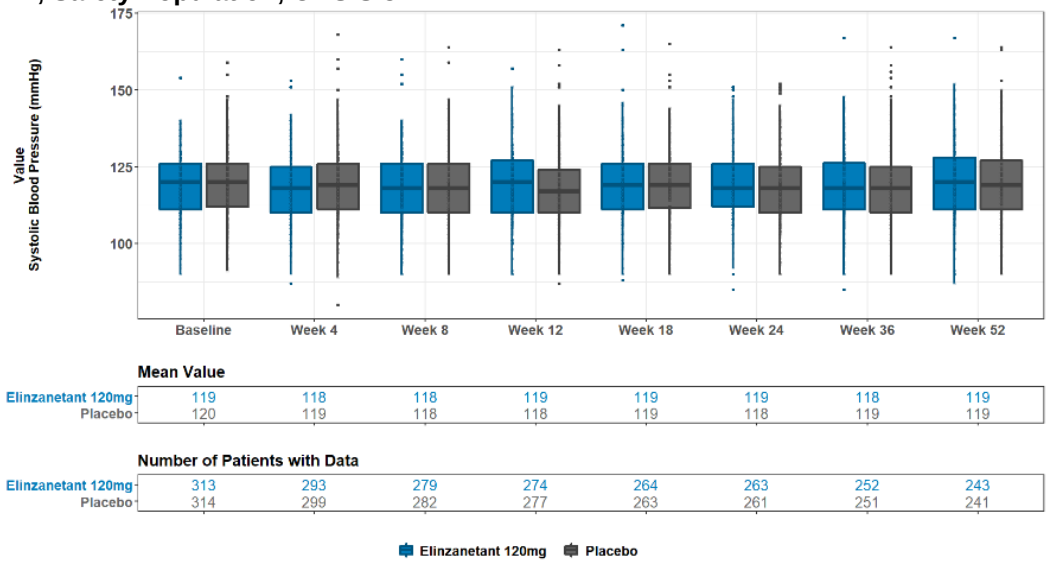
No differences were observed for data of subjects with one or more chemistry analyte levels with elevated or low values. Analytes examined were sodium, potassium, chloride, bicarbonate, glucose, calcium, magnesium, phosphate, protein, albumin, CPK, amylase, lipase, and urea nitrogen. No differences were observed for these values comparing elinzanetant and placebo groups (Source: adlb.xpt; Software: R).

Kidney function (measured as creatinine serum levels), liver function tests, or serum lipids, did not change over time from baseline to end of study when comparing elinzanetant versus placebo groups.

7.6.2.7. Vital Signs, OASIS 3

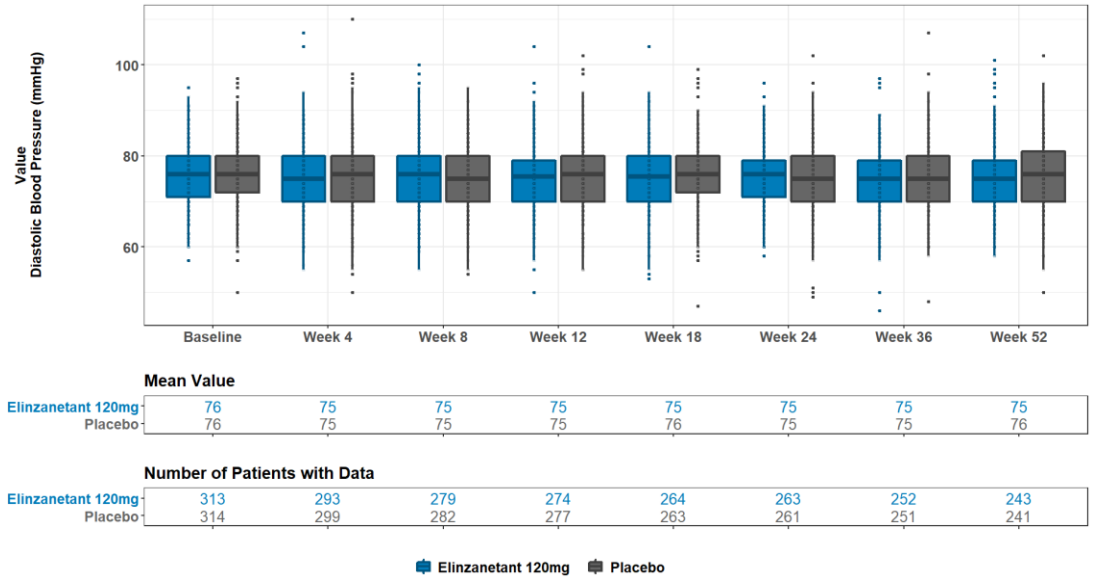
There were no clinically meaningful changes in vital sign measurements during OASIS 3. The median and interquartile range of systolic blood pressure, diastolic blood pressure, and pulse, over time by treatment arm are shown in Figure 23, Figure 24, and Figure 25, respectively. No differences were found for any parameters over the 52-week study. There were no differences between elinzanetant and placebo groups in terms of the percentage of subjects with maximum systolic blood pressure, maximum diastolic blood pressure, or hypotension. See Section 7.6.3.6 for additional discussion of hypotension and syncope.

Figure 23. Median and Interquartile Range of Systolic Blood Pressure Over Time by Treatment Arm, Safety Population, OASIS 3



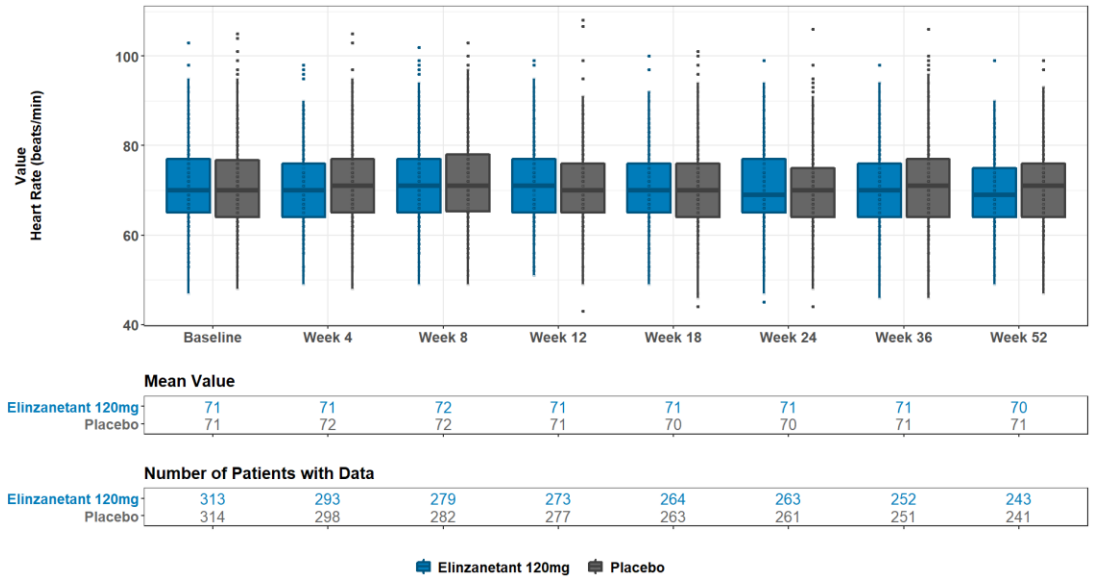
Source: advs.xpt; Software: R
Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

Figure 24. Median and Interquartile Range of Diastolic Blood Pressure Over Time by Treatment Arm, Safety Population, OASIS 3



Source: advs.xpt; Software: R
Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

Figure 25. Median and Interquartile Range of Pulse Rate Over Time by Treatment Arm, Safety Population, OASIS 3



Source: advs.xpt; Software: R
Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.

7.6.2.8. Assessment of Drug-Induced Liver Injury, OASIS 3

Please refer to Section 7.6.3 for a review of this adverse event of special interest.

7.6.2.9. Subgroup Analyses by Baseline Characteristics, OASIS 3

The percentage of subjects with adverse events by demographic subgroup was balanced between treatment arms, with no relevant differences in ethnicity, race, weight, height, or BMI (Table 58). There was a trend towards an increased percentage of subjects with adverse events in the elinzanetant group with increasing age, but the differences were small and of unclear clinical significance. Proportions of subgroups for the different variables were similar to those of the general safety population.

Table 58. Overview of Adverse Events by Demographic Subgroup, Safety Population, OASIS 3

Characteristic	Elinzanetant 120 mg (N=313) n/N_s (%)	Placebo (N=314) n/N_s (%)
Sex		
Female	219/313 (70.0)	192/314 (61.1)
Age group, years		
40 to 49	30/46 (65.2)	23/43 (53.5)
50 to 59	149/211 (70.6)	137/212 (64.6)
60 to 65	40/56 (71.4)	32/59 (54.2)

Characteristic	Elinzanetant 120 mg (N=313) n/N_s (%)	Placebo (N=314) n/N_s (%)
Race		
Asian	2/2 (100)	2/2 (100)
Black or African American	25/50 (50.0)	25/44 (56.8)
Multiple	0/0 (NA)	0/1 (0)
Native Hawaiian or Other Pacific Islander	1/1 (100)	0/0 (NA)
Not reported	18/19 (94.7)	14/15 (93.3)
White	173/241 (71.8)	151/252 (59.9)
Ethnicity		
Hispanic or Latino	30/35 (85.7)	27/33 (81.8)
Not Hispanic or Latino	178/265 (67.2)	161/273 (59.0)
Not reported	11/13 (84.6)	4/8 (50.0)
Is in United States		
United States	74/115 (64.3)	74/129 (57.4)
Not United States	145/198 (73.2)	118/185 (63.8)

Source: adae.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup that were assigned to that specific arm

7.6.3. Adverse Events of Special Interest

For the clinical program, the adverse events of special interest included abuse potential, bone safety, hepatic safety, endometrial safety, cardiac safety, nervous system disorders, fractures, driving ability, and breast safety.

7.6.3.1. Abuse Potential

The Controlled Substance Staff evaluated abuse-related preclinical and clinical data submitted by the Applicant.

The Controlled Substance Staff concluded that elinzanetant appears to be selective for NK1 and NK3 receptors and does not bind with significant affinity to receptor subtypes or targets associated with abuse potential. In nonclinical assessments, elinzanetant was not self-administered by nonhuman primates, suggesting a lack of reinforcing effects and negligible potential for abuse. In nonclinical assessments of physical dependence in nonhuman primates, elinzanetant did not produce a withdrawal syndrome upon discontinuation after 30 days of administration. Elinzanetant did not function as discriminative stimulus in trained nonhuman primates, further supporting its low abuse potential.

In clinical studies, elinzanetant showed no significant abuse potential or risk of physical dependence, as potential abuse-related adverse events were mostly limited to somnolence and dizziness, were self-resolving, and lacked euphoria or other effects attractive to recreational drug users, aligning with nonclinical data.

These data suggest elinzanetant has no, or negligible, potential for abuse.

7.6.3.2. Bone Safety

In OASIS 3, the effect of elinzanetant on BMD was assessed by dual-energy X-ray absorptiometry in 343 women. At baseline, the mean BMD values of the lumbar spine, total hip, and femoral neck were similar in both groups. At Week 52, the mean BMD values numerically decreased at all anatomical sites in both groups. At Week 52, the mean BMD values numerically decreased by <0.01% to 0.7% at all anatomical sites in the elinzanetant treatment group compared to decreases of 1.2% to 1.4% in the placebo group. In both groups, the mean percentage changes in BMD were within the expected age-related loss per year.

7.6.3.3. Hepatic Safety (Drug-Induced Liver Injury)

Elinzanetant inhibits NK1 and NK3 receptors. The clinical program included monitoring for drug induced liver injury as nonclinical data suggested hepatoxicity risk and there were elevated liver enzymes seen in Phase 1 and Phase 2 studies. In May 2023, fezolinetant, another oral NK3 inhibitor, was approved under NDA 216578 for the same indication as elinzanetant. At the time of approval, fezolinetant's labeling had a Warning and Precaution for hepatic transaminase elevation, which was updated with a Boxed Warning based on postmarket cases of DILI leading to jaundice. Given these considerations, hepatic safety was an adverse event of special interest in the elinzanetant program.

Hepatic Safety: Laboratory Data (OASIS, 1, OASIS 2, and OASIS 3)

In the Phase 2b and three Phase 3 studies, there were no cases meeting aminotransferase and total bilirubin criteria for Hy's law.

In OASIS 1, there was a slightly higher percentage of subjects in the elinzanetant group (1%) with ALT >3xULN compared to the placebo group (0.5%) (Table 59). In OASIS 3, this difference was slightly larger (Table 61). This difference did not persist at the ALT >5xULN cut-off and was not seen in OASIS 2 (Table 60).

Table 59. Frequency of Liver Blood Test Elevations Between Elinzanetant and Placebo Groups, OASIS 1

Laboratory Abnormality	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Risk Difference (%) (95% CI)
ALT			
≥1xULN	28/197 (14.2)	39/188 (20.7)	-6.5 (-14.2, 1.1)
≥3xULN	2/197 (1.0)	1/188 (0.5)	0.5 (-2.0, 3.2)
≥5xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
≥10xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
≥20xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
AST			
≥1xULN	21/197 (10.7)	25/188 (13.3)	-2.6 (-9.3, 3.9)
≥3xULN	2/197 (1.0)	0/188 (0)	1.0 (-1.0, 3.6)
≥5xULN	0/197 (0)	0/188 (0)	0 (-2.0, 1.9)
≥10xULN	0/197 (0)	0/188 (0)	0 (-2.0, 1.9)
≥20xULN	0/197 (0)	0/188 (0)	0 (-2.0, 1.9)

Laboratory Abnormality	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Risk Difference (%) (95% CI)
ALP			
≥2xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
≥3xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
Total bilirubin			
≥2xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
≥5xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
≥8xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
Direct bilirubin			
≥2xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
≥5xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
GGT			
≥2xULN	7/197 (3.6)	10/188 (5.3)	-1.8 (-6.4, 2.5)
INR			
≥1.5xULN	0/197 (0)	2/188 (1.1)	-1.1 (-3.8, 0.9)
≥3xULN	0/197 (0)	1/188 (0.5)	-0.5 (-3.0, 1.4)
≥5xULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)

Source: adlb.xpt; Software: R; Generated by: CDS
The frequency represented here are based on peak levels. Appropriate cutoff for liver biochemistries should be adjusted based on the study population (e.g., pediatric population, those with underlying liver disease etc.). For subjects with chronic liver disease, cutoff should be established using multiples of baseline (e.g., 2X, 3X, SX).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, international normalized ratio; N, number of subjects in group; n, number of subjects meeting criteria; ULN, upper level of normal

Table 60. Frequency of Liver Blood Test Elevations Between Elinzanetant and Placebo Groups, OASIS 2

Laboratory Abnormality	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Risk Difference (%) (95% CI)
ALT			
≥1xULN	37/197 (18.8)	46/195 (23.6)	-4.8 (-12.9, 3.3)
≥3xULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥5xULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥10xULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥20xULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
AST			
≥1xULN	21/199 (10.6)	25/195 (12.8)	-2.3 (-8.8, 4.2)
≥3xULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥5xULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥10xULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥20xULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
ALP			
≥2xULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥3xULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
Total bilirubin			
≥2xULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥5xULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥8xULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
Direct bilirubin			
≥2xULN	1/197 (0.5)	0/195 (0)	0.5 (-1.4, 2.8)
≥5xULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)

Laboratory Abnormality	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Risk Difference (%) (95% CI)
GGT			
≥2xULN	5/199 (2.5)	6/195 (3.1)	-0.6 (-4.4, 3.1)
INR			
≥1.5xULN	1/198 (0.5)	0/195 (0)	0.5 (-1.4, 2.8)
≥3xULN	0/198 (0)	0/195 (0)	0.0 (-1.9, 1.9)
≥5xULN	0/198 (0)	0/195 (0)	0.0 (-1.9, 1.9)

Source: adlb.xpt; Software: R; Generated by: CDS
The frequency represented here are based on peak levels. Appropriate cutoff for liver biochemistries should be adjusted based on the study population (e.g., pediatric population, those with underlying liver disease etc.). For subjects with chronic liver disease, cutoff should be established using multiples of baseline (e.g., 2X, 3X, SX).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, international normalized ratio; N, number of subjects in group; n, number of subjects meeting criteria; ULN, upper level of normal

Table 61. Frequency of Liver Blood Test Elevations Between Elinzanetant and Placebo Groups, OASIS 3

Laboratory Abnormality	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference (%) (95% CI)
ALT			
≥1xULN	87/307 (28.3)	113/305 (37.0)	-8.7 (-16.1, -1.3)*
≥3xULN	7/307 (2.3)	5/305 (1.6)	0.6 (-1.8, 3.2)
≥5xULN	1/307 (0.3)	2/305 (0.7)	-0.3 (-2.1, 1.2)
≥10xULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
≥20xULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
AST			
≥1xULN	68/307 (22.1)	80/305 (26.2)	-4.1 (-10.9, 2.7)
≥3xULN	3/307 (1.0)	4/305 (1.3)	-0.3 (-2.5, 1.7)
≥5xULN	0/307 (0)	1/305 (0.3)	-0.3 (1.8, 0.9)
≥10xULN	0/307 (0)	0/305	0.0 (-1.2, 1.2)
≥20xULN	0/307 (0)	0/305	0.0 (-1.2, 1.2)
ALP			
≥2xULN	2/307 (0.7)	2/305 (0.7)	-0.0 (-1.8, 1.8)
≥3xULN	1/307 (0.3)	1/305 (0.3)	-0.0 (-1.5, 1.5)
Total bilirubin			
≥2xULN	1/307 (0.3)	0/305 (0)	0.3 (-0.9, 1.8)
≥5xULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
≥8xULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
Direct bilirubin			
≥2xULN	0/307 (0)	1/305 (0.3)	-0.3 (-1.8, 0.9)
≥5xULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
GGT			
≥2xULN	19/307 (16.2)	24/305 (7.9)	-1.7 (-5.9, 2.5)

Laboratory Abnormality	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference (%) (95% CI)
INR			
≥1.5xULN	2/308 (0.6)	7/305 (2.3)	-1.6 (-4.1, 0.3)
≥3xULN	0/308 (0)	3/305 (1.0)	-1.0 (-2.9, 0.3)
≥5xULN	0/308 (0)	0/305 (0)	0.0 (-1.2, 1.2)

Source: adlb.xpt; Software: R; Generated by: CDS
The frequency represented here are based on peak levels. Appropriate cutoff for liver biochemistries should be adjusted based on the study population (e.g., pediatric population, those with underlying liver disease etc.). For subjects with chronic liver disease, cutoff should be established using multiples of baseline (e.g., 2X, 3X, SX).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, international normalized ratio; N, number of subjects in group; n, number of subjects meeting criteria; ULN, upper level of normal

Close liver observation (CLO**)** of subjects with abnormal liver function tests was instituted upon findings ALT and/or AST >3xULN or AP >2xULN and confirmed at retest.

In OASIS 1, there were two cases triggering CLO reported in the elinzanetant 120 mg arm. The causality was assessed as unlikely by the Liver Safety Monitoring Board (LSMB) and an alternative etiology was documented for both cases.

(1) Subject (b) (6) was a 55-year-old woman who had elevated liver function tests 1 day after starting elinzanetant on (b) (6) (AST 106 U/L [3.03xULN] and ALT 73 U/L [2.09xULN]), which the investigator considered nonserious. Alkaline phosphatase 83 U/L [0.80xULN] and total bilirubin 0.3 mg/dL [0.24xULN] were within reference ranges. The investigator considered this event to be mild in intensity, not related to study intervention, and not related to protocol-required procedures. The subject had a history of hepatic steatosis. None of the medications that she was taking were considered relevant to the current liver event.

The ALT and AST test results returned to baseline levels. The CLO was stopped on (b) (6) because the subject was confirmed to have clinical diagnosis of nonalcoholic steatohepatitis. The subject's study drug was interrupted for 5 days and on Day 6 of interruption study drug treatment was restarted and continued to the end of treatment. Additionally, the investigator provided the following comment: "Drug interrupted per PI due to elevated LFTs. Subject had liver ultrasound on (b) (6) Findings: diffusely echogenic liver parenchyma, normal liver size, normal hepatic blood flow, no masses." The subject received the last dose of study intervention on (b) (6). Study intervention was completed by the subject as per protocol. Given the rapid increase in AST and ALT just one day after starting medication and the lack of recurrence of laboratory abnormalities with rechallenge, it does not appear that this event was secondary to elinzanetant.

(1) Subject (b) (6) was a 59-year-old woman who developed an elevated AST on (b) (6) 71 days after starting elinzanetant. She was reported with an increased ALT (reported term: elevated ALT) (AST 134 U/L [3.83xULN] and ALT 108 U/L [3.09xULN]), which the investigator considered nonserious. AP 98 U/L and total bilirubin 1.09 mg/dL were

within reference ranges. The investigator considered this event to be mild in intensity, not related to study intervention, and not related to protocol-required procedures.

The maximum value of ALT was 132 U/L [ULN 35 U/L] and the maximum value of AST was 164 U/L [ULN 35 U/L]. The ALT and AST test results returned to normal. The CLO was stopped on (b) (6) after the second consecutive normal results for ALT and AST. The subject continued elinzanetant, without a change in dose. The last recorded outcome was recovered/resolved, and the recorded end date was (b) (6) Additionally, the investigator also provided the following comment: "subject was taking Excedrin Migraine very consistently for 2 months prior to lab draw."

The subject received the last dose of study intervention on (b) (6) Study intervention was not completed by the subject as per protocol. The primary reason for premature discontinuation of study intervention was subject decision. This event was assessed by the Liver Safety Monitoring Board, and "the consensus was that the alternative diagnosis of alcohol abuse and use of Excedrin and paracetamol were alternative explanation and that the event did not correspond to liver injury." Therefore, the causality to study drug was assessed as unlikely. The review team agrees with this assessment.

In OASIS 2, there were no CLO cases. There were cases of slight transient increases from baseline of mean value in total bilirubin and direct bilirubin in the elinzanetant arm during Weeks 1 to 12. The mean value of total bilirubin changed from 0.38 mg/dL at baseline to 0.44 mg/dL at Week 12, 0.39 mg/dL at Week 16 and 0.45 mg/dL at Week 26, end-of-treatment (EOT). A similar trend was seen in the mean value of direct bilirubin changing from 0.14 mg/dL at baseline to 0.16 mg/dL at Week 12, 0.14 mg/dL at Week 16, and 0.16 mg/dL at EOT (Week 26). In the placebo-elinzanetant arm, both total bilirubin and direct bilirubin were stable during Weeks 1 to 12 and increased during Weeks 13 to 26 from 0.35 mg/dL to 0.44 mg/dL for total bilirubin and from 0.13 mg/dL to 0.16 mg/dL for direct bilirubin.

In OASIS 3, there were six subjects in the elinzanetant group and two subjects in the placebo group who met the CLO criteria. Of these, there was one case in the elinzanetant arm and two cases in the placebo arm that met the liver injury criteria as per the Applicant's LSMB. The elinzanetant case is described below:

(1) Subject (b) (6) was a 60-year-old female that 399 days after starting study intervention (elinzanetant) was reported with alanine aminotransferase increased (reported term: ALT >8xULN) (AP 413 U/L [3.97xULN], AST 115 U/L [3.29xULN] and ALT 281 U/L 8.03xULN]), which the investigator considered nonserious. Total bilirubin 0.8 mg/dL [0.66xULN] was within reference ranges. The investigator also considered this event to be mild in intensity, not related to study intervention, and not related to protocol-required procedures. The following CLO/liver safety required laboratory assessments gave abnormal test results: alkaline phosphatase in serum or plasma (296.00 U/L), bilirubin in serum or plasma (1.27 mg/dL) and alanine aminotransferase in serum or plasma (59.00 U/L). The maximum value of ALT was 281 U/L [ULN 35 U/L] and the maximum value of AST was 115 U/L [ULN 35 U/L]. The ALT and AST test results were decreasing. The CLO was stopped based on the investigator's medical judgement; although decreased levels were not back to baseline, they still decreased to <2xULN and no further follow up was required. No actions were taken in terms of study medications. The subject did not have any medical

history findings or medications that were considered relevant to the current liver event by the investigator. The last recorded outcome was recovered/resolved. The LSMB consensus was that actual cause for liver event is unclear (possibly a viral syndrome related to laryngitis or recently started citalopram). In addition, it happened more than 5 weeks after the stop of study intervention. The event did correspond to liver injury with mixed pattern and mild severity. The causality to study drug was assessed as unlikely. The DILI team felt this was possible DILI due to elinzanetant (see below).

Table 62 shows adverse events of DILI assessment in the safety population of OASIS 3 for 52 weeks. The overall percentages of adverse events and discontinuations for liver injury were higher in the placebo group than the elinzanetant group.

Table 62. Adverse Events of Drug-Induced Liver Injury Assessment, Safety Population, OASIS 3

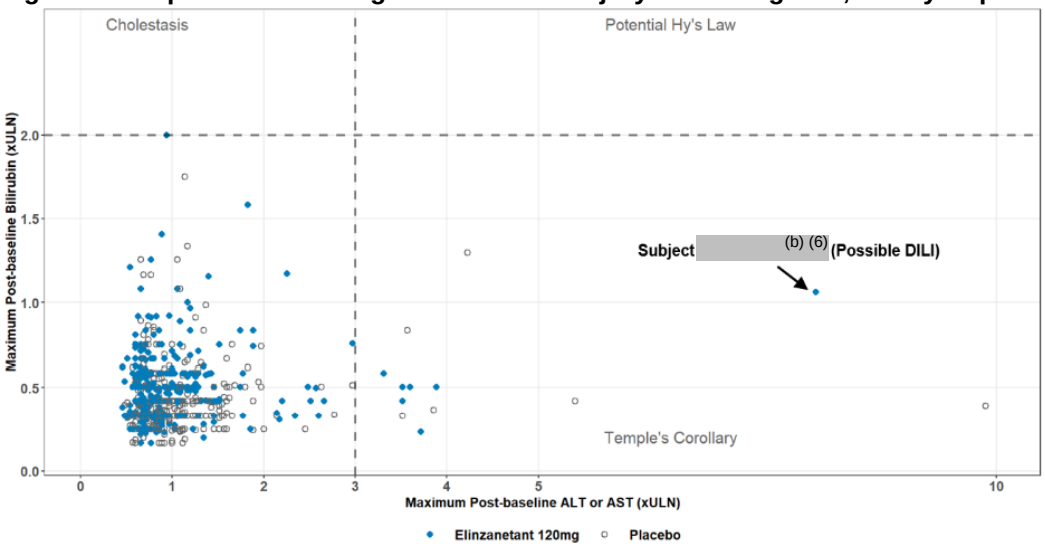
Drug-Induced Liver Injury Assessment	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)
AE grouping related to AESI	7 (2.2)	12 (3.8)
Alanine aminotransferase abnormal	0	1 (0.3)
Alanine aminotransferase increased	5 (1.6)	4 (1.3)
Aspartate aminotransferase abnormal	0	1 (0.3)
Aspartate aminotransferase increased	1 (0.3)	4 (1.3)
Cholestasis	0	1 (0.3)
Gamma-glutamyl transferase increased	0	2 (0.6)
Hepatic enzyme increased	0	1 (0.3)
International normalized ratio increased	1 (0.3)	2 (0.6)
Liver function test abnormal	1 (0.3)	1 (0.3)
Liver function test increased	0	1 (0.3)
Prothrombin time prolonged	0	1 (0.3)
Maximum severity		
Death	0	0
Life-threatening	0	0
Severe	0	1 (0.3)
Moderate	1 (0.3)	5 (1.6)
Mild	6 (1.9)	6 (1.9)
Serious	0	0
Deaths	0	0
Resulting in discontinuation	1 (0.3)	2 (0.6)
Relatedness	2 (0.6)	4 (1.3)
Number of subjects with adverse events with end dates on or before treatment end dates	5/7 (71.4)	7/12 (58.3)
Duration, days (from AE start date to AE end date)		
Mean (SD)	19.4 (12)	67.9 (69.2)
Median (Q1, Q3)	14 (11, 28)	51 (27.5, 78)
Min, max	8, 36	5, 208

Drug-Induced Liver Injury Assessment	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	1/7 (14.3)	3/12 (25.0)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/7 (0)	1/12 (8.3)
Duration, days (from treatment end date to AE end date)		
Mean (SD)	NA	18 (NA)
Median (Q1, Q3)	NA	18 (18, 18)
Min, max	NA, NA	18, 18

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation

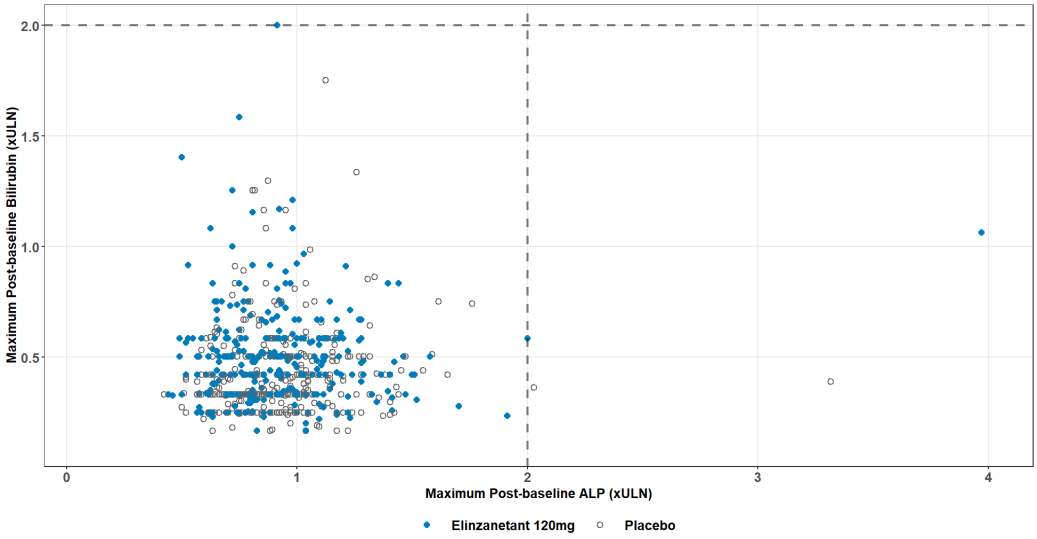
The hepatocellular drug-induced liver injury screening plot (Figure 26) had one subject on elinzanetant outside the left lower quadrant and with ATs over 5xULN. This case (Subject (b) (6)) was deemed possible DILI. There were no cases in potential Hy's law quadrant and only one case just in the cholestasis quadrant. The cholestatic drug-induced liver injury screening plot (Figure 27) showed the same subject (Subject (b) (6) that was seen in the Figure 26.

Figure 26. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, OASIS 3



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2xULN after a postbaseline ALT or AST equal to or exceeding 3xULN. Those subjects who meet total bilirubin equal to or exceeding 2xULN criteria within 30 days of the ALT or AST equal to or exceeding 3xULN criteria are circled in red.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot …" and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening…".
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Figure 27. Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, OASIS 3



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALP versus their maximum total bilirubin values in the postbaseline period.
A potential cholestatic DILI case (red circled) was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2xULN within 30 days after postbaseline ALP became equal to or exceeding 2xULN.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Cholestatic DILI Screening Plot …"
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; ULN, upper limit of normal

The drug-induced liver injury subanalysis from the previous figures (Figure 26 and Figure 27) is presented in Table 63 and Table 64.

Table 63. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, OASIS 3

Quadrant	Elinzanetant 120 mg (N=313) n/N_w (%)	Placebo (N=314) n/N_w (%)
Potential Hy's Law (right upper)	0/307 (0)	0/305 (0)
Cholestasis (left upper)	1/307 (0.3)	0/305 (0)
Temple's corollary (right lower)	7/307 (2.3)	6/305 (2)
Total	8/307 (2.6)	6/305 (2)

Source: adlb.xpt; Software: R
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2xULN after a postbaseline ALT or AST equal to or exceeding 3xULN.
The within 30 days analysis window rule does not apply to cholestasis and Dr. Temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Table 64. Subjects in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, OASIS 3

Quadrant	Elinzanetant 120 mg (N=313) n/N_w (%)	Placebo (N=314) n/N_w (%)
Bilirubin ≥2xULN and ALP ≥2xULN (right upper)	0/307 (0)	0/305 (0)
Bilirubin ≥2xULN and ALP <2xULN (left upper)	1/307 (0.3)	0/305 (0)
Bilirubin <2xULN and ALP ≥2xULN (right lower)	2/307 (0.7)	2/305 (0.7)
Total	3/307 (1)	2/305 (0.7)

Source: adlb.xpt; Software: R
A potential cholestatic DILI case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2xULN within 30 days after postbaseline ALP became equal to or exceeding 2xULN. The within 30 days analysis window rule does not apply to cholestatic DILI cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

The Drug Induced Liver Injury Team conducted a review (See DARRTS dated May 13, 2025) for liver signals in the clinical program focusing on the Phase 2b and the three Phase 3 studies (OASIS 1, OASIS 2, and OASIS 3). In the consult, they reviewed four cases in detail.

(1) Subject (b) (6) (Study NIRVANA): Probable DILI due to elinzanetant. The latency (85 days) and dechallenge washout were consistent with DILI.

(2) Subject (b) (6) (Phase 1 Study): Probable DILI due to elinzanetant. The latency (Day 7) and dechallenge improvement were consistent with DILI.

(3) Subject (b) (6) (OASIS 3): Possible DILI due to elinzanetant (described above). The dechallenge washout implicates elinzanetant, but the long latency weakens the case to just possible DILI.

(4) Subject (b) (6) (OASIS 4): Possible to unlikely DILI due to elinzanetant. The latency (32 days) and dechallenge were consistent with DILI, however there were other features of the case (such as upper respiratory tract infection and fever) that might suggest another cause (such as an infection or antibiotic use).

In summary, the DILI team determined that:

While the nonclinical data (in vitro and animal) supports a hepatotoxicity risk, for the Phase 2b and three Phase 3 studies, there were no clinically significant events of hepatotoxicity with elinzanetant. There were two cases of liver injury that were attributable to elinzanetant. There were no cases meeting Hy's law. There were slightly higher proportion of subjects with ALT >3xULN in the elinzanetant 120 mg arm than that in the placebo arm during the double-blind, placebo-controlled treatment period in OASIS 3 and OASIS 1, but not OASIS 2. The liver injury signal was described as weak, but the number of women exposed is still low relative to the number of women who may be treated postmarket. Thus, liver injuries of clinical significance could still arise in postmarket, similar to what was seen for fezolinetant. Furthermore, the risk tolerance for fatal or life-threating liver injury for both elinzanetant and fezolinetant is low due to the targeted disease, which has substantial morbidity but low risk of mortality. Also, more substantial liver injury may have been mitigated by the scheduled liver blood test monitoring and EOT. The two probable cases of DILI had liver injury as elinzanetant was stopped per protocol EOT, not because of liver enzyme elevations.

7.6.3.4. Endometrial Safety

As noted in Section 7.1, there were positive carcinogenicity findings in the 2-year rat study. These findings included malignant lymphoma, malignant adenocarcinoma of the uterus, malignant and benign endometrial tumors, and malignant squamous cell carcinoma of the uterus. The highest noncarcinogenic dose of elinzanetant was 20 mg/kg/day (7.5X the human therapeutic exposure on an AUC basis) and the lowest dose found to be carcinogenic was 60 mg/kg/day (~29X the human therapeutic exposure on an AUC basis).

There were no neoplastic findings in the 26-week transgenic mice study, and the in vitro and in vivo genotoxicity studies with elinzanetant and its three main metabolites showed negative results.

Given the neoplastic findings that were observed in the uterus and the hematolymphoid system of the female rat, FDA performed an extensive evaluation of the clinical data related to malignancy and endometrial safety.

In OASIS 3, the percentage of subjects with AEs in the SOC neoplasms benign, malignant, and unspecified was higher for the elinzanetant group (five subjects, 1.6%) than the placebo group (two subjects, 0.6%). However, the PTs were generally for single terms that did not raise specific concerns of a pattern that would be suggestive of a malignancy signal (PTs for elinzanetant group: melanocytic nevus (2), fibroadenoma of breast, hypergammaglobulinemia benign monoclonal, invasive ductal breast cancer, and squamous cell carcinoma of skin).

Endometrial safety was assessed in OASIS 1, OASIS 2, and OASIS 3 by TVU and endometrial biopsies according to FDA draft guidance for industry *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation* (January 2003).

In OASIS 3, out of the 170 women with an intact uterus who completed one year of treatment with elinzanetant 120 mg, biopsy samples could be obtained from 140 women providing 116

samples with adequate tissue. Thirty women did not have an EOT biopsy sample collected, primarily due to subject refusal (n=22) or unsuccessful attempts (n=6). End-of-treatment TVU results indicated that the women who failed to provide EOT biopsy samples had relatively thin endometrium.

Overall, 609 EOT endometrial biopsies were obtained from women receiving elinzanetant 120 mg or placebo in OASIS 1, OASIS 2, and OASIS 3 (pooled data, including 272 biopsies after about one year of treatment). Among these, 140 received elinzanetant for up to 52 weeks, 162 received elinzanetant for up to 26 weeks, and 175 received elinzanetant for up to 14 weeks. In addition, 132 women in the placebo arm in OASIS 3 also had EOT endometrial biopsies.

All endometrial biopsies obtained at the end of treatment in all studies showed a benign endometrium and no cases of endometrial hyperplasia or malignant neoplasm were reported (based on majority reads of three blinded independent pathologists). There were no clinically relevant changes observed in TVU examinations performed during the Phase 3 studies.

Per the Applicant, there were 14 cases of uterine bleeding in 726 nonhysterectomized postmenopausal women. Ten of these were reported as study drug related. Two of the 10 subjects discontinued study drug due to uterine bleeding. Endometrial biopsies did not show pathologies in any if these cases.

The hyperplasia rate in women who were treated with elinzanetant 120 mg for approximately one year was below the FDA-specified background incidence rate of ≤1% with an upper bound of the one-sided 95% CI below 4%. However, review of endometrial safety revealed minimal discrepancies among pathologists such as atrophic versus inactive endometrium, and a handful of cases of disordered proliferative endometrium.

Upon FDA review, four subjects in the elinzanetant group (Subjects (b) (6) (b) (6) had discrepant readings among the three independent pathologists in the EOT endometrial biopsies. In each of these four cases, at least one pathologist diagnosed endometrial hyperplasia. In one of the four cases (Subject (b) (6) one pathologist diagnosed endometrial hyperplasia with atypia, a precursor of endometrial malignancy.

For Subject (b) (6) repeated readings of the three pathologists, in addition to two new pathologists, revealed that by a majority of readings the final diagnosis would be benign (3/5), although there were readings of endometrial hyperplasia by two evaluators.

In addition, there was one subject whose EOT had a central read of endometrial polyp. Repeated readings of the three pathologists, in addition to two new pathologists, revealed 4/5 benign diagnosis, compared to one pathologist who diagnosed glandular hyperplastic polyp without atypia.

In summary, the available clinical data, from TVUs and endometrial biopsies did not show any safety concerns regarding endometrial safety. Given the availability of controlled clinical data from a large group of women, exposed up to one year duration and the large exposure multiple for the one nonclinical study, additional postmarketing clinical safety data will not be required. However, the results of the nonclinical study and the clinical

cases of endometrial hyperplasia and polyp will be described in labeling to communicate these findings to prescribers.

7.6.3.5. Cardiac Safety

The cardiac safety of elinzanetant including effects on the QT interval has been investigated by means of standard 12-lead ECG and continuous 12-lead Holter ECG in various Phase 1 studies in healthy volunteers, as well as in Phase 2a and 2b studies in women with VMS. Doses in these studies were up to elinzanetant 600 mg. The highest clinically observed geometric mean plasma concentration in these studies were 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.

According to the Applicant, based on the study results there is no indication of a QTc interval prolongation or other relevant cardiac safety risk 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 nonclinical cardiac safety studies.

The data were reviewed by the Interdisciplinary Review Team for Cardiac Studies. In summary, elinzanetant did not prolong the QTcF interval in the QTc assessment of PK/ECG data from Study 21670. However, due to the limitations of the clinical study and the nonclinical assays, this QTc assessment does not sufficiently characterize QTc effects of elinzanetant at the anticipated high clinical exposure scenario which is in patients coadministered with strong CYP3A4 inhibitors. The labeling will indicate that patients should avoid concomitant use with strong CYP3A4 inhibitors.

Among subjects in OASIS 1, OASIS 2, and OASIS 3, there was an imbalance in adverse events in the cardiovascular system organ class with more events in the elinzanetant group compared to the placebo group. In OASIS 3, 1.9% of subjects in the elinzanetant versus 0.6% of subjects in the placebo group had treatment-emergent AEs in the SOC cardiac disorders. The cardiac disorders SOC was made up of single terms (elinzanetant group: acute myocardial infarction and sinus tachycardia), except for palpitations which occurred in a higher percentage of subjects in the elinzanetant arm (1.6%) compared to the placebo arm (0%). All the AEs of palpitations were mild or moderate.

7.6.3.6. Nervous System Disorders

In OASIS 3, adverse events in the SOC nervous system disorders occurred in a greater percentage of subjects in the elinzanetant group (22%) compared to the placebo group (11.8%). Adverse events of interest included somnolence, fatigue, vertigo/dizziness, syncope, and hypotension/orthostatic hypotension. While it is possible for hypotension/orthostatic hypotension to be secondary to CNS or cardiac/vascular causes, it was considered in the context of nervous system disorders given the imbalances in other nervous system disorders. In addition, it is possible for syncope to be secondary to multiple etiologies, such as cardiovascular or metabolic causes.

Upon Agency request, the Applicant provided groupings (based on MedDRA labeling grouping) for adverse events of special interest as outlined in Table 65. In each study phase (Table 66),

more subjects on elinzanetant compared to placebo experienced nervous system disorders (including CNS depression, vertigo/dizziness, syncope/presyncope/hypotension, and all nervous system events).

Table 65. Applicant's AE Grouping for Nervous System Disorders of Special Interest

Adverse Event Groupings	Preferred Terms
CNS depression (such as somnolence and fatigue)	Asthenia Decreased activity Fatigue Fatigue management Hypersomnia Mental fatigue Physical deconditioning Sleep disorder due to general medical condition, hypersomnia type Sluggishness Somnolence
Vertigo/dizziness	Dizziness Dizziness exertional Dizziness postural Persistent postural-perceptual dizziness Vertigo Vertigo CNS origin Vertigo labyrinthine Vertigo positional
Syncope/presyncope/hypotension	Blood pressure ambulatory decreased Blood pressure decreased Blood pressure diastolic decreased Blood pressure systolic decreased Diastolic hypotension Hypotension Loss of consciousness Mean arterial pressure decreased Orthostatic hypotension Presyncope Syncope

Source: .1.1.1.1.2; Listing 1; Applicant's IR response dated July 22, 2025
Abbreviations: AE, adverse event; CNS, central nervous system

Table 66. Summary of Nervous System Disorder Adverse Events of Special Interest by Study Phase Group

Nervous System Disorder AESIs	Elinzanetant n/N (%)	Placebo n/N (%)
CNS depression		
Phase 1 (total)	159/653 (24.3%)	22/175 (12.6%)
Phase 2 (total)	19/152 (12.5%)	1/47 (2.1%)
Phase 3 (total)	77/1061 (7.3%)	21/707 (3.0%)
OASIS 1	21/367 (5.7%)	3/194 (1.5%)
OASIS 2	19/381 (5.0%)	6/199 (3.0%)
OASIS 3	37/313 (11.8%)	12/314 (3.8%)

Nervous System Disorder AESIs	Elinzanetant n/N (%)	Placebo n/N (%)
Vertigo/dizziness		
Phase 1 (total)	41/653 (6.3%)	3/175 (1.7%)
Phase 2 (total)	6/152 (3.9%)	0/47 (0)
Phase 3 (total)	36/1061 (3.4%)	12/707 (1.7%)
OASIS 1	10/367 (2.7%)	3/194 (1.5%)
OASIS 2	8/381 (2.1%)	3/199 (1.5%)
OASIS 3	18/313 (5.8%)	6/314 (1.9%)
Syncope/presyncope/hypotension		
Phase 2 (total)	1/152 (0.7%)	0/47 (0)
Phase 3 (total)	7/1061 (0.7%)	1/707 (0.1%)
OASIS 1	2/367 (0.5%)	0/194 (0)
OASIS 2	1/381 (0.3%)	0/199 (0)
OASIS 3	4/313 (1.3%)	1/314 (0.3%)
All CNS events		
Phase 1 (total)	185/653 (28.3%)	22/175 (12.6%)
Phase 2 (total)	25/152 (16.4%)	1/47 (2.1%)
Phase 3 (total)	102/1061 (9.6%)	33/707 (4.7%)
OASIS 1	28/367 (7.6%)	6/194 (3.1%)
OASIS 2	23/381 (6.0%)	9/199 (4.5%)
OASIS 3	51/313 (16.3%)	18/314 (1.9%)

Source: .1.1.1.1.3; Table 1; Applicant's IR response dated July 22, 2025
Phase 1 includes studies: 21665, 21666, 21667, 21668, 21670, 21673, 21674, 21675, 21676, 21677, 21678, 21684, 21703, 21756, 21772, 21774, 21840, 22004, 22081, 22653
Phase 2 includes study: 21686
Phase 3 includes studies: 21651, 21652, 21810
Abbreviations: AESIs, adverse events of special interest; CNS, central nervous system; IR, information request; N, number of subjects in treatment arm; n, number of subjects in treatment arm with given characteristic

The Applicant performed subgroup analyses and did not identify a specific subgroup of subjects at higher risk of nervous system disorders. Similarly, the Agency did not identify a specific subgroup at higher risk.

The Applicant noted that adverse events of hypotension and syncope could be of vascular origin and also provided the adverse events with these PTs removed (Table 67).

Table 67. Treatment-Emergent Adverse Events Fatigue, Somnolence, and Dizziness up to Week 12: Number of Subjects by AE Grouping and Preferred Term, OASIS 1, OASIS 2, and OASIS 3 (SAF)

Treatment-Emergent Adverse Events	Elinzanetant n/N (%) (N=713)	Placebo n/N (%) (N=707)
Number of subjects with at least one such event	85 (11.9%)	25 (3.5%)
Dizziness	27 (3.8%)	11 (1.6%)
Balance disorder	1 (0.1%)	0
Dizziness	20 (2.8%)	8 (1.1%)
Presyncope	0	1 (0.1%)
Vertigo	4 (0.6%)	2 (0.3%)
Vertigo CNS origin	1 (0.1%)	0
Vertigo positional	1 (0.1%)	0
Fatigue	41 (5.8%)	11 (1.6%)
Asthenia	2 (0.3%)	1 (0.1%)
Fatigue	40 (5.6%)	10 (1.4%)

Treatment-Emergent Adverse Events	Elinzanetant n/N (%) (N=713)	Placebo n/N (%) (N=707)
Somnolence	27 (3.8%)	3 (0.4%)
Lethargy	3 (0.4%)	0
Somnolence	24 (3.4%)	3 (0.4%)

(b) (4)

Abbreviations: AE, adverse event; CNS, central nervous system; N, number of subjects in treatment arm; n, number of subjects in treatment arm with given characteristic; SAF, safety analysis set

Somnolence/Fatigue

Somnolence and fatigue were considered an adverse event of special interest in the development program given that clinical data suggested an increased risk of somnolence and fatigue following elinzanetant exposure. In the clinical development program, women took the study drug at bedtime and were instructed neither to drive nor operate machinery if they experienced somnolence or fatigue.

In the SAF, pooled safety population, (up to Week 12) somnolence or fatigue occurred in a higher percentage of subjects treated with elinzanetant (7.0%) compared to placebo (2.3%). When using broader MedDRA PTs (somnolence, hypersomnia, asthenia, decreased activity, fatigue, fatigue management, mental fatigue, physical deconditioning, and sluggishness) the imbalance was larger (elinzanetant arm: 8.6% compared to placebo: 2%). None of the AEs of somnolence or fatigue were serious.

In the SAF, pooled safety population, more subjects in the elinzanetant discontinued due to an AE of somnolence or fatigue (1.8%) compared to the placebo group (0%). The majority of events occurred during the first two weeks of treatment, were mild or moderate and resolved. No difference in the incidence rates (100 person-years) in accidents and injuries, Standard Medical Dictionary for Regulatory Activities Query (SMQ), were seen for the elinzanetant and placebo groups.

In OASIS 1 and OASIS 2, the fatigue OCMQ (narrow), was made up of the following PTs: asthenia, fatigue, and lethargy, all of which occurred in a higher percentage of subjects in the elinzanetant group compared to the placebo group (Table 68). All the events were mild to moderate in severity and none were serious. In the elinzanetant group (pooled data), 2% of subjects discontinued due to fatigue compared to no subjects in the placebo group. In OASIS 3, the fatigue OCMQ (narrow) was made up of the same PTs, all of which occurred in a higher percentage of subjects in the elinzanetant group compared to the placebo group (Table 69). A similar percentage of subjects discontinued due to fatigue in OASIS 1, OASIS 2, and OASIS 3.

Table 68. Adverse Events Assessment of Fatigue OCMQ (Narrow) Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled	
OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)
Fatigue (OCMQ)	17 (8.5)	3 (1.5)	11 (5.5)	4 (2.0)	28 (7.0)	7 (1.8)
Asthenia	1 (0.5)	0	1 (0.5)	1 (0.5)	2 (0.5)	1 (0.3)
Fatigue	14 (7.0)	3 (1.5)	11 (5.5)	3 (1.5)	25 (6.2)	6 (1.5)
Lethargy	2 (1.0)	0	0	0	2 (0.5)	0
Maximum severity						
Death	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Moderate	5 (2.5)	0	7 (3.5)	0	12 (3.0)	0
Mild	12 (6.0)	3 (1.5)	4 (2.0)	4 (2.0)	16 (4.0)	7 (1.8)
Serious	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	4 (2.0)	0	4 (2.0)	0	8 (2.0)	0
Relatedness	13 (6.5)	2 (1.0)	11 (5.5)	0	24 (6.0)	2 (0.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Relatedness is determined by the investigator.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; OCMQ, OND custom medical query

Table 69. Adverse Events Assessment of Fatigue OCMQ (Narrow), Safety Population, OASIS 3

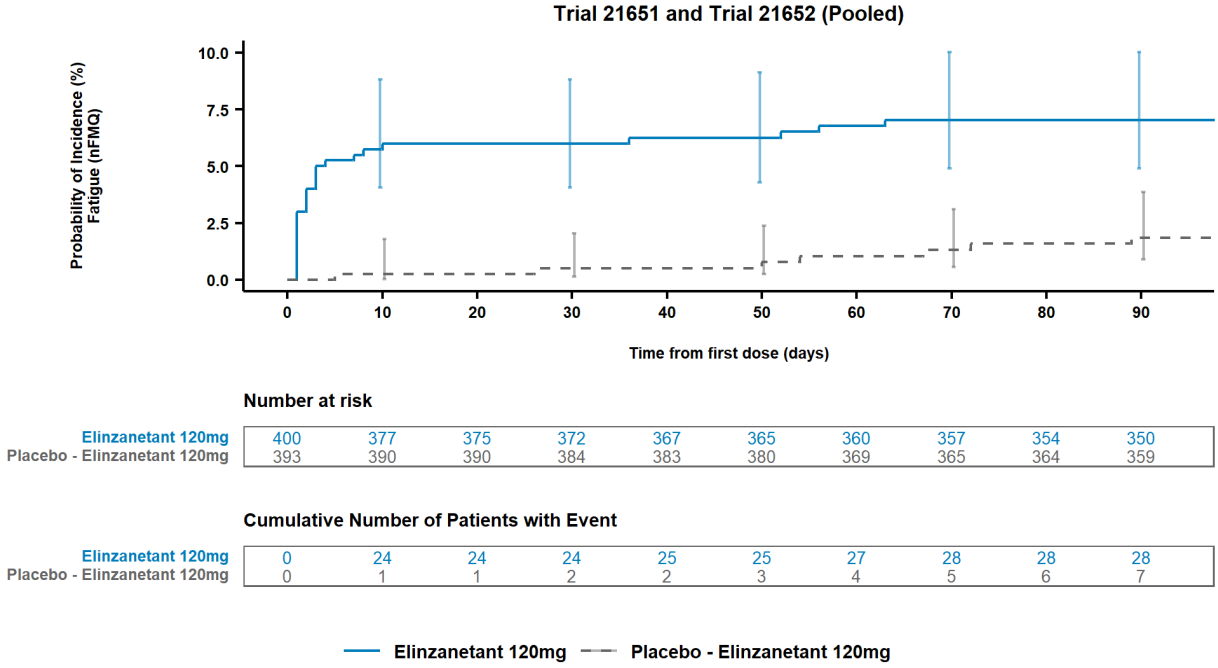
OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)
Fatigue (OCMQ)	24 (7.7)	9 (2.9)
Asthenia	2 (0.6)	0
Fatigue	21 (6.7)	9 (2.9)
Lethargy	1 (0.3)	0
Maximum severity		
Death	0	0
Life-threatening	0	0
Severe	0	0
Moderate	9 (2.9)	1 (0.3)
Mild	15 (4.8)	8 (2.5)
Serious	0	0
Deaths	0	0
Resulting in discontinuation	6 (1.9)	0

OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)
Relatedness	14 (4.5)	5 (1.6)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Relatedness is determined by the investigator.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

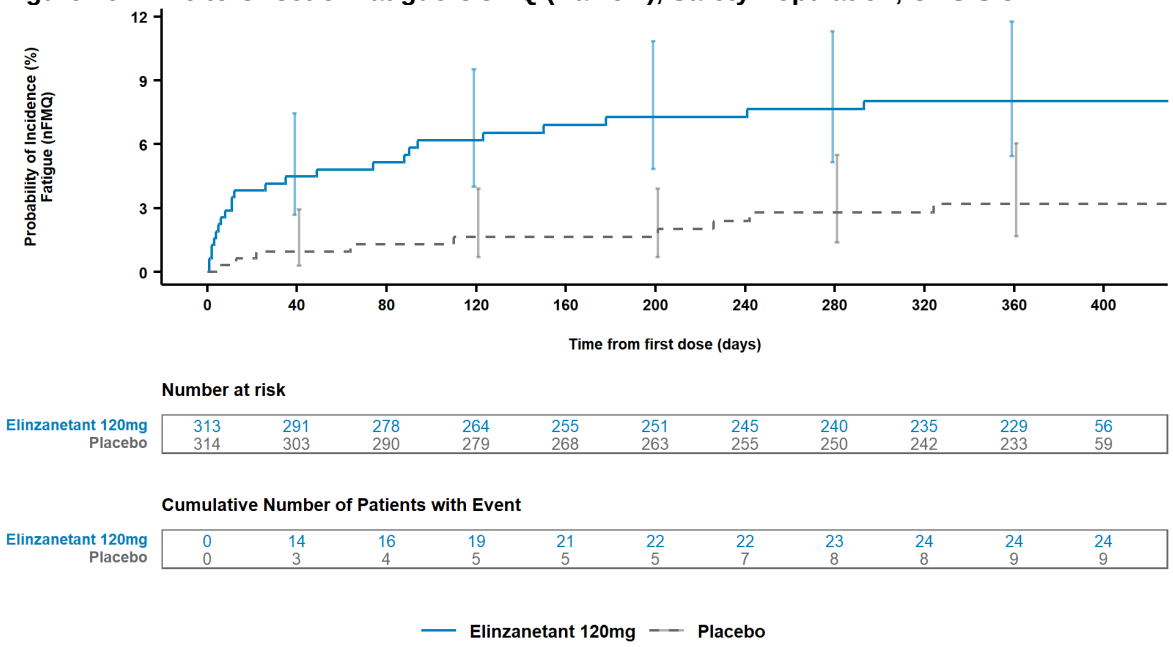
The onset of fatigue for OASIS 1 and OASIS 2 (pooled data) for most cases occurred in the first 10 days of treatment (Figure 28). After the initial separation, the difference between elinzanetant and placebo for fatigue was fairly stable, with a slight upward trend, through 52 weeks (OASIS 3; Figure 29).

Figure 28. Time to Onset of Fatigue OCMQ (Narrow), Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)



Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Abbreviations: nFMQ, narrow FDA medical query; OCMQ, OND custom medical query

Figure 29. Time to Onset of Fatigue OCMQ (Narrow), Safety Population, OASIS 3



Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Abbreviations: nFMQ, narrow FDA medical query; OCMQ, OND custom medical query

Similar findings were seen for the somnolence OCMQ compared to the fatigue OCMQ.

In OASIS 1 and OASIS 2, the somnolence OCMQ (narrow) was made up of the following PTs: hypersomnia, lethargy, sedation, and somnolence, all of which occurred in a higher percentage of subjects in the elinzanetant group compared to the placebo group, except for sedation (Table 70). All of the events were mild to moderate severity and none were serious. In the elinzanetant group (pooled data), 0.2% of subjects on elinzanetant compared to 0% of subjects on placebo discontinued due to somnolence. In OASIS 3, the OCMQ (narrow) was made up of two PTs: lethargy and somnolence, both of which occurred in a higher percentage of subjects in the elinzanetant group compared to the placebo group (Table 71). A similar percentage of elinzanetant-treated subjects discontinued due to somnolence in OASIS 1, OASIS 2, and OASIS 3 (0 to -0.6%).

Table 70. Adverse Events Assessment of Somnolence OCMQ (Narrow), Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled	
OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)
Somnolence (OCMQ)	8 (4.0)	0	4 (2.0)	3 (1.5)	12 (3.0)	3 (0.8)
Hypersomnia	1 (0.5)	0	0	0	1 (0.2)	0
Lethargy	2 (1.0)	0	0	0	2 (0.5)	0
Sedation	0	0	0	1 (0.5)	0	1 (0.3)
Somnolence	5 (2.5)	0	4 (2.0)	2 (1.0)	9 (2.2)	2 (0.5)

OCMQ (Narrow) Preferred Term	OASIS 1 Elinzanetant 120 mg (N=199) n (%)	OASIS 1 Placebo (N=194) n (%)	OASIS 2 Elinzanetant 120 mg (N=201) n (%)	OASIS 2 Placebo (N=199) n (%)	Pooled Elinzanetant 120 mg (N=400) n (%)	Pooled Placebo (N=393) n (%)
Maximum severity						
Death	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Moderate	2 (1.0)	0	1 (0.5)	1 (0.5)	3 (0.8)	1 (0.3)
Mild	6 (3.0)	0	3 (1.5)	2 (1.0)	9 (2.2)	2 (0.5)
Serious	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	0	0	1 (0.5)	0	1 (0.2)	0
Relatedness	6 (3.0)	0	4 (2.0)	3 (1.5)	10 (2.5)	3 (0.8)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Relatedness is determined by the investigator.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

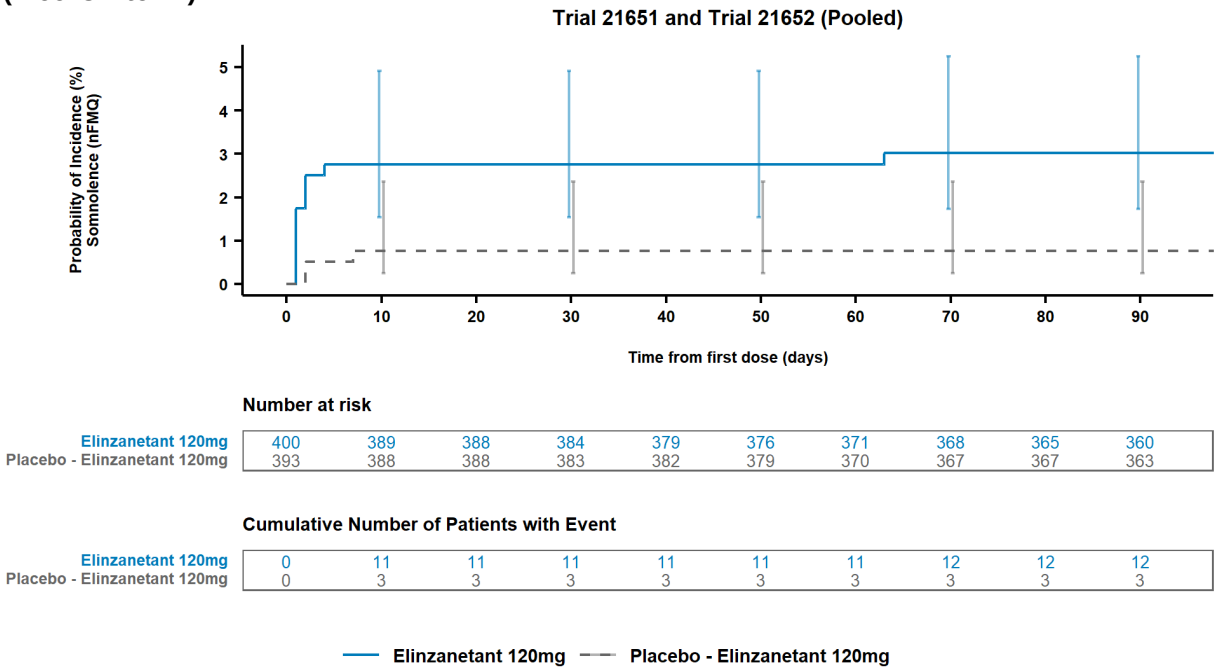
Table 71. Adverse Events Assessment of Somnolence OCMQ (Narrow), Safety Population, OASIS 3

OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)	Risk Difference % (95% CI)
Somnolence (OCMQ)	17 (5.4)	4 (1.3)	4.2 (1.5, 7.4) *
Lethargy	1 (0.3)	0	0.3 (-0.9, 1.8)
Somnolence	16 (5.1)	4 (1.3)	3.8 (1.2, 7.0) *
Maximum severity			
Death	0	0	0.0 (-1.2, 1.2)
Life-threatening	0	0	0.0 (-1.2, 1.2)
Severe	0	0	0.0 (-1.2, 1.2)
Moderate	6 (1.9)	0	1.9 (0.7, 4.1) *
Mild	11 (3.5)	4 (1.3)	2.2 (-0.2, 5.1)
Serious	0	0	0.0 (-1.2, 1.2)
Deaths	0	0	0.0 (-1.2, 1.2)
Resulting in discontinuation	2 (0.6)	0	0.6 (-0.6, 2.3)
Relatedness	16 (5.1)	3 (1.0)	4.2 (1.6, 7.3) *

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

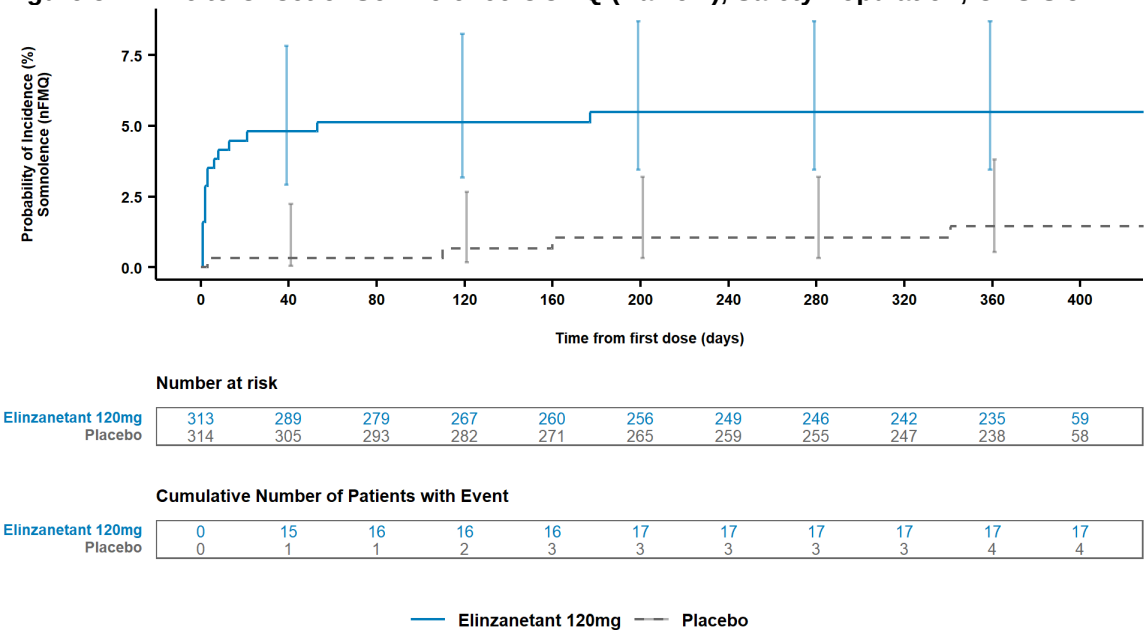
The onset of somnolence for OASIS 1 and OASIS 2 (pooled data) for most cases occurred in the first 10 days of treatment (Figure 30). After the initial separation, the difference between elinzanetant and placebo for fatigue was stable through 52 weeks (OASIS 3; Figure 31).

Figure 30. Time to Onset of Somnolence OCMQ (Narrow), Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)



Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Abbreviations: nFMQ, narrow FDA medical query; OCMQ, OND custom medical query

Figure 31. Time to Onset of Somnolence OCMQ (Narrow), Safety Population, OASIS 3



Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Abbreviations: nFMQ, narrow FDA medical query; OCMQ, OND custom medical query

Given the findings in the clinical program, somnolence and fatigue will be included in the USPI.

Dizziness/Vertigo

In OASIS 1, OASIS 2, and OASIS 3, AEs of dizziness occurred more frequently in subjects in the elinzanetant group compared to the placebo group. In OASIS 3, dizziness occurred in 2.2% of the elinzanetant group compared to 1.0% of the placebo group.

In OASIS 1 and OASIS 2, the dizziness OCMQ (narrow) was made up of the following PTs: balance disorder, dizziness, and vertigo (Table 72). In the pooled OASIS 1 and OASIS 2 studies, more subjects in the elinzanetant arm had dizziness OCMQ (narrow) AEs (3.2%) than the placebo arm (1.5%). In OASIS 3, the dizziness OCMQ (narrow) was made up of the following PTs: balance disorder, dizziness, presyncope, vertigo, vertigo CNS origin, vertigo positional, and vestibular neuronitis, all of which occurred in a higher percentage of subjects in the elinzanetant group compared to the placebo group, except for presyncope (Table 73). All the events were mild to moderate severity, except one event that was severe. In the elinzanetant group, 1% of subjects discontinued due to dizziness compared to 0% in the placebo group.

In OASIS 3, two subjects discontinued due to an adverse event with a PT of dizziness and one subject discontinued due to AEs of fatigue and vertigo.

(1) Subject (b) (6) was 54-year-old woman with moderate dizziness felt to be related to study intervention. She discontinued elinzanetant 11 days after starting the drug due to dizziness and headache.

(2) Subject (b) (6) was a 57-year-old woman who developed dizziness, fatigue, and tinnitus 12 days after starting elinzanetant and she stopped the study drug due to these AEs. The dizziness was moderate in intensity and felt to be related to study intervention.

(3) Subject (b) (6) was a 53-year-old woman who developed AEs of fatigue and vertigo, 2 and 3 days after starting elinzanetant, respectively. The subject stopped elinzanetant one day before developing the vertigo. The investigator considered the vertigo to be moderate in intensity and related to elinzanetant. She was described as feeling dizzy when she stood up and with head movements and had associated nausea.

Table 72. Adverse Events Assessment of Dizziness OCMQ (Narrow), Safety Population, OASIS 1 and OASIS 2 (Weeks 1 to 12)

	OASIS 1		OASIS 2		Pooled	
OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=199) n (%)	Placebo (N=194) n (%)	Elinzanetant 120 mg (N=201) n (%)	Placebo (N=199) n (%)	Elinzanetant 120 mg (N=400) n (%)	Placebo (N=393) n (%)
Dizziness (OCMQ)	5 (2.5)	3 (1.5)	8 (4.0)	3 (1.5)	13 (3.2)	6 (1.5)
Balance disorder	0	0	1 (0.5)	0	1 (0.2)	0
Dizziness	5 (2.5)	2 (1.0)	6 (3.0)	2 (1.0)	11 (2.8)	4 (1.0)
Vertigo	0	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.2)	2 (0.5)
Maximum severity						
Death	0	0	0	0	0	0
Life-threatening	0	0	0	0	0	0
Severe	0	0	1 (0.5)	0	1 (0.2)	0
Moderate	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	2 (0.5)	2 (0.5)
Mild	4 (2.0)	2 (1.0)	6 (3.0)	2 (1.0)	10 (2.5)	4 (1.0)
Serious	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	1 (0.5)	2 (1.0)	2 (1.0)	2 (1.0)	3 (0.8)	4 (1.0)
Relatedness	3 (1.5)	2 (1.0)	6 (3.0)	3 (1.5)	9 (2.2)	5 (1.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration of treatment is 26 weeks, consisting of a first 12-week period during which all subjects receive either 120 mg of elinzanetant or matching placebo orally once daily at randomization, and followed by a second 14-week period where subjects in both treatment groups receive elinzanetant 120 mg once daily.
Relatedness is determined by the investigator.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

In OASIS 1 and OASIS 2, there were no SAEs related to dizziness.

In OASIS 3, one subject had an SAE related to dizziness (PT vertigo) that required or prolonged hospitalization.

(1) Subject (b) (6) was a 60-year-old woman who reported peripheral vertigo 58 days after starting elinzanetant. The SAE was of severe intensity. The investigator did not think it was related to elinzanetant. The subject continued treatment and the SAE resolved.

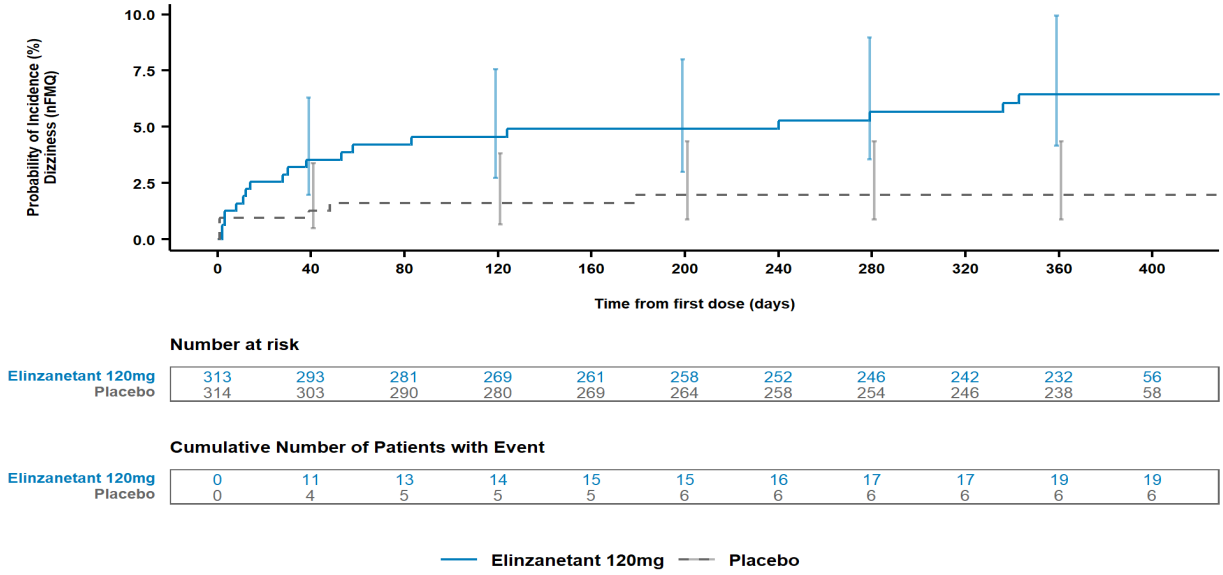
Table 73. Adverse Events Assessment of Dizziness OCMQ (Narrow), Safety Population, OASIS 3

OCMQ (Narrow) Preferred Term	Elinzanetant 120 mg (N=313) n (%)	Placebo (N=314) n (%)
Dizziness (OCMQ)	19 (6.1)	6 (1.9)
Balance disorder	1 (0.3)	0
Dizziness	12 (3.8)	5 (1.6)
Presyncope	0	1 (0.3)
Vertigo	4 (1.3)	1 (0.3)
Vertigo CNS origin	1 (0.3)	0
Vertigo positional	1 (0.3)	0
Vestibular neuronitis	1 (0.3)	0
Maximum severity		
Death	0	0
Life-threatening	0	0
Severe	1 (0.3)	0
Moderate	5 (1.6)	1 (0.3)
Mild	13 (4.2)	5 (1.6)
Serious	1 (0.3)	0
Deaths	0	0
Resulting in discontinuation	3 (1.0)	0
Relatedness	9 (2.9)	3 (1.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Relatedness is determined by the investigator.
Abbreviations: AE, adverse event; CNS, central nervous system; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, OND custom medical query

Figure 32 displays the time to onset of dizziness in OASIS 3. The figure displays the early separation between the treatment arms, with subjects experiencing more dizziness in the elinzanetant group than the placebo group.

Figure 32. Time to Onset of Dizziness OCMQ (Narrow), Safety Population, OASIS 3



Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event occurring or worsening on or after the date of the first dose of study intervention drug up to 14 days after the date of the last dose of study intervention.
Duration is 52 weeks.
Abbreviations: nFMQ, narrow FDA medical query; OCMQ, OND custom medical query

Given the events of vertigo and dizziness in the clinical development program, these adverse events will be included in the USPI.

Syncope

In the Phase 2/3 clinical studies, three subjects in the elinzanetant arm (0.3%) compared to no cases in the placebo arm experienced syncope. None of the subjects reported syncope experienced accident, injury, fall or concussion. There was a total of five cases of syncope in the entire clinical development program and the narratives are included below:

(1) Subject [redacted] (b) (6) was a 52-year-old woman in OASIS 1 who had an SAE of syncope that led to study discontinuation. Five days after starting elinzanetant, the subject reported syncope of severe intensity. It was noted that the subject did not observe any symptoms before or after onset. Evaluations, including laboratory tests, chest X-ray, electrocardiogram, and head CT, were normal. The investigator did not think the SAE was related to elinzanetant use. The review team notes that the etiology of syncope is unclear.

(2) Subject [redacted] (b) (6) was a 56-year-old woman who had an SAE of syncope 55 days after starting elinzanetant (discussed in the review of SAE narratives for OASIS 3 and Section 7.7.4). Elinzanetant was interrupted and then the subject was able to complete the study per protocol. The cause of the syncope was unclear. She reported that she felt disoriented and passed out while in her car. She was admitted to the hospital and experienced

slurred speech, blurred vision, and elevated blood pressure and heart rate. It was noted that she may have had a seizure and would require additional follow-up. See Section 7.7.4 for additional discussion of this adverse event of special interest given the question of whether she had a seizure.

(3) Subject (b) (6) was a 60-year-old woman who developed an AE of syncope 286 days after starting elinzanetant in OASIS 3. The reported term was orthostatic hypotonia. The event was of moderate intensity, and the investigator did not think it was related to elinzanetant. Vital signs were not assessed at the time of the event for this subject. Her systolic and diastolic blood pressure measurements were all within normal ranges at all study visits. Her heart rate was slightly decreased (53 to 57 beats/min) at three visits. She continued elinzanetant and completed participation in the study.

(4) Subject (b) (6) was a 53-year-old woman enrolled in North America in Study 21686 (a double-blind, randomized, placebo controlled, adaptive design study of the efficacy, safety and pharmacokinetics of NT-814 in female subjects with moderate to severe vasomotor symptoms associated with the menopause). She was reported with syncope (reported term: faintness), which the investigator considered nonserious. The investigator considered this event to be mild in intensity and unrelated to elinzanetant 120 mg daily. The event resolved on the same day without a change in study intervention dose. The ECGs performed at all study visits were reported as sinus bradycardia and assessed as not clinically significant by the investigator, except for the Week 8 ECG that was considered clinically significant because of an HR of 48 bpm. Of note, the subject did have bradycardia at screening (59 bpm) and at the baseline visit (56 bpm). The subject was reported with AEs of low heart rate and dizziness on Days 36 and 41. She was able to complete participation in the study protocol.

(5) Subject (b) (6) is discussed in the review of hypotension/orthostatic hypotension (below).

In summary, there were a limited number of syncope events in the clinical database. The etiology of one of the cases of syncope was unclear (Subject (b) (6) For another subject (Subject (b) (6) the adverse event of syncope may have been a potential seizure. There were features of two cases that suggested they were not secondary to elinzanetant (Subject (b) (6) [able to resume study medication and complete participation in the study] and Subject (b) (6) [no change in study medication and completed participation in the study]). Another subject (Subject (b) (6) appeared to have a vasovagal event associated with blood drawing. Given the limited events, and lack of clear attribution to study drug, syncope will not be included in labeling at this time. The Applicant proposed to include "presyncope", which the review team agreed to given the features of some of the nervous system disorders reported. We will continue to monitor the safety of the drug postmarketing.

Hypotension/Orthostatic Hypotension

In the clinical program, there were cases of hypotension and orthostatic hypotension. There were six TEAEs with PTs of hypotension or orthostatic hypotension and there was one AE that was posttreatment for a subject on placebo. The subjects on elinzanetant with hypotension and orthostatic hypotension are in Table 74.

Table 74. Subjects on Elinzanetant With Events of Hypotension or Orthostatic Hypotension, Phase 1, 2, and 3 Studies

Subject ID	Study (Phase)	Treatment Arm	Latency (Days)*	MedDRA Preferred Term**
(b) (6)	OASIS 1 (3)	Elinzanetant 120 mg	6	Orthostatic hypotension
	OASIS 2 (3)	Elinzanetant 120 mg	8	Hypotension
	OASIS 3 (3)	Elinzanetant 120 mg	192	Hypotension
	OASIS 3 (3)	Elinzanetant 120 mg	90	Hypotension
	21674 (1)	Elinzanetant 45 mg, oral suspension, SD	1	Orthostatic hypotension
	21674 (1)	Treatment Period 1: Elinzanetant 90 mg, oral suspension, SD*** Treatment Period 2: Elinzanetant 90 mg, oral suspension, MD***	10	Orthostatic hypotension

Source: Reviewer generated based on IR response received July 22, 2025
* Days from treatment start of the event
** Retrieval criteria (PTs): Blood pressure ambulatory decreased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure systolic decreased, Diastolic hypotension, Hypotension, Mean arterial pressure decreased, Orthostatic hypotension
*** dose of elinzanetant was split in up to three doses on each dosing occasion
Abbreviations: ID, identifier; IR, information request; MD, multiple dose; MedDRA, Medical Dictionary for Regulatory Activities; PTs, preferred terms; SD, single dose

Narratives

(1) Subject (b) (6) was a 60-year-old woman who reported orthostatic hypotension 6 days after staring elinzanetant. The investigator considered the event mild in intensity and not related to elinzanetant. The event resolved on the same day without change in elinzanetant dose. Her blood pressure and heart rate measurements were normal at all study visits.

(2) Subject (b) (6) was a 58-year-old woman who reported hypotension and dizziness eight days after starting elinzanetant. The investigator considered the event to be mild in intensity and related to elinzanetant. The events resolved approximately 80 days later. Vital sign measurements were not available at the time of the event. Approximately 56 days after the onset of the event, her blood pressure was normal.

(3) Subject (b) (6) was a 58-year-old woman who developed hypotension 192 days after starting elinzanetant. The investigator considered the event to be moderate in intensity and not related to elinzanetant.

(4) Subject (b) (6) was a 65-year-old woman who developed hypotension 90 days after starting elinzanetant. The hypotension lasted for nine days and resolved without a change in elinzanetant. She also had AEs of asthenia (mild) and sinus tachycardia (mild) on the same day. She started the concomitant medication ivabradine the day after the AE of hypotension. It is noted that the ivabradine was started for sinus tachycardia. The investigator considered the event of hypotension to be mild in intensity and not related to elinzanetant. The event was assessed as related to the new concomitant medication (ivabradine) however it appears from the data provided that the hypotension started the day before she started ivabradine. Her blood pressure the day after the reported event of hypotension was normal (132/73 mm Hg). While the review team does not agree with assigning the adverse event to

the concomitant medication ivabradine (as it appeared to start before the concomitant medication was started), the fact that the event resolved while continuing elinzanetant suggests that the event is not related to elinzanetant.

(5) Subject (b) (6) was a 41-year-old Asian-Southeast Asian Heritage man enrolled in the United Kingdom in Study 21674 (a healthy volunteer repeat-disease study to evaluate the safety, tolerability, pharmacokinetics, effects on the pharmacokinetics of midazolam and the NK1 receptor occupancy of GSK1144814). The study was single-blind, randomized, placebo-controlled, and performed in healthy male and female subjects. The subject was randomized to Part A, Cohort 2, treatment group elinzanetant 90 mg single total dose (oral suspension 45 mg, followed by two times 22.5 mg). He received a total dose of 45 mg elinzanetant because he withdrew from the study after the first split dose. He was not receiving any concomitant medications. He received the elinzanetant 45 mg dose at 8:10 a.m. At 9:16 a.m., he had "vasovagal syncope (with loss of consciousness)" after blood collection via syringe. The vasovagal syncope was associated with a 12 second pause on Holter monitor at 9:16 a.m. His supine blood pressure at the time was 74/58 mm Hg and pulse of 97 bpm. He was asymptomatic by 9:20 a.m. Starting at 9:20 a.m., he had palpitations and the Holter monitor showed atrial fibrillation and other cardiac arrhythmias. At 13:41 p.m., he spontaneously reverted to normal sinus rhythm, and his palpitations stopped. At this time, he noted orthostatic dizziness with a blood pressure of 70/46 (pulse 59). This was resolved at 14:20 p.m. The atrial fibrillation was thought to be secondary to the vasovagal event. It was noted that it cannot be ruled out that elinzanetant contributed to the event and thus, it is considered possibly related to treatment with elinzanetant. The review team agrees with this assessment.

(6) Subject (b) (6) was a 24-year-old white man enrolled in Study 21674 who developed orthostatic hypotension 10 days after starting elinzanetant (b) (6) The investigator considered the event mild in intensity and related to elinzanetant. He also was reported with orthostatic dizziness of moderate severity and headache of mild severity 4 days after starting elinzanetant (b) (6) and decreased mental concentration of mild severity 6 days after starting elinzanetant (b) (6) His blood pressure and pulse measurements were relatively stable before and after dosing with elinzanetant. His heart rate was less than 60 bpm at several timepoints but was also low at screening, suggesting that the low heart rate was not secondary to elinzanetant.

See Section 7.6.1.7 and Section 7.6.2.7 for a discussion of vital signs in OASIS 1, OASIS 2, and OASIS 3.

Table 75 through Table 78 shows the percentage of subjects with minimum blood pressure values by category. In OASIS 1 (1 to 12 weeks), the percentage of subjects with systolic blood pressure <90, diastolic blood pressure <60, and blood pressure <90/60 was higher in the placebo group than the elinzanetant group. In OASIS 2 (Weeks 1 to 12), there was a higher percentage of subjects on elinzanetant with diastolic blood pressure <60 and blood pressure of <90/60 compared to subjects on placebo. In OASIS 3, the percentage of subjects with systolic blood pressure <90, diastolic blood pressure <60, and blood pressure <90/60 was higher in the elinzanetant group than the placebo group, however the imbalances were small.

Table 75 includes a total of 78 subjects. Review of the details of these subjects showed that many of them had low blood pressure measurements at screening and baseline or were on concomitant medications that can be associated with blood pressure changes. In addition, many of the low values did not appear to be significant changes from the subject's baseline values. Out of the 78 subjects (all on elinzanetant treatment), there were 3 who were symptomatic and none required medical intervention. Details of the three subjects are provided below:

(1) Subject (b) (6) The subject experienced dizziness 17 days before the recorded low DBP measurement (105/50 on Week 16). She recovered on the same day that the low DBP measurement was taken.

(2) Subject (b) (6) The subject had a history of orthostatic hypotension since (b) (6) and had low SBP/DBP measurements during screening and baseline. She had SBP/DBP <90/60 and DBP <60 at multiple timepoints, but these values were similar to her screening and baseline values. She developed fatigue and lack of energy 1 day after starting elinzanetant. They were moderate in intensity and did not recover. The investigator assessed the fatigue as related and lack of energy as unrelated to the study drug. She developed concentration loss 10 days after starting elinzanetant; it was moderate in intensity and did not recover. The investigator assessed concentration loss as not related to the study drug. The clinical review team does not assess as the AEs of fatigue, lack of energy, or concentration loss as directly related to the low blood pressure values, given that the values were similar to her baseline. However, these AEs appear to be secondary to elinzanetant.

(3) Subject (b) (6) The subjects had low DBP during screening and at multiple study visits. She had an AE of mild drowsiness that lasted 19 days and recovered 1 day before the low BP measurement was recorded. The investigator assessed the drowsiness as mild and related to the study. Given that her DBP was low at screening, it does not appear that the drowsiness was directly related to the low DBP.

Table 75. Percentages of Subjects With Minimum Blood Pressure Values by Category of Blood Pressure Postbaseline, OASIS 1 (Weeks 1 to 12)

OASIS 1 (Weeks 1 to 12)	Elinzanetant (N=199) n (%)	Placebo (N=194) n (%)
Systolic blood pressure <90	1 (0.5%)	2 (1.0%)
Diastolic blood pressure <60	3 (1.5%)	5 (2.6%)
Blood pressure <90/60	0	1 (0.5%)

Source: Reviewer generated based on Table 2 (page 11) Applicant IR response dated July 22, 2025
Blood pressure of <90/60: Systolic blood pressure <90 and diastolic blood pressure <60 at the same assessment
Abbreviations: IR, information request; N, number of subjects in corresponding treatment group with available blood pressure data; n, number of subjects with adverse event

Table 76. Percentages of Subjects With Minimum Blood Pressure Values by Category of Blood Pressure Postbaseline, OASIS 1 (Weeks 12 to 26)

OASIS 1 (Weeks 13 to 26)	Elinzanetant-Elinzanetant (N=171) n (%)	Placebo-Elinzanetant (N=199) n (%)
Systolic blood pressure <90	1 (0.6%)	2 (1.2%)
Diastolic blood pressure <60	4 (2.3%)	4 (2.4%)
Blood pressure <90/60	0	1 (0.6%)

Source: Reviewer generated based on Table 2 (page 11) Applicant IR response dated July 22, 2025
Blood pressure of <90/60: Systolic blood pressure <90 and diastolic blood pressure <60 at the same assessment
Abbreviations: IR, information request; N, number of subjects in corresponding treatment group with available blood pressure data; n, number of subjects with adverse event

Table 77. Percentages of Subjects With Minimum Blood Pressure Values by Category of Blood Pressure Postbaseline, OASIS 2 (Weeks 1 to 12)

OASIS 2 (1 to 12 weeks)	Elinzanetant (N=201) n (%)	Placebo (N=199) n (%)
Systolic blood pressure <90	4 (2.0%)	2 (1.0%)
Diastolic blood pressure <60	10 (5.0%)	3 (1.5%)
Blood pressure <90/60	2 (1.0%)	1 (0.5%)

Source: Reviewer generated based on Table 2 (page 11) Applicant IR response dated July 22, 2025
Blood pressure of <90/60: Systolic blood pressure <90 and diastolic blood pressure <60 at the same assessment
Abbreviations: IR, information request; N, number of subjects in corresponding treatment group with available blood pressure data; n, number of subjects with adverse event

Table 78. Percentages of Subjects With Minimum Blood Pressure Values by Category of Blood Pressure Postbaseline, OASIS 2 (Weeks 13 to 26)

OASIS 2 (13 to 26 weeks)	Elinzanetant-Elinzanetant (N=171) n (%)	Placebo-Elinzanetant (N=180) n (%)
Systolic blood pressure <90	1 (0.6%)	2 (1.1%)
Diastolic blood pressure <60	5 (2.9%)	4 (2.2%)
Blood pressure <90/60	0	0

Source: Reviewer generated based on Table 2 (page 11) Applicant IR response dated July 22, 2025
Blood pressure of <90/60: Systolic blood pressure <90 and diastolic blood pressure <60 at the same assessment
Abbreviations: IR, information request; N, number of subjects in corresponding treatment group with available blood pressure data; n, number of subjects with adverse event

Table 79. Percentages of Subjects With Minimum Blood Pressure Values by Category of Blood Pressure Postbaseline, OASIS 3 (Weeks 1 to 52)

OASIS 3 (1 to 52 weeks)	Elinzanetant (N=313) n (%)	Placebo (N=314) n (%)
Systolic blood pressure <90	5 (1.6%)	3 (1.0%)
Diastolic blood pressure <60	18 (5.8%)	18 (5.7%)
Blood pressure <90/60	3 (1.0%)	2 (0.6%)

Source: Reviewer generated based on Table 2 (page 11) Applicant IR response dated July 22, 2025
Blood pressure of <90/60: Systolic blood pressure <90 and diastolic blood pressure <60 at the same assessment
Abbreviations: IR, information request; N, number of subjects in corresponding treatment group with available blood pressure data; n, number of subjects with adverse event

While there was a notable case of hypotension early in development (Subject (b) (6) it is not clear if this was related to elinzanetant or a vasovagal reaction. In Phase 2 and 3 studies, there were not notable imbalances or clinical impactful cases of

hypotension. The Applicant agreed to include a Warning and Precaution related to nervous system effects, (b) (4) The review team agrees with this assessment.

Accidental Injury Associated With Nervous System Disorders

The safety data were evaluated to assess whether nervous system disorders (including CNS depression [somnolence or fatigue], vertigo/dizziness, or hypotension/syncope) were associated with accidental injuries (such as fractures, accidents, or falls). At the Agency's request, the Applicant assessed all PTs under the MedDRA SMQ accidents and injuries in subjects with nervous system disorders. There were eight subjects with an AE assigned to both "SMQ accidents and injuries" and "AE CNS depression including somnolence or fatigue, vertigo/dizziness, or hypotension/syncope" (Table 80). Of these eight subjects, two subjects had an injury event on the same day as the nervous system disorder AE. One subject (Subject (b) (6) had a mild muscle strain and mild vertigo on the same day. Relevant medical history included Meniere's disease. Another subject (Subject (b) (6) [(b) (6) in the CSR]) had fatigue and a thermal burn on the same day. In the remaining six subjects, there did not appear to be an association between the injury/accident and the nervous system disorder AE. The review team agrees with the Applicant's conclusion that there did not appear to be a clinically relevant association between CNS depressive effects, vertigo/dizziness, and/or hypotension/syncope with accidents or injuries in the submitted data. However, there are inherent limitations to the data given that it is challenging to assess AEs and vital signs before an accident given that these events were not anticipated.

Table 80. Listing of Subjects With Any Event of Accidental Injury or Injuries Retrieved Using All PTs Under MedDRA SMQ Accidents and Injuries and CNS Depression (Somnolence or Fatigue), Vertigo/Dizziness, or Hypotension/Syncope

Patient ID/Age/Sex/Race/Drug	Baseline: BP in mmHg (HR in BPM)	PT/Date/Time of Onset (Days)	BP in mmHg (HR in BPM)
(b) (6)/53/F/W, EZN 120 mg (soft gel capsule)	85/51 (57)	Fatigue/ (b) (6)/2	(b) (6): 85/51 (57)
		Asthenia/ (b) (6)/2	
		Ligament sprain/ (b) (6)/171	(b) (6): 94/51 (62)
(b) (6)/51/F/W, PLC-EZN 120 mg (soft gel capsule)	124/80 (80)	Muscle strain/ (b) (6)/22 (AE on placebo)	(b) (6): 130/85 (80)
		Fatigue/ (b) (6)/89 (AE on EZN)	(b) (6): 145/90 (84)
(b) (6)/54/F/W, EZN 120 mg (soft gel capsule)	107/76 (93)	Muscle strain/ (b) (6)/28	(b) (6): 114/78 (79)
		Vertigo/ (b) (6)/28	
(b) (6)/59/F/W, EZN 120 mg (soft gel capsule)	104/78 (70)	Rotator cuff syndrome/ (b) (6)/79	(b) (6): 101/76 (75)
		Rotator cuff syndrome/ (b) (6)/164	(b) (6): 118/89 (76)
		Craniofacial fracture (orbital base) (b) (6) (b) (6)/292	*No data available for* (b) (6)
		Craniofacial fracture (sinus maxillaris)/ (b) (6) (b) (6)/292	
		Concussion/ (b) (6)/292	(b) (6): 111/76 (79)
		Fatigue/ (b) (6)/ (no further details available)	(b) (6): 103/72 (75)
		Subdural hematoma (b) (6)/386	(b) (6): 119/87 (71)
(b) (6)/52/F/NR, EZN 120 mg (soft gel capsule)	122/80 (68)	Post-traumatic pain (trauma on (b) (6) *pretreatment event*)/ (b) (6)/36	(b) (6): 116/80 (79)
			(b) (6): 125/84 (84)
		Dizziness/ (b) (6)/279	(b) (6): 120/80 (81)
(b) (6)/50/F/W, EZN 120 mg (soft gel capsule)	120/68 (63)	Presyncope/ (b) (6)/39	(b) (6): 113/56 (76)
		Heat stroke/ (b) (6)39	(b) (6): 119/68 (77)
		Dizziness/ (b) (6)196	*No data available for* (b) (6)
			(b) (6): 94/51 (76)
			(b) (6): 112/70 (72)

Patient ID/Age/Sex/Race/Drug	Baseline: BP in mmHg (HR in BPM)	PT/Date/Time of Onset (Days)	BP in mmHg (HR in BPM)
(b) (6), EZN 300 mg hard gel capsule	Screening: 148/84 (62) standing 144/88 (56) sitting day -1: 147/89 74/sitting; 147/97/standing	Somnolence/ (b) (6) /1 (lasted 3h) Somnolence/ (b) (6) /9 Contusion (bruising bilateral forearms)/ (b) (6) (b) (6) /2	(b) (6) pre-dose sitting (8:25h): 135/87 standing (8:28h) 131/92 (b) (6) 109/74 (62 sitting); 124/81 (standing)
(b) (6), 100mg hard gel capsule	Screening: 111/81 (88) Day -1: 110/79 (80)	Somnolence/ (b) (6) / 94/65 (75) Fatigue/ (b) (6) /15 Thermal burn/ (b) (6) /15	(b) (6): 94/65 (75) (b) (6): 94/59 (79)

Source: Reviewer generated based on Table 4 (pages 16-19) Applicant IR response dated July 22, 2025
Abbreviations: BP, blood pressure; BPM, beats per minute; EZN, elinzanetant; F, female; HR, heart rate; ID, identifier; IR, information request; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in corresponding treatment group with available blood pressure data; NR, not reported; PT, preferred term; SMQ, Standard Medical Dictionary for Regulatory Activities Query; W, white

Fractures

A total of 25 subjects in pooled studies OASIS 1, OASIS 2, and OASIS 3 reported 30 events of fractures, including two events of tooth fractures. There were five cases suggestive of fragility fractures, while the remaining cases appeared to be secondary to major trauma (such as a motor vehicle accident). Except for one tibial fracture (SID (b) (6)), all the events were assessed as nonserious and unrelated to study drug. Most were mild to moderate intensity, and none led to permanent drug discontinuation. During the placebo-controlled period (Week 1 to 12), out of 713 subjects in the elinzanetant group, 5 (0.7%) reported fracture events compared to 4 (0.6%) out of 713 subjects in the placebo arm. Many of the narratives specifically noted that there were no other symptoms, injury or relevant central nervous system adverse events, which is important to consider given that elinzanetant is associated with CNS events, such as fatigue and somnolence.

7.6.3.7. Dedicated Driving Ability Study

To further investigate the potential safety risk of somnolence and fatigue, the Applicant conducted a dedicated driving ability study with elinzanetant. These data were reviewed by the Division of Pharmacometrics. The results of the study and the assessment are summarized below.

The driving ability study with elinzanetant was performed in healthy women (mean age 52.1 years). This study was conducted in a single center based on randomized, double-blind, placebo- and active-controlled, 4-fold crossover design with oral administration of multiple doses (over 5 subsequent days to achieve steady state) of elinzanetant 120 mg (intended therapeutic dose), elinzanetant 240 mg, placebo, or zopiclone 7.5 mg as positive control (on Days 1 and 5 only) per treatment period. There were 61, 63, 62, and 61 subjects per group, respectively. The 240 mg/day dose was selected as supratherapeutic dose as it covers a potential maximum exposure increase of elinzanetant that could occur when it is administered with a weak CYP3A4 inhibitor as a comedication. The predicted steady-state plasma concentrations have been investigated in healthy subjects.

The study duration of 5 days was chosen because study state concentrations would be achieved after 5 days of once daily dosing. Each treatment period was separated by a 7- to 14-day washout period, which was assessed to be adequate.

Study interventions were administered in the evening via oral administration together with 240 mL of noncarbonated water at room temperature. Driving simulator assessments were performed the next morning, approximately 9 to 10 hours after dosing. This timing was chosen to reflect the recommended intake time of elinzanetant according to the intended label and to investigate potential residual driving impairment and cognitive effects which might pose a risk for patients. Blood samples for PK analysis were collected predose on Days 1 and 6- and 8.5-hours postdose on Days 2 and 6.

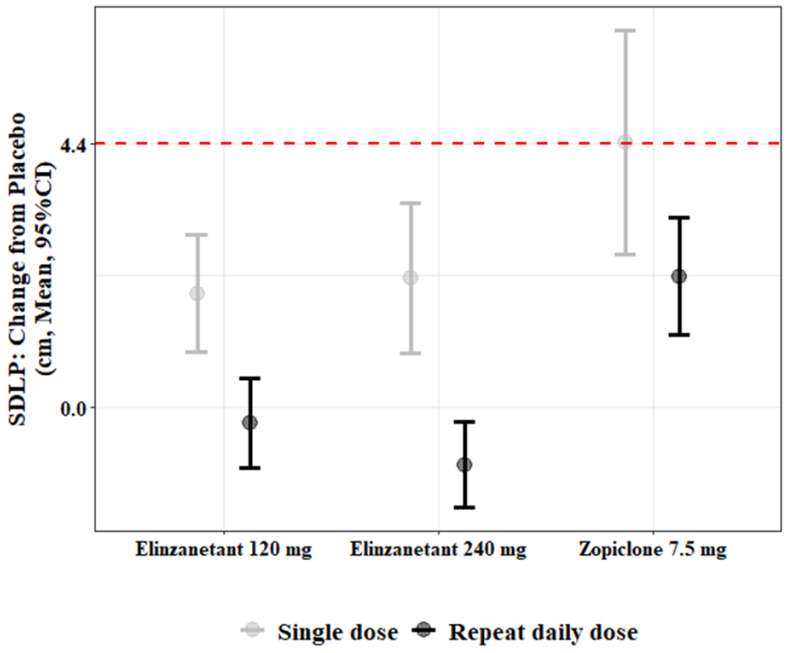
The simulated driving performance was measured using standard deviation of lateral position (SDLP) in the CRCDS-MiniSim™ 9 to 10 hours after dosing. SDLP data was analyzed using a mixed model with fixed effects for sequence, period, and treatment, with repeated periods for subjects. Noninferiority testing was applied, with a noninferiority margin of 4.4 cm. Additional

measures of simulated driving performance in the CRCDS-MiniSim™ included lane exceedance, excessive speed count, average speed and speed deviation, excessive ay, total collisions, and divided attention. Somnolence was measured using the Karolinska Sleepiness Scale score.

The primary outcome measure was the difference from placebo in the SDLP. Driving performance was evaluated using a validated threshold established in a population with blood alcohol concentration of 0.05%. 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. A small percentage of subjects (3% elinzanetant 120 mg; 2% elinzanetant 240 mg) had driving impairment after 5 consecutive days of elinzanetant administration.

Although the mean SDLP did not reach the threshold for driving impairment after administration of elinzanetant 120 or 240 mg, driving ability was impaired in some subjects. Analysis of the distribution of within-subject differences in SDLP from placebo on Day 2 by treatment showed that 17% of subjects treated with elinzanetant 120 mg exceeded the 4.4 cm threshold. Similarly, on Day 2, 23% of subjects treated with elinzanetant 240 mg exceeded the 4.4 cm threshold. Figure 33 shows the mean estimates of placebo-corrected next-day morning SDLP (cm, 95% CI) after single and repeated doses.

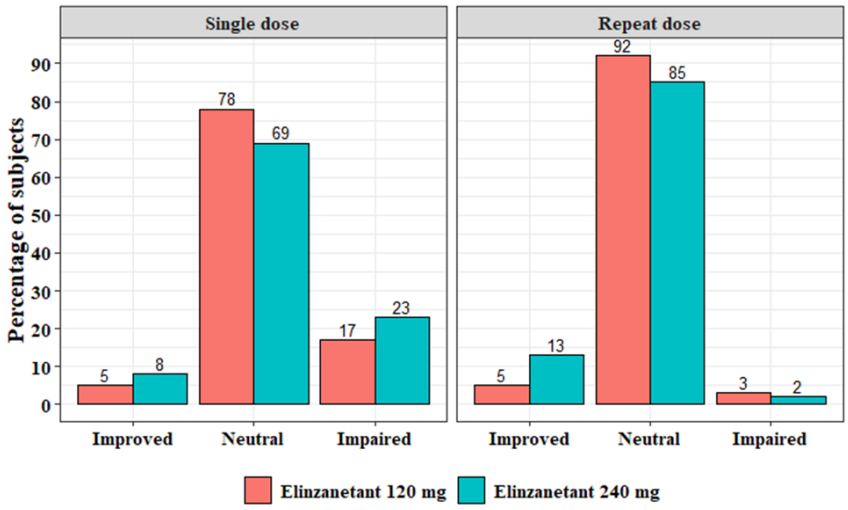
Figure 33. Mean Estimates of Placebo-Corrected Next-Day Morning SDLP [cm, 95% CI] After Single Dose and Repeated Doses



Source: Division of Pharmacometrics Driving study review dated 3/24/25
Note: Shown as Red Line is the Noninferiority Margin of 4.4 cm
Abbreviations: SDLP, standard deviation of lateral position

Figure 34 shows the proportion of improved (SDLP <4.4 cm), neutral (SDLP ≥4.4 and SDLP <4.4 cm), and impaired (SDLP ≥4.4 cm) SDLP changes after single and repeat dosing. Analysis of the distribution of within-subject differences in SDLP from placebo on Day 2 by treatment showed that 17% of subjects treated with elinzanetant 120 mg exceeded the 4.4 cm threshold. Similarly, on Day 2, 23% of subjects treated with elinzanetant 240 mg exceeded the 4.4 cm threshold.

Figure 34. Proportion of Improved (SDLP <4.4 cm), Neutral (SDLP ≥4.4 and SDLP <4.4 cm), and Impaired (SDLP ≥4.4 cm) Subjects After Single and Repeat Doses of 120 or 240 mg



Source: Division of Pharmacometrics Driving study review dated 3/24/25
Abbreviations: SDLP, standard deviation of lateral position

In summary, findings on primary and secondary endpoints in the driving study suggest that next day driving performance is impaired in some subjects taking single and repeat dose of elinzanetant 120 mg and 240 mg. In the WARNINGS AND PRECAUTIONS section, the label will note that there is a potential for next-day residual effects in some patients taking elinzanetant 120 mg. In addition, patients will be advised to take elinzanetant at bedtime.

7.6.3.8. Breast Safety

Mammograms were required in OASIS 1, OASIS 2, and OASIS 3 at screening and at the end-of treatment visit (if applicable). Prior mammogram results could be used for eligibility if obtained no more than 6 months prior to start of screening. At the end of treatment, a mammogram had to be obtained if the time that had elapsed since the previous mammogram was in line with local medical guidelines for the frequency of mammograms in the respective age group.

No clinically significant mammogram findings were reported in OASIS 1 or OASIS 2. In OASIS 3, there were two women with clinically significant abnormal mammogram findings after completing study treatment. For one of these two subjects, an SAE of invasive ductal carcinoma was reported. The other subject had a procedure, and a normal result was reported. At unscheduled visits, two subjects in the elinzanetant arm with normal results at baseline had clinically significant abnormalities after completion of the 52-week treatment. For one of these

subjects, an SAE of invasive breast carcinoma was reported. For the other subject, a follow-up procedure showed a clinically insignificant finding. The two cases of breast cancer were:

(1) Subject (b) (6) had an SAE of invasive breast carcinoma diagnosed 397 days after starting elinzanetant. The investigator considered this event to be moderate in intensity and related to elinzanetant. The last dose of elinzanetant had been received approximately 1 month prior. It is challenging to assess causality given the period without elinzanetant exposure prior to the AE.

(2) Subject (b) (6) was a 52 year old with invasive ductal breast carcinoma 361 days after starting elinzanetant. The investigator considered the event to be severe in intensity and not related to elinzanetant.

Given the limited number of events and the unclear causality with a common cancer, breast cancer will not be included in the USPI at this time.

7.7. Key Safety Review Issues

7.7.1. Hepatic Transaminase Elevation

Issue

There is nonclinical evidence for hepatotoxicity risk in short-term toxicity studies, and there is a risk of hepatotoxicity with another drug that inhibits NK3 (fezolinetant).

Background

Elinzanetant, is an oral, small molecule that inhibits NK1 and NK3 receptors. The clinical program included liver safety monitoring and there were two liver injury cases attributable to elinzanetant. The cases of DILI were hepatocellular and relatively modest in severity and recovered fully. While there were minimal imbalances in hepatic transaminases across the clinical development program, there were some imbalances in ALT elevations >3xULN on the elinzanetant arm compared to the placebo arm in OASIS 1 and OASIS 3.

Assessment

Although we did not identify a clinically significant hepatotoxicity risk with elinzanetant, there were cases of DILI and elevations in liver function tests. Also, postapproval, the drug will be used by patients with additional comorbidities and with less frequent monitoring. The number of subjects exposed in the clinical studies is relatively low compared to the potential postmarket use. Thus, clinically significant liver injuries could arise postmarketing, similar to what was seen with another NK3 inhibitor for the same indication (fezolinetant). It is important to alert patients and prescribers to this risk and to outline measures to take to monitor for hepatoxicity and evaluate patients prior to starting the medication.

Conclusion

Hepatic transaminase elevations are a risk with elinzanetant. To mitigate this risk, the labeling will include a Warning and Precaution to indicate that:

- Providers conduct:
  - Baseline bloodwork for hepatic function and injury prior to initiation of elinzanetant. Do not start elinzanetant if serum transaminase concentration is equal to or exceeds two times the ULN or if total bilirubin is equal to or exceeds two times the ULN
  - Follow-up blood work of hepatic transaminase concentrations 3 months after initiation
  - Unscheduled liver biochemical tests if new onset symptoms occur (new onset fatigue, decreased appetite, nausea, vomiting, pruritus, jaundice, pale feces, dark urine, or abdominal pain) suggestive of acute liver injury occur during elinzanetant treatment
- Not recommended for use in patients with moderate to severe cirrhosis (Child-Pugh B or C)
- Providers advise patients to discontinue elinzanetant immediately and seek medical attention including hepatic laboratory tests if they experience signs or symptoms that may suggest liver injury.

In addition, the Applicant will report postmarket cases of acute liver injury as AESIs to ensure their timely reporting and follow-up to the Agency. This enhanced pharmacovigilance (ePV) program will consist of (1) expeditious reports of AEs of interest beyond minimum reporting requirements, and (2) a summary and assessment of AEs of interest at a frequency defined by FDA.

7.7.2. Risk of Pregnancy Loss

Issue

Based on findings from animal reproduction studies, elinzanetant may cause pregnancy loss or stillbirth when administered during pregnancy.

Background

In reproductive and developmental toxicity studies, elinzanetant administration prior to or during pregnancy caused fetal harm in rats in the form of pre- and postimplantation loss, reduced litter size or total litter loss, decrease in fetal body weight, and decrease in neonatal pup viability. In a fertility and early embryonic development study in rats, there was an increase in the percentage of pre- and postimplantation embryo loss and decrease in fetal body weights at 14-fold the human therapeutic exposure when rat dams were treated orally prior to mating and through the early embryonic period.

In a pre- and postnatal developmental study in rats, a higher incidence of still born pups, an increase in total litter loss, a decrease in pup viability between postnatal Days 0 and 4, and an increase in the number of neonatal pups without milk in the stomach were observed in the mid- and high-dose groups, with maternal systemic exposures that were within the range of human

therapeutic exposure. Decreased maternal care was also a clinical observation in these treatment groups. Whether the neonatal effects were due to decreased maternal care or other potential elinzanetant-related effects on the offspring could not be definitively concluded from this study.

In an embryofetal development study in rabbits, maternal toxicity was noted in the form of marked body weight loss and decreased food consumption at systemic exposures that were within the range of human therapeutic exposure.

No teratogenicity was observed in the reproductive and developmental studies with elinzanetant in rats or rabbits.

These nonclinical data indicate that elinzanetant may cause pregnancy loss or stillbirth when administered during pregnancy.

Elinzanetant is indicated for the treatment of moderate to severe VMS due to menopause. Despite its intended use in menopausal women, there is a need to address the potential risks for females of reproductive potential who might inadvertently use the drug.

Assessment

Given the risk of pregnancy loss or still birth based on data from animal studies, elinzanetant is contraindicated during pregnancy.

Conclusion

To mitigate the risk of pregnancy loss or still birth due to exposure to elinzanetant during pregnancy, the labeling will include:

(1) A contraindication for use in pregnancy

(2) A Warning and Precaution with instructions to:

   (a) exclude pregnancy in females of reproductive potential prior to initiating elinzanetant, and

   (b) advise females of reproductive potential to use effective contraception during treatment with elinzanetant and for 2 weeks after stopping elinzanetant

These measures aim to prevent potential exposure to elinzanetant during pregnancy, thereby reducing the risk of pregnancy loss or stillbirth in case of accidental use by pregnant women or women who may become pregnant. Importantly, elinzanetant is intended for you in woman experience symptoms associated with menopause.

7.7.3. Endometrial Tumor Abnormality

Issue

Based on findings from a 2-year carcinogenicity study in female rats, there was an increase in incidence of endometrial adenocarcinoma and the combination of malignant and benign endometrial tumors and squamous cell carcinoma of the uterus.

Background

In a 2-year carcinogenicity study in female rats, oral doses of elinzanetant ≥60 mg/kg/day (29-fold the total $AUC_{(0-24)}$ at the human therapeutic dose) increased the incidence of endometrial adenocarcinoma, the combination of malignant and benign endometrial tumors and squamous cell carcinoma of the uterus, and lymphomas of the hematolymphoid system. These effects were not observed at a dose representing 7-fold the total $AUC_{(0-24)}$ at the human therapeutic dose.

In a 26-week carcinogenicity study in rasH2 transgenic mice, there was no evidence of drug-related carcinogenicity at 85 or 70 mg/kg/day in males or females, respectively.

Elinzanetant showed no genotoxic potential in bacterial mutation assay (Ames test), mouse lymphoma assay, and in vivo bone marrow micronucleus test in rats. Additionally, the principal human metabolites of elinzanetant were negative for genotoxicity in vitro in the Ames and micronucleus test.

In terms of clinical safety data, endometrial safety was assessed in OASIS 1, OASIS 2, and OASIS 3 by TVU and endometrial biopsies according to FDA draft guidance for industry *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation* (January 2003).

Overall, 609 women underwent end-of treatment-endometrial biopsies in OASIS 1, OASIS 2, and OASIS 3. A total of 477 women received elinzanetant 120 mg had endometrial biopsies. Among these, 140 received elinzanetant for up to 52 weeks, 162 received elinzanetant for up to 26 weeks, and 175 received elinzanetant for up to 14 weeks. Three cases of endometrial hyperplasia (one with and two without atypia), and a case of endometrial glandular hyperplastic polyp (without atypia), were identified upon examination of individual pathologists' readings. Overall, the incidence of endometrial abnormality in all three OASIS studies combined was 0.8% (4 out of 477).

Assessment

In a 2-year carcinogenicity study in female rats, there was a statistically significant and dose-related increase in the incidence of endometrial adenocarcinoma and the combination of malignant and benign endometrial tumors and squamous cell carcinoma of the uterus. However, this finding was at exposures much higher than the clinical dose (29 times the recommended clinical dose), and the clinical significance of these nonclinical findings is unknown. Further, there were no concerning findings in other nonclinical carcinogenicity assessments. Transvaginal ultrasounds and endometrial biopsy data up to 52 weeks from the clinical safety did not reveal a rate of endometrial abnormality above the background rate in this population (1%).

The review team considered whether the carcinogenicity information warranted inclusion of the concern for endometrial safety as a Warning and Precaution in labeling. The review team also considered whether additional safety mitigation measures, such as a postmarketing requirement or ePV would better characterize the endometrial safety risk. Given that the clinical significance of the nonclinical findings is unknown and that the rate of endometrial abnormalities in women who received elinzanetant was in line with expected background rate, it was determined that a

Warning was not necessary and that postmarketing requirement or ePV are not needed to further characterize the risk endometrial abnormality.

Conclusion

In light of the within background rate of endometrial abnormalities in the Phase 3 database with up to 52 weeks of surveillance, the clinical significance of nonclinical findings of endometrial malignancies, at an exposure 29 times the recommended clinical dose, is unknown. The nonclinical findings and clinical endometrial abnormalities will be communicated in Sections 13.1 and 14.2 of labeling, respectively. Enhanced surveillance postmarket is not necessary.

7.7.4. Seizures

Issue

Convulsions were observed in nonclinical studies conducted in male and female rats.

Background

Given the nonclinical observations related to convulsions, the clinical data were reviewed for safety signals related to seizures/convulsions. In OASIS 1, OASIS 2, and OASIS 3, there were seven women with a medical history of epilepsy or seizure (four in the elinzanetant group and three in the placebo group). In OASIS 1, OASIS 2, and OASIS 3, there was one case of generalized tonic-clonic seizure. An Information Request was sent to the Applicant, and they responded on March 10, 2025, with additional details of the case and seizures in the clinical program. The subject was a 58-year-old woman who had a history of generalized tonic-clonic seizures greater than 30 years ago. She had been treated with various medications, and in (b) (6) treatment (most likely Zarontin [ethosuximide] and Tegretol [carbamazepine]) was discontinued since she was doing well and had been seizure free. On (b) (6), 46 days after staring elinzanetant, she had two seizures at home and did not initially seek medical care. She then had a third seizure on the same day and went to the hospital. The generalized tonic-clonic seizure was felt to be related to study intervention and of mild intensity. The event was considered serious as it required or prolonged hospitalization. She was treated for the seizure, discontinued study medication, and withdrew from the study. She was noted to have recovered.

There was another case of a potential seizure during the clinical development program. Subject (b) (6) was a 56-year-old woman who had an SAE of syncope 55 days after starting elinzanetant. The drug was interrupted and then the subject was able to complete the study per protocol. The cause of the syncope was unclear. She reported that she felt disoriented and passed out while in her car. She was admitted to the hospital and experienced slurred speech, blurred vision, and elevated blood pressure and heart rate. It was noted that she may have had a seizure and would require additional follow-up. Seizures were not included in her medical history. Records noted that she had left-sided facial numbness, tremors, confusion, and hypomagnesemia. Diagnostic evaluations included angiogram, chest X-ray, computerized tomogram head, electrocardiogram, and magnetic resonance imaging of the head. The investigator considered the SAE not related to the study medication, which is supported by the observation that the subject was able to restart elinzanetant and complete the study.

There were no additional cases of seizures detected in any other Phase 3 clinical studies. There was no specific inquiry into seizure history at enrollment and no specific exclusion criterion for seizure history. However, investigators had the possibility to screen-fail based on the inclusion criterion "In good general health…". In addition, the list of prohibited medications may have precluded inclusion of some subjects receiving treatments to prevent seizures.

Assessment

There was only one definitive serious adverse event of seizure. However, it is notable that the event occurred in an individual whose seizure disorder was well controlled for years without antiseizure medications and who experienced three seizures within two months after starting elinzanetant. Given that seizure history was not specifically solicited at baseline, having an isolated case of seizure in the clinical database makes it unclear if patients with a history of seizures are at greater risk for recurrence with elinzanetant treatment. However, the only individual with a seizure in the clinical program did have a history of seizures.

Conclusion

Given the nonclinical and clinical findings related to seizures/convulsions, these findings will be communicated in labeling as a Warning and Precaution. Since only one case occurred and a lack of clarity if patients with a history of seizure disorder are at increased risk of recurrence, there will not be a specific contraindication to the use of elinzanetant in patients with a history of seizure disorder.

7.7.5. Nervous System Effects

Issue

Increased nervous system disorders (including fatigue, somnolence, and dizziness/vertigo) were observed in subjects treated with elinzanetant in the clinical development program.

Background

Adverse events in the SOC nervous system disorders occurred in a greater percentage of subjects in the elinzanetant group (22%) compared to the placebo group (11.8%) in OASIS 3. An in-depth analysis was performed of adverse events of interest including somnolence, fatigue, vertigo/dizziness, syncope, and hypotension/orthostatic hypotension.

Assessment

In the SAF, pooled safety population, (up to Week 12) somnolence or fatigue occurred in a higher percentage of subjects treated with elinzanetant (7.0%) compared to placebo (2.3%). None of the AEs of somnolence or fatigue were serious. More subjects in the elinzanetant discontinued due to an AE of somnolence or fatigue (1.8%) compared to the placebo group (0%). The majority of events occurred during the first two weeks of treatment and were mild or moderate and resolved. No difference in the incidence rates (100 person-years) in accidents and injuries (SMQ) was seen for the elinzanetant and placebo groups.

Similar trends were seen for AEs of dizziness. In OASIS 1, OASIS 2, and OASIS 3, AEs of dizziness occurred more frequently in subjects in the elinzanetant group compared to the placebo group. In OASIS 3, dizziness occurred in 2.2% of the elinzanetant group compared to 1.0% of the placebo group. The majority of these events were mild or moderate. In OASIS 3, in the elinzanetant group, 1% of subjects discontinued due to dizziness compared to 0% in the placebo group. The two subjects who developed dizziness leading to discontinuation developed the dizziness on Day 11 to 12. There was also one subject in OASIS 3 with an SAE of dizziness (PT vertigo) who reported peripheral vertigo 58 days after starting elinzanetant. The SAE was of severe intensity. The investigator did not think it was related to elinzanetant. The subject continued treatment and the SAE resolved.

The Applicant conducted a driving study that suggested that next day driving performance is impaired in some subjects taking single and repeat dose of elinzanetant 120 mg and 240 mg.

There was one notable event of hypotension in a healthy volunteer, however it was unclear if it was secondary to a vasovagal event or elinzanetant. There were small imbalances related to decreased blood pressure in the clinical development program, but not clinically significant findings. Given that hypotension and syncope could be secondary to vascular etiologies and given the lack of significant clinical findings, they will not be described in the product labeling at this time.

Conclusion

The label will mention that there is a potential for next-day residual effects in some patients taking elinzanetant 120 mg. The labeling will include a Warning and Precaution of CNS Depressant Effects and Daytime Impairment. The Warning and Precaution will describe the nervous system effects (including somnolence, fatigue, vertigo, dizziness, and presyncope). In addition, patients will be advised to take elinzanetant at bedtime. Dizziness, fatigue, and somnolence will be mentioned in Section 6 of the labeling.

7.7.6. Photosensitivity

Issue

In vitro studies suggest a potential risk of photosensitivity reactions with elinzanetant.

Background

An in vitro study demonstrated that elinzanetant has some potential for photosensitization. While studies of photosensitivity in animals were not conducted, there is evidence that elinzanetant distributes to and accumulates in melanin-containing tissues in the rats. Based on the in vitro phototoxicity assay, the most conservative MOE for phototoxicity was approximately 7-fold. The MOE should be interpreted with caution because elinzanetant concentrations in human pigmented tissues are derived based on the distribution of elinzanetant to rat pigmented tissues (eyes and skin) and no additional in vivo animal photosensitivity studies have been conducted.

Photosensitivity is a reaction that occurs when a drug causes the skin to become more sensitive to ultraviolet (UV) light or visible light, leading to skin reactions upon exposure to sunlight or

other light sources. Understanding the risk and characteristics of phototoxicity is important for patient safety and appropriate use of elinzanetant.

In OASIS 1, OASIS 2, and OASIS 3, five subjects developed phototoxicity reactions. Four out of five subjects did not have a history of photosensitivity. One subject had a previous sun-exposure reaction.

Three cases occurred in OASIS 1:

(1) Subject (b) (6) was a 52-year-old woman who developed phototoxicity reaction 1 day after starting elinzanetant. The AE was mild in severity and recovered/resolved.

(2) Subject (b) (6) was a 52-year-old woman who developed a phototoxicity reaction 46 days after starting elinzanetant. The AE was described as itchy skin on sun-exposed areas. The AE was mild in severity and considered related to study drug.

(3) Subject (b) (6) was a 58-year-old woman who developed a photosensitivity reaction 120 days after starting elinzanetant. The AE was of moderate intensity and considered related to elinzanetant.

Two cases occurred in OASIS 3:

(1) Subject (b) (6) was a 60-year-old woman who developed an AE of phototoxicity reaction 290 days after starting elinzanetant that led to discontinuation. The event was moderate in intensity and considered related to study intervention. The event resolved after stopping the medication.

(2) Subject (b) (6) was a 59-year-old woman who developed a photosensitivity reaction 157 days after starting elinzanetant. The event was mild and considered not related to study treatment. Given the risk of photosensitivity observed in the clinical program, the review team would consider this AE related to elinzanetant. The subject was able to continue participation in the study and discontinued the study later due to subject decision.

Assessment

An in vitro study demonstrated that elinzanetant has some potential for photosensitization. While the MOE for phototoxicity is approximately 7-fold, this must be interpreted with caution because elinzanetant concentrations in human pigmented tissues are derived based on the distribution of elinzanetant to rat pigmented tissues (eyes and skin) and no additional in vivo animal photosensitivity studies have been conducted.

In the clinical program, the photosensitivity events occurred over a wide range of times from initial exposure to elinzanetant. However, this does not rule out a photosensitivity reaction, since the reaction is dependent on exposure to sunlight, which would not be controlled over the clinical study. While the frequency of photosensitivity reactions was low in the clinical program, it is important to communicate the risk to patients so that it can be mitigated.

Conclusion

The risk of photosensitivity will be communicated in labeling in Section 6 Adverse Reactions to communicate this safety consideration. There was consideration of including the safety consideration as a Warning, but it was determined that it was reasonable to include the information in Section 6 with routine postmarketing surveillance.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Elinzanetant is also referred to as GSK1144814, BAY 3427080, and NT-814.

Renal Impairment

The effects of renal impairment on the pharmacokinetics of elinzanetant were assessed (Study 21669) following a single 120 mg dose (2 x 60 mg soft gel capsules) in male and female subjects with varying degrees of renal function: mild (estimated glomerular filtration rate [eGFR] 60 to 90 mL/min), moderate (eGFR 30 to 59 mL/min), and severe (eGFR <30 mL/min), as compared to those with normal renal function (≥90 mL/min). For elinzanetant, individuals with mild renal impairment exhibited a 1.61-fold increase in AUC and a 1.86-fold increase in C_{max} compared to healthy subjects. In those with moderate renal impairment, the AUC and C_{max} increased by 1.73-fold and 1.84-fold, respectively. Notably, individuals with severe renal impairment showed a 1.12-fold increase in AUC and a 1.2-fold increase in C_{max} compared to healthy subjects. For metabolites (M18/21, M27, and M30/34), the extent of exposure increase in individuals with mild, moderate, and severe renal impairment to those with normal renal function was less than that for elinzanetant (see Section 14.2.3.1).

Population PK analysis showed that mild (n=402) or moderate (n=23) renal impairment does not significantly affect the drug exposure (AUC) of elinzanetant in the Phase 3 study population (see Section 14.5). The safety evaluation by the clinical review team did not identify additional safety concerns for subjects with mild or moderate renal impairment who participated in the Phase 2 (SWITCH-1) and Phase 3 (OASIS 1, OASIS 2, and OASIS 3) clinical studies. Therefore, dose adjustment of elinzanetant for patients with mild or moderate renal impairment is not warranted.

Study 21669 demonstrated that severe renal impairment did not result in a significant change in elinzanetant exposure (1.12-fold) and the extent of C_{max} increase in subjects with severe renal impairment (1.56-fold) is less than that in subjects with mild to moderate renal impairment (1.84 to 1.86-fold). Considering that renal clearance plays a minimal role in the elimination of elinzanetant (less than 1% of the dose is excreted in urine), the review team recommends no dose adjustment for patients with severe renal impairment as well. Elinzanetant is not recommended for patients with end-stage renal disease because the impact of end-stage renal disease on the pharmacokinetics of elinzanetant has not been evaluated.

Hepatic Impairment

A dedicated hepatic impairment study (Study 21668) was conducted to evaluate the pharmacokinetics, safety, and tolerability of elinzanetant in subjects with impaired hepatic function, categorized as Child-Pugh A (mild) or Child-Pugh B (moderate), in comparison to matched controls with normal hepatic function. Elinzanetant total maximum concentration at steady state ($C_{max,ss}$) increased by 1.16-fold in subjects with mild hepatic impairment (90%CI: [0.81; 1.67]) and by 2.32-fold in subjects with moderate hepatic impairment (90%CI: [1.61; 3.34]). Similarly, AUC over 24 hours at steady state (AUC_{ss}) increased by 1.45-fold in subjects with mild hepatic impairment (90%CI: [1.04; 2.04]) and by 2.34-fold in subjects with moderate hepatic impairment (90%CI: [1.67; 3.28]). The total exposure of the metabolites M18/M21, M27, and M30/34 ($C_{max,ss}$ and AUC_{ss}]) did not exhibit significant changes (<2-fold) in subjects with mild or moderate hepatic impairment (refer to Section 14.2.3.2; Table 154, Table 155, and Table 156).

A population PK analysis revealed that mild hepatic impairment does not significantly affect the drug exposure (AUC) of elinzanetant in the Phase 3 study population (refer to Section 14.5). The safety evaluation by the clinical review team did not identify additional safety concerns for subjects with mild hepatic impairment who participated in the Phase 2 (SWITCH-1) and Phase 3 (OASIS 1, OASIS 2, and OASIS 3) clinical studies. Therefore, no dose adjustment of elinzanetant is recommended for patients with mild hepatic impairment.

Individuals with moderate hepatic impairment, as assessed in the dedicated study, exhibited a 2.32-fold increase in AUC compared to healthy subjects. Additionally, the Phase 2 and 3 clinical studies did not include subjects with moderate or severe hepatic impairment and, thus, the impact of moderate or severe hepatic impairment on the safety of elinzanetant remains unknown. Therefore, elinzanetant is not recommended for patients with moderate or severe hepatic impairment.

Subgroup Analyses by Race, Age, and Geriatric Use

Race

The population PK analysis demonstrates that race is not a significant covariate and there was no significant difference in elinzanetant exposure (AUC) between Black and non-Black subjects in the OASIS 1, OASIS 2, and OASIS 3 studies (refer to Section 14.5).

Age

Clinical pharmacology studies with elinzanetant included subjects with an age range of 18 to 75 years. There were no apparent age-related differences in the safety and tolerability of elinzanetant.

Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing elinzanetant to determine whether those over 65 years of age differ from younger women in their response to elinzanetant.

8.2. Extrinsic Factors

Food Effect

Study 21678 assessed the effect of a high-fat breakfast (800 to 1000 kcal, with 500 to 600 kcal derived from fat and 250 kcal from carbohydrates) on the bioavailability of elinzanetant following 40, 80, 120, and 160 mg once-daily (QD) administration. Under fed conditions, C_{max} of elinzanetant was reduced by approximately 70%, and $AUC_{(0-24)}$ by 30 to 40% compared to the fasted state. Additionally, the median time to maximum concentration (T_{max}) was approximately doubled in the fed state. These effects were consistent across the dosage range of 40 to 160 mg QD.

Despite the exposure reduction due to food intake, the clinical pharmacology review team concluded that the exposure change was clinically insignificant. This assessment was based on the outcomes from Phase 3 clinical studies (OASIS 1, OASIS 2, and OASIS 3) and the Phase 2b (SWITCH-1) study, where elinzanetant 120 mg was administered before bedtime regardless of food intake. These clinical studies demonstrated a statistically significant and clinically meaningful reduction in both the frequency and severity of hot flashes in patients with VMS (refer to Section 6). Therefore, elinzanetant can be administered with or without food at bedtime.

Drug Interactions

Effect of Other Drugs on Elinzanetant

Elinzanetant is primarily metabolized by CYP3A4 and is a substrate of P-glycoprotein (P-gp) (refer to Section 14.1.2).

CYP3A4 Inhibitors

Strong CYP3A4 and P-gp Inhibitors

The effect of multiple doses of the strong CYP3A4 and P-gp inhibitor, itraconazole 200 mg (2x100 mg capsules), on pharmacokinetics of a single dose of elinzanetant 40 mg was assessed in Study 21679. Study results showed that elinzanetant C_{max} increased by 3.3-fold and AUC_{inf} increased by 6.32-fold following concomitant use with itraconazole. These data indicate that elinzanetant is a sensitive substrate of CYP3A4 and/or P-gp. The increased exposure of elinzanetant by strong CYP3A4 and/or P-gp inhibitors may increase the risk of elinzanetant-associated adverse events. Therefore, concomitant use of elinzanetant with strong CYP3A4 or P-gp inhibitors is not recommended.

Moderate CYP3A4 Inhibitors

A physiologically based pharmacokinetic (PBPK) model was employed to predict the concentration-time profiles of elinzanetant when coadministered with the moderate CYP3A4 inhibitor erythromycin and the weak CYP3A inhibitor cimetidine.

Following multiple dosing of elinzanetant 120 mg QD and coadministration of the moderate CYP3A4 inhibitor erythromycin (500 mg three times daily), the predicted mean $AUC_{(0-24)}$ values were increased by 3.01-fold for elinzanetant (Table 81).

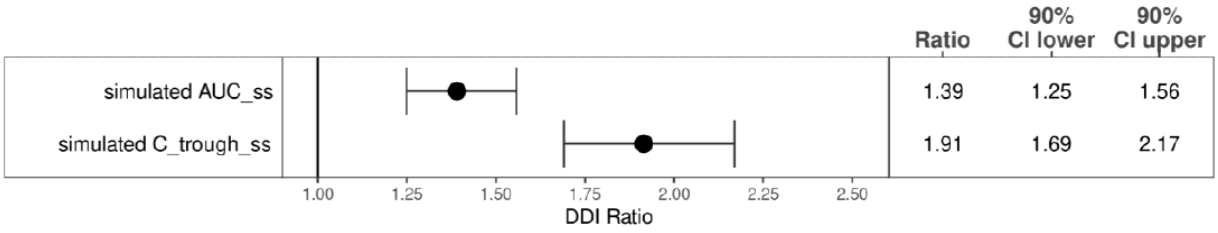
Table 81. PBPK Model-Based Geometric Mean Ratios (90% CI) of AUC and C_{max} of Elinzanetant and the Major Metabolite M30/34 With Different CYP3A4 Inhibitors vs. Elinzanetant Alone

Victim Component	Precipitant Drug	Type of CYP3A4 Inhibitor	PK Parameter (Simulated)	Geometric Mean Ratio	CI (90%)
Elinzanetant	Erythromycin	Moderate	$AUC_{(0-24)}$	3.01	2.71; 3.33
			$C_{max,md}$	2.00	1.83; 2.19
	Cimetidine	Weak	$AUC_{(0-24)}$	1.47	1.35; 1.60
			$C_{max,md}$	1.30	1.19; 1.43
M30/34	Erythromycin	Moderate	$AUC_{(0-24)}$	2.60	2.33; 2.88
			$C_{max,md}$	2.57	1.41; 1.75
	Cimetidine	Weak	$AUC_{(0-24)}$	1.28	1.18; 1.41
			$C_{max,md}$	1.11	1.02; 1.21

Source: Applicant summary of clinical pharmacology, Figure 3-4, and PBPK report CPMX 50214, Figure 5-37 and 5-38
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CYP, cytochrome; M, metabolite; $_{md}$, multiple dose; PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic

Therefore, the review team requested the Applicant to conduct additional PBPK simulations to explore the option of managing this drug-drug interaction (DDI) by reducing the dose of elinzanetant by half (i.e., from 120 mg QD to 60 mg QD) for subjects who have concomitant use of moderate CYP3A4 inhibitors. The simulation results suggest that the dose reduction to 60 mg QD would reduce the systemic exposure of elinzanetant to a level that is slightly higher (i.e., 39% for steady state AUC) than elinzanetant 120 mg QD alone (Figure 35). The 39% increase in AUC_{ss} resulting from elinzanetant 60 mg QD in subjects with concomitant use of moderate CYP3A inhibitors compared to subjects taking elinzanetant 120 mg QD alone is not considered clinically significant. Therefore, the review team recommends reducing the dose of elinzanetant from 120 mg QD to 60 mg QD for patients with the concomitant use of moderate CYP3A4 inhibitors.

Figure 35. Geometric Mean Ratio (90% CI) of Steady-State AUC and Steady-State C_{trough} for Elinzanetant 60 mg QD With the Concomitant Use of the Moderate CYP3A4 Inhibitor Erythromycin in Comparison to Elinzanetant 120 mg QD Alone



Source: Applicant's response to FDA's information request dated December 17, 2024
Abbreviations: AUC, area under the concentration-time curve; C_{trough}, lowest plasma concentration; CYP, cytochrome; DDI, drug-drug interaction; QD, once daily; ss, steady-state

Weak CYP3A4 Inhibitors

The PBPK model predicted that concomitant use with cimetidine results in a 1.3-fold increase in the C_{max} and a 1.5-fold increase in AUC for elinzanetant, and a 1.1-fold increase in C_{max} and a 1.3-fold increase in AUC for M30/34 (Table 81).

The effect of weak CYP3A4 inhibitors (such as alprazolam, amiodarone, amlodipine, atorvastatin, berberine, chlorzoxazone, fluoxetine, ginkgo biloba, isoniazid, propiverine, ranitidine, tacrolimus, ticagrelor) on the exposure of elinzanetant and its major metabolite M30/34 was investigated in all Phase 3 studies using the population pharmacokinetic (popPK) model. As shown in Table 82, no clinically relevant effect was observed on the exposure of elinzanetant and M30/34 when administered with weak CYP3A4 inhibitor. The predicted DDI effects of a weak CYP3A inhibitor (Table 81) is consistent with popPK analysis.

Table 82. Summary Statistics of Elinzanetant $AUC_{(0-24)\ ss}$ And M30/34 $AUC_{(0-24)\ ss}$ Stratified by Coadministration of Weak CYP3A4 Inhibitors for Subjects, OASIS 1, OASIS 2, and OASIS 3

Object Component	Type of CYP3A4 Inhibitor	PK Parameter (Simulated)	Geometric Mean Ratio	CI (90%)
Elinzanetant	Weak	$AUC_{(0-24)}$	1.13	1.10; 1.20
M30/34	Weak	$AUC_{(0-24)}$	1.13	1.10; 1.21

Source: Applicant's summary of clinical pharmacology, figure 3-4
Abbreviations: AUC, area under the concentration-time curve; CYP, cytochrome; M, metabolite; PK, pharmacokinetic; $_{ss}$, steady-state

Given these considerations, the Applicant's proposal that no dose adjustment is necessary when weak CYP3A4 inhibitors are used concurrently is deemed acceptable.

CYP3A4 Inducers

The effect of carbamazepine (a moderate to strong CYP3A4 inducer and a P-gp inducer) on the exposure of elinzanetant and metabolites, M30/34, M27, and M18/21, was investigated in healthy subjects in Study 21667. The study showed that the AUC of elinzanetant was reduced by 64% and C_{max} was reduced by 44% by the concomitant use of 600 mg carbamazepine daily. The extent of reduction in the exposure of metabolites M18/M21, M27 and M30/M34 was comparable (Table 83).

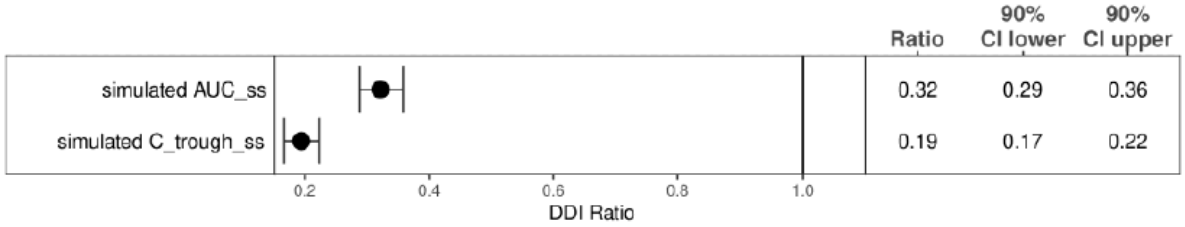
Table 83. Assessment of Drug-Drug Interaction With Carbamazepine – Point Estimates and 90% Confidence Intervals of the Treatment Ratios "Elinzanetant With Carbamazepine/Elinzanetant Without Carbamazepine" of Elinzanetant and its Metabolites (N=14)

Parameter	Ratio Elinzanetant with carbamazepine/ elinzanetant without carbamazepine for	Geo. LS mean	90% confidence interval	Geo. CV (%)
AUC	Elinzanetant	0.3591	[0.3144 ; 0.4101]	20.05
	M18/M21 (BAY 3462934)	0.4141	[0.3697 ; 0.4639]	17.08
	M27 (BAY 3462932)	0.3511	[0.3028 ; 0.4027]	22.41
	M30/M34 (BAY 3462933)	0.2958	[0.2560 ; 0.3417]	21.83
C_{max}	Elinzanetant	0.5572	[0.5032 ; 0.6171]	15.33
	M18/M21 (BAY 3462934)	0.7771	[0.6832 ; 0.8839]	19.41
	M27 (BAY 3462932)	0.6343	[0.5630 ; 0.7146]	17.96
	M30/M34 (BAY 3462933)	0.6316	[0.5567 ; 0.7166]	19.03

Source: Table 9-7 of the CSR for Study 21667
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geo, geometric; LS, least squares; M, metabolite; N, number of subjects in treatment group

Physiologically based pharmacokinetic simulations were conducted to assess the steady-state exposures ($AUC_{(0-24),ss}$ and $C_{trough,ss}$) of elinzanetant when administered once daily at a repeated dose of 120 mg, with or without coadministration of carbamazepine (2 x 300 mg). The PBPK simulations indicated that the concomitant use of 600 mg carbamazepine resulted in a 68% reduction in the $AUC_{(0-24),ss}$ of elinzanetant. Moreover, the $C_{trough,ss}$ of elinzanetant was decreased to a greater extent, with a reduction of 81%, as illustrated in Figure 36.

Figure 36. Model-Predicted Geometric Mean Ratio (90% CI) of $AUC_{(0-24),ss}$ and $C_{trough,ss}$ for Elinzanetant 120 mg With/Without Concomitant use of the CYP3A4 Inducer Carbamazepine



Source: Applicant's IR response dated January 3, 2025
Abbreviations: AUC_{ss}, area under the curve during the steady-state period; $C_{trough,ss}$, lowest plasma concentration at steady-state; CYP, cytochrome; DDI, drug-drug interaction; IR, information request

The observed/simulated reduction in elinzanetant exposures by the concomitant use of moderate to strong CYP3A4 and P-gp inducers may reduce the effectiveness of elinzanetant because elinzanetant at doses of 40 mg and 80 mg QD was less effective in reducing the frequency and severity of HF compared to the dose of 120 mg dose QD in the Phase 2b study (SWITCH-1) and based on the Phase 2b study results, elinzanetant 120 mg QD was selected for safety and efficacy evaluation in the Phase 3 studies OASIS 1, OASIS 2, and OASIS 3.

In Phase 3 clinical studies, PK data were collected from 10 subjects who received moderate CYP3A4 inducers, constituting 0.5% of total PK data observations. However, only one subject used a moderate CYP3A4 inducer throughout the entire treatment period. The limited number of PK observations in subjects using moderate CYP3A4 inducers concurrently did not meet the requirement of at least 10% categorical covariate inclusion in popPK analysis. Consequently, the

effect of moderate CYP3A4 inducers on the pharmacokinetics of elinzanetant was not evaluated in the popPK analysis. Furthermore, no observations were available for concomitant use with strong CYP3A4 inducers in the Phase 3 studies.

In the Phase 3 clinical studies, nine subjects used weak CYP3A4 inducers (e.g., armodafinil, modafinil, or rufinamide) chronically throughout the study period. Elinzanetant exposures in these subjects were estimated using a population PK approach and compared to those without the use of any CYP3A4 inducers. This analysis revealed that with chronic use of weak CYP3A4 inducers, neither elinzanetant nor M30/34 $AUC_{(0\text{-}24),ss}$ were reduced but were instead increased by ~approximately 20%, as indicated in Table 84 and Table 85. As further confirmation of the PK results, the observed efficacy data (appendix 4, submitted in DARRTS dated May 28, 2025) did not demonstrate a reduction in the frequency and severity of daily hot flushes with chronic concomitant administration of weak CYP3A4 inducers in these 9 subjects in the Phase 3 clinical studies, indicating that the concomitant use of weak inducers has no clinically relevant impact on the efficacy of elinzanetant.

Table 84. Geometric Mean $AUC_{(0\text{-}24),ss}$ Ratios of Elinzanetant Stratified by Coadministration of Weak CYP3A4 Inducers for Subjects, OASIS 1, OASIS 2, and OASIS 3

Covariate categories[#]	N	Minimum (h·µg/L)	Maximum (h·µg/L)	Median (h·µg/L)	Arithmetic mean (h·µg/L)	Geometric mean (h·µg/L)	Geometric SD	Geometric CV (%)	Geometric mean category ratio	Geometric mean ratio (90% CI)
CYPIND1=0	982	950.2	50586.3	8808.5	9411.6	8552.9	1.56	47.1	CYPIND1=1 :	1.169
CYPIND1=1	9	5400.8	21321.1	9112.8	11227.5	9990.7	1.66	53.8	CYPIND1=0	(0.900 – 1.564)

Source: Applicant's response to FDA's comment on April 28, 2025, table 7
[#] CYPIND1:
0, no coadministration of CYP3A4 inducer at any point in time
1, chronic coadministration of weak CYP3A4 inducer
Abbreviations: CV, coefficient of variation; CYP, cytochrome; N, number of subjects in treatment group; SD, standard deviation

Table 85. Geometric Mean $AUC_{(0\text{-}24),ss}$ Ratios of M30/34 Stratified by Coadministration of Weak CYP3A4 Inducers for Subjects, OASIS 1, OASIS 2, and OASIS 3

Covariate categories[#]	N	Minimum (h·µg/L)	Maximum (h·µg/L)	Median (h·µg/L)	Arithmetic mean (h·µg/L)	Geometric mean (h·µg/L)	Geometric SD	Geometric CV (%)	Geometric mean category ratio	Geometric mean ratio (90% CI)
CYPIND1=0	982	499.9	20686.1	4685.8	4974.4	4560.6	1.54	45.3	CYPIND1=1 :	1.181
CYPIND1=1	9	3135.0	11492.4	5077.7	5999.5	5364.2	1.63	52.2	CYPIND1=0	(0.928 – 1.530)

Source: Applicant's response to FDA's comment on April 28, 2025, table 8
[#] CYPIND1:
0, no coadministration of CYP3A4 inducer at any point in time
1, chronic coadministration of weak CYP3A4 inducer
Abbreviations: CV, coefficient of variation; CYP, cytochrome; N, number of subjects in treatment group; SD, standard deviation

Taking into account all the considerations described above, the clinical pharmacology review team recommends avoiding concomitant use of elinzanetant with strong and moderate CYP3A4 inducers.

Proton Pump Inhibitor Esomeprazole

Elinzanetant is a lipophilic base showing a strong pH-dependent solubility. Elinzanetant is slightly soluble as a protonated cation under acidic conditions whereas the neutral base is insoluble at neutral pH. Therefore, a DDI study with the proton pump inhibitor esomeprazole

was conducted (Study 21772). No clinically significant drug-drug interaction on the pharmacokinetics of elinzanetant and its metabolites was observed when elinzanetant was coadministered with the proton pump inhibitor esomeprazole (refer to Section 14.2.4.7)

Effects of Elinzanetant on Other Drugs

Inhibition Potential

The in vitro study showed that elinzanetant and its metabolite M27, M30/34, and M18/21 had no significant inhibitory effect on the enzyme activity of human CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 2J2. However, elinzanetant and its metabolites showed inhibitory effect on CYP3A4. Therefore, the effect of elinzanetant on the pharmacokinetics of midazolam (MDZ), a sensitive CYP3A4 substrate, was evaluated in vivo following single-dose administration (Table 86) and multiple dosing (Study 21674, Figure 37) of elinzanetant and following single- and multiple-dose administration of elinzanetant in Study 21840 (Figure 37) (see Section 14.2.4.2, Section 14.2.4.8, and Section 14.2.4.3, respectively).

In Study 21667, coadministration of MDZ 1 mg with a single dose of elinzanetant 120 mg resulted in 14% increase in C_{max} and 45% increase in the AUC of MDZ. These findings suggest that elinzanetant is a weak inhibitor of CYP3A4 (Table 86). In Study 21840, the effect of elinzanetant on the pharmacokinetics of MDZ was investigated after a single dose of elinzanetant 120 mg and following repeated once daily oral administration of elinzanetant 120 mg over 14 days. Following a single dose of elinzanetant, a C_{max} increase of 15%, and an AUC increase of 50% was observed. Following multiple doses of elinzanetant, an increase of C_{max} by 49%, and an increase of AUC by 80% was observed for midazolam, confirming that elinzanetant is a weak inhibitor (<2-fold) of CYP3A4 after repeated dosing (Figure 37). Since the study results demonstrated that the concomitant use of elinzanetant increases the exposure of CYP3A4 substrates, this may elevate the risk of adverse reactions associated with these substrates. Therefore, the clinical pharmacology review team recommends avoiding concomitant use of CYP3A4 substrates.

In vitro studies revealed that elinzanetant and its metabolites M27, M30/34, and M18/21 had inhibitory effect on the activity of human uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) enzyme. By applying the mechanistic-static model described in the FDA guidance for industry *M12 Drug Interaction Studies* (August 2024), no risk for clinically relevant DDIs due to UGT1A1 inhibition by elinzanetant or its metabolites M27, M30/34, or M18/21 was identified.

In vitro studies have demonstrated that elinzanetant and its metabolites M18/21, M27, and M30/34 exhibit inhibitory activity against P-gp. However, clinical DDI Study 22081, which involved the coadministration of dabigatran (DBG) etexilate and elinzanetant, revealed no clinically significant inhibition of P-gp. In another study, Study 22004, following a single dose administration of 20 mg tamoxifen (a P-gp substrate) together with multiple once daily doses of 120 mg elinzanetant, the effect of elinzanetant on the pharmacokinetics of tamoxifen and its principal metabolites (N-desmethyltamoxifen, 4-hydroxytamoxifen, and endoxifen) were investigated. The study results (Figure 37) showed that there were no clinically relevant changes

in the pharmacokinetics of tamoxifen and its metabolites. Therefore, no tamoxifen dose adjustments are needed when elinzanetant is taken concomitantly.

In vitro analyses also indicated that elinzanetant and its metabolites inhibit breast cancer resistance protein (BCRP) and elinzanetant possesses possible inhibitory potential for organic anion transporting polypeptide (OATP) 1B1, and OATP1B3. Nevertheless, the results of the dedicated clinical DDI Study 21666 did not identify clinically significant change in the exposure of rosuvastatin (a sensitive substrate of BCRP, OATP1B1/1B3 and organic anion transporter [OAT] 3) when rosuvastatin was administered either simultaneously with elinzanetant or 3 hours after elinzanetant (Figure 37).

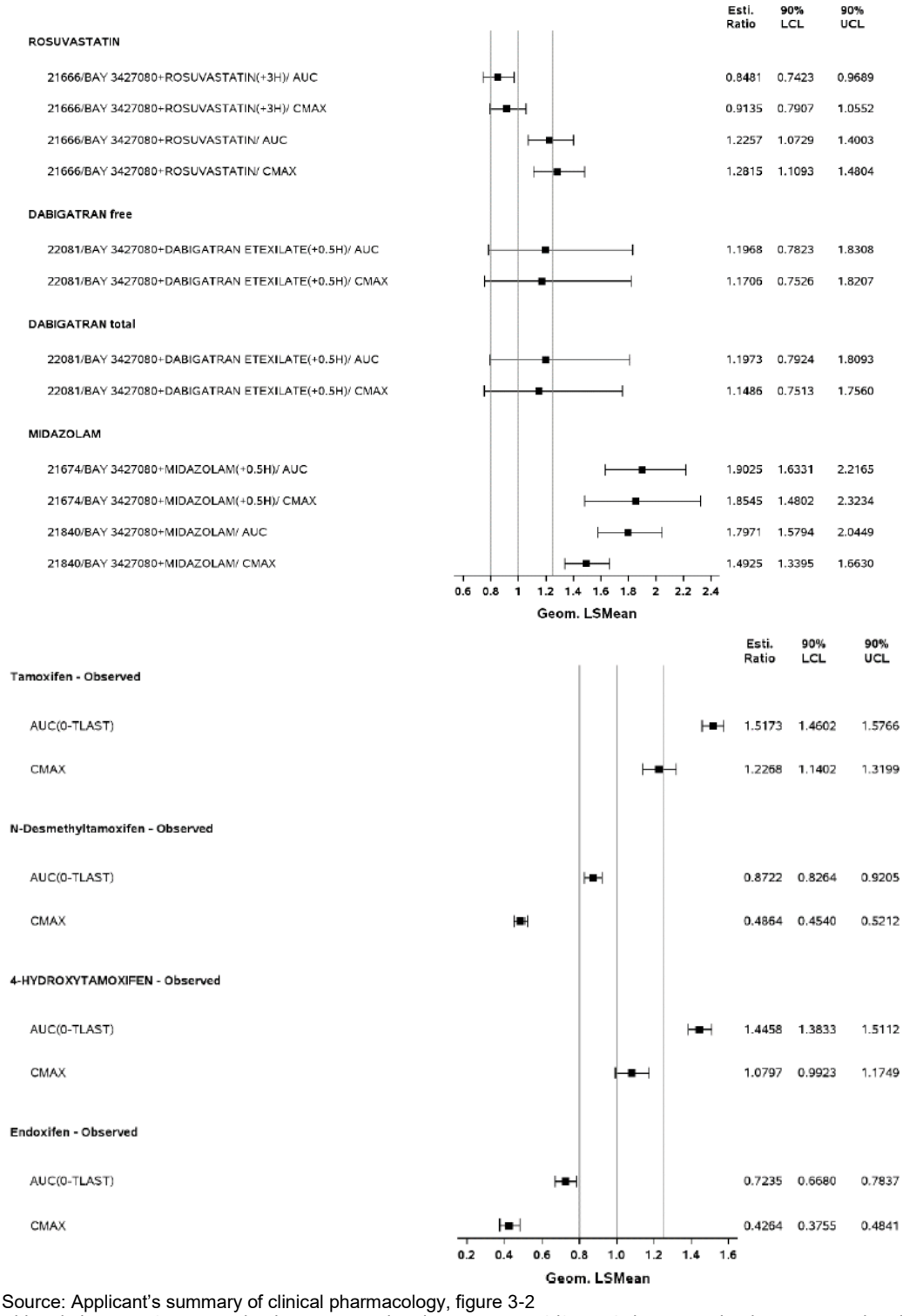
Clinical DDI studies were not conducted to assess elinzanetant and its metabolites M18/21, M27, and M30/34 as inhibitors of OAT1, OAT3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion protein 2 splice variant K (MATE2K), or multidrug resistance-associated protein 2 (MRP2) since in vitro data indicated no inhibitory effect on these transporters.

Moreover, the risk of clinically relevant inhibition of the multidrug and toxin extrusion protein 1 (MATE1) and bile salt export pump (BSEP) by elinzanetant and its metabolites is low based on FDA's guidance.

Induction Potential

In vitro studies using human hepatocyte demonstrated that elinzanetant and its metabolites (M18/21, M27, and M30/34) did not induce CYP1A2. Similarly, elinzanetant and its metabolite M30/34 did not induce CYP3A4 enzyme activity level. However, metabolites M18/21 and M27 exhibited slight induction of CYP3A4. Furthermore, elinzanetant and its metabolites M18/21, M27, and M30/34 induced the coregulated CYP isoforms CYP2B6 and CYP2C19. Despite the observed slight induction potential for certain CYP enzyme isoforms in vitro, per *M12 Drug Interaction Studies* guidance (August 2024), elinzanetant and its metabolites M18/21, M27, M30/34 have low induction potential on CYP enzymes in vivo. In addition, clinical studies 21667 and 21840 revealed no clinically relevant induction of CYP3A4 activity after multiple dosing with elinzanetant (Figure 37).

Figure 37. Geometric Mean Ratio (90% CI) of AUC and C_{max} of Object Drugs With/Without Elinzanetant as a Precipitant



Source: Applicant's summary of clinical pharmacology, figure 3-2
Abbreviations: AUC, area under the concentration-time curve; AUC(0-TLAST), area under the concentration-time curve from the start of infusion to the last quantifiable sampling point; C_{max}, maximum plasma concentration; Esti., estimated; Geom., geometric; LCL, lower confidence limit; LS, least squares; UCL, upper confidence limit

Table 86. Geometric Mean Ratio (90% CI) of AUC and C_{max} of Object Drug, Midazolam, With/Without Elinzanetant as a Precipitant, Study 21667

Parameter	Ratio	Geo. LS mean	90% confidence interval	Geo. CV (%)
AUC	Midazolam with elinzanetant / midazolam alone	1.4484	[1.3667 ; 1.5350]	9.38
C_{max}	Midazolam with elinzanetant / midazolam alone	1.1432	[1.0637 ; 1.2286]	11.67

Source: Table 9-9 of the CSR for Study 21667
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geo., geometric; LS, least squares

8.3. Plans for Pediatric Drug Development

The elinzanetant clinical development program was undertaken to address an indication which is applicable only to postmenopausal women. Therefore, no pediatric studies or assessments of effects on growth were conducted for elinzanetant. In accordance with the Pediatric Research Equity Act, Bayer requested a full waiver from the requirement to submit data adequate to assess the safety and efficacy of the elinzanetant in all relevant pediatric subpopulations in accordance with 21 CFR 314.55(c)(2)(ii).

Under IND 129492, the Applicant submitted an Initial Pediatric Study Plan on January 6, 2021, and a Request for Full Waiver of Pediatric Studies on January 8, 2021. The Pediatric Review Committee met on March 16, 2021, and agreed with issuing a full waiver for pediatric studies because necessary studies are impossible or highly impracticable as the number of subjects would be too small. On April 25, 2021, FDA issued an Agreed Initial Pediatric Study Plan letter stating FDA's agreement with the Applicant's plan to request a full waiver of pediatric studies. The Pediatric Review Committee reviewed and agreed with this waiver on June 17, 2025.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Use of elinzanetant is contraindicated in pregnancy. Based on nonclinical findings, exposure to elinzanetant may cause pregnancy loss or stillbirth when administered during pregnancy. Before starting treatment with elinzanetant, pregnancy should be ruled out. If pregnancy occurs during use of elinzanetant, treatment should be withdrawn. In addition, because postmenopausal status is a typically retrospective diagnosis and it may be difficult for perimenopausal women to know whether they are postmenopausal with certainty, women who are of child-bearing potential should use effective methods of contraception during treatment with elinzanetant.

Regarding the risk of lactation, there are no data on the presence of elinzanetant or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production.

Animal Data

Nonclinical findings from developmental and reproductive toxicology studies conducted in rats and rabbits were used in support of the drug's labeling. Main nonclinical data supporting labeling on fertility, pregnancy, and lactation are listed in Table 87. The reproductive and

developmental toxicity safety margins from the studies are listed in the Table 88. Additional details on the developmental and reproductive toxicology studies are available in Section 13.

Table 87. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Details
8.1 Pregnancy	(b) (4)

Labeling Section	Details
	(b) (4)
8.2 Lactation	

Source: Reviewer generated table from proposed product labeling

(b) (4)

Table 88. Safety Margins and Multiples of Exposure for Adverse Findings in Reproductive and Developmental Toxicity Studies

Study	NOAEL	Systemic Exposures $AUC_{(0-24)}$	Safety Margin/MOE*
FEED study, rat 0, 5, 25, 100 mg/kg/day, QD, from 22 days before mating to postcoitum day 6 Study R-13611	25 mg/kg/day (maternal and fetal)	27500µg.h/L (at 25 mg/kg/day) 11600µg.h/L (at 100 mg/kg/day)	3X MOE =14X for increased pre-post implantation loss at 100 mg/kg/day
EFD study, rat 0, 5, 25, 100 mg/kg/day, QD, from GD6 to GD17 Study R-13610	25 mg/kg/day (maternal) 100 mg/kg/day (fetal)	57200 µg.h/L 197000 µg.h/L	6.7X (maternal) 23X (fetal)
EFD study, rabbit	90 mg/kg/day (maternal)	2160 µg.h/L	0.25X (no safety margin for maternal exposure)

Study	NOAEL	Systemic Exposures $AUC_{(0-24)}$	Safety Margin/MOE*
0, 60, 90, 140 mg/kg/day (as 0, 30, 45, 70 mg/kg, BID) from GD7 to GD19 Study R-13597	140 mg/kg/day (fetal)	10600 µg.h/L	1.2X
PPND study, rat 0, 1.5, 5, 15 mg/kg/day, QD, from GD 6 to lactation day (LD) 21. Study B003187	1.5 mg/kg/day (maternal and fetal)	2000 µg.h/L (at 1.5 mg/kg/day) 8960 µg.h/L (at 5 mg/kg/day)	0.2X (no safety margin for maternal and fetal exposure and for metabolites in rat pup plasma) MOE =1X for increased litter deaths at 5 mg/kg/day

Source: Reviewer generated table
* Safety margins and multiples of exposures (MOE) calculated based on clinical exposure at the Maximum Recommended Human Dose (MRHD) of $AUC_{(0-24)}$ =8572.0 µg.h/L [from the clinical study number CPM50130 (report number B002427)]
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; EFD, embryofetal development; FEED, fertility and early embryonic development; GD, gestation day; NOAEL, no observed adverse effect level; PPND, pre- and postnatal developmental; QD, daily

Human Data

Pregnancy

No human pregnancies occurred during the development program for elinzanetant. Notably, elinzanetant is intended for symptoms due to menopause.

Lactation

There are no data on the presence of elinzanetant or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Elinzanetant is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Females and Males of Reproductive Potential

Based on findings from animal reproduction studies, elinzanetant may cause pregnancy loss or stillbirth but not fetal malformations when administered during pregnancy. For women of reproductive potential, providers should exclude pregnancy before initiating treatment with elinzanetant and perform pregnancy testing if pregnancy is suspected during treatment with elinzanetant, and discontinue treatment if pregnancy is confirmed. Pregnancy should be prevented in women of reproductive potential by using effective contraception during and for 2 weeks after stopping treatment because elinzanetant can cause pregnancy loss or stillbirth.

9. Product Quality

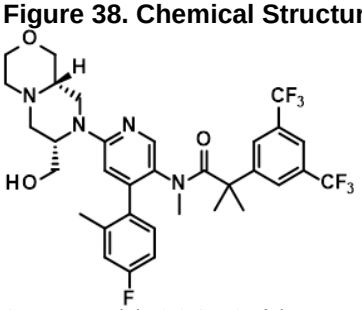
Drug Substance

Elinzanetant is a selective, nonhormonal NK1 and NK3 receptor antagonist. Elinzanetant has not been previously approved or marketed as a drug in the United States and therefore, it is classified as an NME.

Elinzanetant is a white (b) (4) to yellowish solid that is practically insoluble in water with estimated pKa of 4.8 and 6.4. It is slightly soluble in 0.1N hydrochloride (HCl) and freely soluble in methanol, ethanol, 2-propanol, acetone, acetonitrile, and dimethyl sulfoxide. It has two chiral centers, (b) (4)

Elinzanetant has the chemical name, 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]-3-pyridinyl}-N,2-dimethylpropanamide, a molecular formula of $C_{33}H_{35}F_7N_4O_3$, a molecular weight of 668.7 g/mol, and the chemical structure is shown in Figure 38.

Figure 38. Chemical Structure of Elinzanetant



Source: Module 3.2.S.1.2 of the NDA

The chemical structure for elinzanetant has been provided in Module 3.2.S.1.2 of the application. The proposed structure has been characterized and confirmed by appropriate analytical techniques, and the characterization data is submitted in Module 3.2.S.3 of the application.

For this application, elinzanetant is manufactured by Bayer AG, Bergkamen, Germany for Bayer HealthCare Pharmaceuticals Inc. in accordance with the current Good Manufacturing Practices requirements. It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout; it is assigned a retest date of (b) (4) months. Sufficient stability data in support of the assigned retest date of (b) (4) months has been provided in the application.

Drug Product

LYNKUET (elinzanetant) Capsule, 60 mg is proposed for the treatment of moderate to severe vasomotor symptoms associated with menopause.

LYNKUET capsules are oblong, opaque-red, soft-gel capsules printed with “EZN60” in white ink. Each capsule contains 60 mg of elinzanetant as the active ingredient and caprylocaproyl macrogolglycerides, glycerol monocaprylocaprate, glycerol mono-oleate, polysorbate 80 and all-rac-α-tocopherol as inactive ingredients. All excipients are within the limits specified in the Agency’s Inactive Ingredient Database of previously approved drug products for oral use. A statement stipulating the gelatin capsule as free of bovine spongiform encephalopathy /transmissible spongiform encephalopathy has been submitted to the application.

LYNKUET® (elinzanetant) capsules are manufactured by [redacted] (b) (4) for Bayer HealthCare Pharmaceuticals Inc. in accordance with the current Good Manufacturing Practices requirements. It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug product at release. Sufficient stability data in support of the proposed expiration dating period of 30 months has been submitted to the application. The proposed expiration dating period of 30 months is granted.

LYNKUET capsules are packaged as two capsules in a blister, supplied in a blister card with 6 blisters with a total 12 capsules per blister card. This drug product is also supplied as 5 blister cards in a carton. LYNKUET capsules should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Office of Pharmaceutical Quality Conclusion and Recommendation

- The Applicant of this 505(b)(1) NDA has provided sufficient chemistry, manufacturing, and controls (CMC) information to assure the identity, strength, purity, and quality of the drug substance, elinzanetant and the drug product, LYNKUET (elinzanetant) Capsule, 60 mg.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC recommended changes/revisions to the Prescribing Information (PI) labeling as well as container and carton labels have been communicated through the clinical review team to the Applicant, and the recommended CMC changes/revisions have been accepted by the Applicant.
- The Applicant's environmental assessment and Finding of No Significant Impact for this application have been reviewed by the Office of Pharmaceutical Quality Environmental Assessment Team and have been found adequate to support the approval of this application.

Therefore, this application is recommended for approval from the Office of Pharmaceutical Quality perspective with an expiration dating period of 30 months.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Human Subjects Protections

As stated by the Applicant, the clinical studies were conducted in substantial conformance with ICH good clinical practice (GCP) requirements and with applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and protection of human

subjects participating in biomedical research. All studies submitted in this application were conducted according to FDA requirements, under IND 129492.

Clinical Site Inspections

FDA clinical site inspections were performed on-site at six sites in the United States (two), Czech Republic, and Poland (two) (refer to Section 22 for details).

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the FDA guidance for industry *Financial Disclosure by Clinical Investigators* (February 2013) (see Section 25), and by 21 CFR 54.4. A review of financial disclosure information did not identify concerns about the integrity and validity of the data. See also Section 25 Financial Disclosure.

11. Advisory Committee Summary

An advisory committee meeting was not held to discuss this application because there were no considerations that warranted a discussion at an advisory committee meeting.

III. Additional Analyses and Information

12. Summary of Regulatory History

NeRRE acquired NT-814 from GlaxoSmthKline (GSK) in 2012. On April 4, 2016, FDA provided written responses to a pre-IND meeting request submitted by NeRRe Therapeutics Ltd. (NeRRe) for NT-814 (later renamed elinzanetant). From a CMC perspective, the information on drug substance and drug product appeared adequate to open an IND. Similarly, the pharmacology/toxicology studies appeared adequate to open an IND, pending final review of the study reports. In terms of the clinical study design, FDA did not agree with the proposed Phase 2a proof-of-concept study design. FDA recommended that the Applicant open the IND with a stand-alone Phase 1, dose-escalating, PK/bioavailability study in postmenopausal women. FDA expressed concerns about the proposed starting dose of (b) (4) mg once daily, citing cardiovascular adverse events (including atrial fibrillation, ventricular tachycardia, syncope, and orthostatic hypotension) observed at lower doses in previous studies. The Agency recommended starting at 50 mg with dose escalation by 50 mg increments up to 150 mg. Following completion of the stand-alone PK/bioavailability study, FDA recommended the Applicant submit the results for review and submit a protocol for a Phase 2 proof-of-concept study that could identify the lowest effective dose to be studied in Phase 3. There was also discussion of the overall clinical development program, and FDA emphasized the recommendations in the FDA draft guidance for industry *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation* (January 2003). Specific considerations included the anticipated study population for an indication of the treatment of moderate to severe VMS due to menopause, and the FDA recommended four coprimary endpoints: mean change in frequency and severity of moderate to severe vasomotor symptoms from baseline to Weeks 4 and 12.

The investigational new drug application (IND 129492) was initially submitted by NeRRe on June 6, 2016, and was allowed to proceed. On August 14, 2020, NeRRe submitted a special protocol assessment (SPA) request for a 104-week Sprague Dawley rat carcinogenicity protocol. The Agency denied the request on September 1, 2020, because it was an incomplete submission. A SPA was resubmitted for a carcinogenicity protocol on September 4, 2020. The Executive Carcinogenicity Assessment Committee agreed with the protocol and provided comments and recommendations to the Applicant on October 21, 2020.

Bayer acquired NT-814 from NeRRe in September 2020.

On November 17, 2020, an EOP2 Type B meeting was held via teleconference (meeting minutes dated December 17, 2020). The purpose of the meeting was to discuss the findings of the Phase 2b dose-finding study (SWITCH-1) and the Phase 3 clinical program. During this meeting, FDA disagreed with Bayer's proposed single 120 mg dose for Phase 3 studies, noting that in SWITCH-1, the 120 mg dose failed to meet all four coprimary endpoints, specifically lacking statistical significance for severity reduction at Weeks 4 and 12 despite showing significant frequency reduction. FDA recommended conducting dose-ranging Phase 3 studies including both effective and ineffective doses. Bayer noted that with the planned sample size in the Phase 3

studies, they expected to be able to demonstrate statistically significant differences in the planned endpoints for the 120 mg NT-814 dosage group. FDA noted that Bayer was at risk of not identifying an effective dose of NT-814. FDA agreed with the design of the two proposed 52-week Phase 3 clinical studies but required specific safety monitoring including endometrial biopsies for all non-hysterectomized women at study completion, mammograms, and exclusion of women taking certain nonhormonal medications that could confound efficacy results. There were discussions of the inclusion and exclusion criteria and study procedures. In addition, it was noted that outcomes of secondary endpoints, (b) (4) are not used to determine effectiveness of a drug product for a VMS indication and would not be included in labeling. (b) (4)

On January 6, 2021, Bayer submitted an agreed initial pediatric study plan, which FDA agreed to on April 25, 2021. The initial pediatric study plan requested a full waiver of pediatric studies under 21 CFR 314.55(c)(2)(ii) since menopause is an adult-related condition that rarely or never occurs in pediatrics, consistent with FDA's automatic full waiver list.

On May 27, 2021, FDA did not agree with a SPA of a clinical protocol for 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 (OASIS 1). FDA provided comments on the proposed study population, safety monitoring, and dose selection.

On December 15, 2022, FDA provided an advice/information request response regarding an SPA for a 26-week carcinogenicity study in transgenic mice. The Agency disagreed with the proposed approach, referring to Executive Carcinogenicity Assessment Committee protocol minutes and noting that study reports should be audited and finalized for complete review. FDA also requested clarification on how the metabolite M27 would be assessed in the proposed protocol.

On February 16, 2023, FDA provided Type C written responses regarding a web-based patient preference study. FDA disagreed with the proposed study design, stating it was unlikely to generate information that would be useful for informing the benefit-risk assessment and FDA did not anticipate putting the results of patient preference studies in the labeling for this product. Concerns with the proposed study included that the (b) (4) (b) (4)

On March 8, 2023, FDA provided written responses to a Type D guidance meeting request submitted January 27, 2023, regarding chemistry, manufacturing, and controls development. The FDA agreed that the proposed starting materials and final intermediate selections appeared reasonable, though final determinations would be made during NDA review.

On November 14, 2023, FDA provided preliminary responses to a Type D meeting request submitted October 6, 2023, regarding the environmental assessment. The meeting was subsequently cancelled on November 20, 2023, after Bayer indicated the preliminary responses were adequate. FDA generally agreed with the environmental fate and aquatic toxicity studies

Reference (b) (4) 5682958

planned to be included in the environmental assessment, however provided recommendations on the Applicant's plans. On November 30, 2023, FDA issued a correction acknowledging agreement for final Zebrafish Extended One-Generation Reproduction Test study report submission within 60 days after initial NDA submission and terrestrial studies during the NDA review cycle.

On February 1, 2024, a pre-NDA Type B meeting was held via teleconference (meeting minutes dated February 26, 2024). FDA disagreed with Bayer's proposal to submit the driving ability study final report after the NDA submission, noting that all final study reports should be included at initial NDA submission. FDA agreed with the proposed efficacy presentation strategy based on individual results from OASIS 1 and OASIS 2. FDA recommended basing the primary long-term safety assessment on the 52-week OASIS 3 study. FDA recommended using exposure-adjusted incidence rates for adverse events in pooled safety analyses and indicated they intended to consult the DILI team on cases of elevated hepatic enzymes.

On April 8, 2024, the Division of Medication Error Prevention and Analysis informed the Applicant that the proposed proprietary name, LYNKUET, is conditionally acceptable.

On July 26, 2024, the Applicant submitted NDA 219469 for elinzanetant 60 mg capsules, seeking marketing approval for the indication of treatment of moderate to severe VMS associated with menopause. On September 24, 2024, the NDA was accepted for filing. A major amendment was received on July 22, 2025, extending the user fee goal date to October 26, 2025.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Selected nonclinical studies were originally submitted and reviewed under IND 129492. All nonclinical safety studies conducted in support of elinzanetant were also submitted to the present NDA, and Section 13.2 highlights key findings of those studies.

All nonclinical studies submitted by the Applicant under the NDA and IND are captured in the nonclinical review archived in DARRTS dated July 11, 2025 (DARRTS°ID:°5623053 2025).

13.2. Individual Reviews of Studies Submitted With the New Drug Application

The Applicant refers to elinzanetant in the nonclinical studies by the code name BAY 3427080. Previous code names (NT-814 and GSK1144814A) are still noted in earlier study reports and hence also occur in this review in some tables and figures.

Three forms of elinzanetant (free base [BAY 3427080], [HCl] salt [BAY 3453656], and tosylate salt [BAY 3453651]) were used in nonclinical studies. However, all doses and concentrations in the tables, figures, and text descriptions are expressed in terms of free base.

13.2.1. Pharmacology

13.2.1.1. Primary Pharmacology

Elinzanetant is an NME that acts as a noncompetitive antagonist of both NK1R and NK3R.

In binding assays, elinzanetant displayed high affinity for human NK1R (pKi values of 8.71 to 10.15 [mean pKi of 9.43]) and NK3R (pKi values of 8.03 to 8.8 [mean pKi of 8.42]). Elinzanetant has ~10-fold lower affinity towards human NK3R compared to human NK1R. Additionally, elinzanetant has higher affinity for human NK1R and NK3R than for human NK2 receptors (pKi values of approximately 6.0). In functional in vitro assays, elinzanetant inhibited the activity of human NK1R and NK3R, with calculated pKB values of 9.02 to 9.1 for human NK1R and 8.17 to 8.5 for human NK3R.

Drug Activity Related to Proposed Indication

In the context of VMS due to menopause, NK1R and NK3R antagonists are thought to act by inhibiting the activity of KNDy neurons, which project to the vasomotor center in the median preoptic nucleus to modulate neuronal activity involved in thermoregulation. This inhibition of KNDy neurons, which are thought to be in a hyperactivated state because of estrogen decline in menopause, is proposed to result in improvement of menopause-associated VMS (Figure 1).

KNDy neurons also synapse onto hypothalamic neurons that secrete GnRH, and, by suppressing the activity of NK1R/NK3R in KNDy neurons, elinzanetant may suppress hypothalamic GnRH secretion and, consequently, reduce the release of gonadotropins (LH and FSH) from the pituitary (Figure 1). Although the relationship between gonadotropin levels and VMS is poorly understood, studies have reported synchrony between hot flushes and LH secretion (Sassarini and Anderson 2024). It is unknown whether suppression of gonadotropin levels contributes to the effectiveness of elinzanetant to mitigate menopause-associated VMS.

Table 89 and Table 92 summarize key findings from in vitro receptor binding studies and in vitro functional assays, respectively, conducted with elinzanetant.

Table 89. Key Findings of In Vitro Receptor Binding Studies of Elinzanetant

In Vitro Receptor Binding Studies		
Study No.	**Study Aim**	**Findings**
Study R-13857	Determination of the affinity of elinzanetant for NK1R/NK3R across species (gerbil, rat, guinea pig, baboon, or human) using radioligand assay	As summarized in Table 90, elinzanetant (HCl salt) displayed high affinity for human and baboon cloned NK1R and gerbil and guinea pig striatal NK1Rs. Elinzanetant had low affinity for rat striatal NK1Rs, human cloned NK3Rs, and gerbil and guinea pig cortical NK3Rs.

In Vitro Receptor Binding Studies		
Study No.	**Study Aim**	**Findings**
		Table 90. Binding Affinity of Elinzanetant [HCl salt] and GR-205171A [NK1R Antagonist] at NK1R and NK3R Across Species **Receptor/species** | **pK_i (mean ± SEM (n ≥ 3))** | **GR-205171A[a]** | **Hydrochloride salt of elinzanetant** **NK-1** Human | 10.56 ± 0.16 | 10.15 ± 0.06 Baboon | 10.97 ± 0.05 | 9.91 ± 0.10 Gerbil | 10.8 ± 0.06[b] | 10.2 ± 0.03 Guinea pig | 10.9 ± 0.14[b] | 9.91 ± 0.02 Rat | 9.75 ± 0.13 | 8.40 ± 0.05 **NK-3** Human | - | 8.03 ± 0.03 Gerbil | - | 7.84 ± 0.14 Guinea pig | - | 7.48 ± 0.06 a NK-1 receptor antagonist tool compound for comparison (vofopitant dihydrochloride) b pK_i value derived from saturation analysis Source: Module 2.6.2 (Pharmacology written summary)
Study R-13886	Determination of the affinity of elinzanetant at native NK1R/NK3R across species (gerbil, guinea pig and human striatal NK1Rs) using radioligand assay	As illustrated in Table 91, elinzanetant (free base) displayed high affinity for gerbil, guinea pig, and human striatal NK1Rs and lower affinity for gerbil and guinea pig cortical NK3Rs. While the K_is of the selective NK1R inhibitor/antagonist [GR-205171A] for NK1R and NK3R differ by more than 10,000x, the K_is of elinzanetant for NK1R and NK3R differ by only 10x. **Table 91. Binding Affinity of Elinzanetant and GR-205171A [NK1R Antagonist] at NK1Rs and NK3Rs Across Species** **Receptor/species** | **pK_i (mean ± SEM (n ≥ 3))** | **GR-205171A[a]** | **Elinzanetant** | **Hydrochloride salt of elinzanetant** **NK-1** Human | 10.70 ± 0.10 | 8.71 ± 0.08 | - Gerbil | 10.81 ± 0.06 | 8.95 ± 0.09 | 8.85 ± 0.08 Guinea pig | 11.06 ± 0.02 | 8.89 ± 0.01 | - **NK-3** Gerbil | ≤ 6.00 | 8.22 ± 0.04 | - Guinea pig | ≤ 6.00 | 7.83 ± 0.02 | - a NK-1 receptor antagonist tool compound for comparison (vofopitant dihydrochloride) Source: Module 2.6.2 (Pharmacology written summary) Abbreviations: NK1R. neurokinin 1 receptor; NK3R, neurokinin 3 receptor; pK_i, inhibition constant; SEM, standard error of mean
Study R-13699	Saturation binding studies at human NK1R (hNK1R) stably expressed in Chinese Hamster Ovary (CHO) cells	• Elinzanetant (HCl salt) displays noncompetitive antagonism at hNK1R. • Statistically significant decrease of the maximal binding (B_{max}) of [^{3}H]-substance P [NK1R agonist] (P<0.05) in the presence of unlabeled elinzanetant was seen at 6nM and 10nM, but there was no statistically significant variation of the Kd for NK1R.

Source: Reviewer-generated table
Abbreviations: HCl, hydrochloride; *K*d, dissociation constant; NK1R. neurokinin 1 receptor; NK3R, neurokinin 3 receptor

Table 92. Key Findings of In Vitro Functional Studies of Elinzanetant

In Vitro Functional Assessments		
Study No.	**Study Aim**	**Findings**
Study R-13859	Antagonist activity of elinzanetant (HCl salt) at	Elinzanetant exhibited:

In Vitro Functional Assessments		
Study No.	**Study Aim**	**Findings**
	the human cloned NK1R and at human, marmoset and rat cloned NK3Rs assessed using an inositol phosphate scintillation proximity assay.	• Potent, nonsurmountable antagonist profiles at the human cloned NK1R (pKB =9.02±0.07) and NK3R (pKB =8.20±0.07). • Potent nonsurmountable antagonism at the marmoset NK3R (pKB =8.74±0.17). • Surmountable antagonist profile at the rat NK3R with a reduced potency (pA2=6.77±0.06) compared to that at the human NK3R.
Study R-13879	Functional activity of elinzanetant HCl and free base at endogenous human NK1R and at human and guinea pig NK3R.	Elinzanetant exhibited: • Nonsurmountable human NK1R antagonist profile with an apparent pKB of 9.1±0.13 (calculated using an operational model for noncompetitive antagonism). • Nonsurmountable antagonist profile at both human and guinea pig NK3Rs.
Study R-13877	Effect of elinzanetant on neurokinin B (NKB) induced cell firing in the medial habenula (mHb) of guinea pigs	Elinzanetant (1 & 10µM) decreased the maximum response to the NK3R agonist NKB (consistent with elinzanetant-induced unsurmountable inhibition of NK3Rs). FDA Analysis: (1) The habenula is connected to brain regions such as the amygdala (which plays a central role in seizures) and the hippocampus (which is essential for cognitive processing) (Norden and Blumenfeld 2002). (2) The finding that elinzanetant inhibits the excitability of habenula neurons suggests that the seizures noted in some repeat-dose toxicity studies of elinzanetant-treated rats may not be due to elinzanetant itself. (3) Elinzanetant-induced inhibition of NK3Rs in the habenula (and other brain regions involved in cognitive processing) could contribute to cognitive deficits noted in elinzanetant-treated human subjects in the Clinical Driving Study (Study B003054/22653).

Source: Reviewer-generated table
Abbreviations: HCl, hydrochloride; NK1R, neurokinin 1 receptor; NK3R, neurokinin 3 receptor; pA2, antagonist potency, pKB, apparent affinity

Studies on Principal Metabolites

Each of the principal metabolites of interest–M27 (BAY 34629332), M30/34 (BAY 3462933), and M18/21 (BAY 3462934), which accounted for 6%, 11% and 5.5%, respectively, of total radioactivity in the human biotransformation clinical Study CPMX 50130/B002427–showed high affinity and noncompetitive antagonistic activity at the human NK1R and NK3R. The in vitro affinities and potencies of the metabolites at human NK1R and NK3R are similar to those of elinzanetant, as summarized in Table 93 and Table 94.

Table 93. Binding Affinity and Functional Antagonism of Elinzanetant and its Metabolites at Human NK1R and NK3R

Compound	Binding assay [pK_i]	Functional assay [pK_B]
Elinzanetant		
NK-1R	8.71 – 10.15	9.02 – 9.1
NK-3R	8.03 - 8.8	8.17 – 8.5
Metabolite M18/21		
NK-1R	9.62	9.80
NK-3R	7.89	8.64
Metabolite M22§		
NK-1R	8.96	9.89
NK-3R	8.38	8.77
Metabolite M27		
NK-1R	8.96	9.89
NK-3R	7.96	8.52
Metabolite M30/34		
NK-1R	8.77	9.42
NK-3R	8.30	7.96

pK_B: -log of K_B, pK_i: -log of K_i; NK: neurokinin; R: receptor.

Source: Module 2.6.2 (Pharmacology written summary)

Table 94. Binding and Cellular Agonist or Antagonist Effect of Metabolites of Elinzanetant, M27, M18/21, M30/34, and M22, to NK1R(h) and NK3R(h)

Assay/metabolite	IC_{50} (nM)	K_i (nM)	K_B (nM)	EC_{50} (nM)	nH
Metabolite M18/21					
NK-1(*h*) (agonist radioligand)	0.55	0.24	-	-	1
NK-1(*h*) (antagonist effect)	1.1	-	0.16	-	-
NK-3(*h*) (antagonist effect)	26	-	2.3	-	-
NK-3(*h*) (antagonist radioligand)	23	13	-	-	1
Metabolite M22					
NK-1(*h*) (agonist radioligand)	2.4	1.1	-	-	1.8
NK-1(*h*) (antagonist effect)	0.92	-	0.13	-	-
NK-3(*h*) (antagonist effect)	19	-	1.7	-	-
NK-3(*h*) (antagonist radioligand)	7.7	4.2	-	-	0.8
Metabolite M27					
NK-1(*h*) (agonist radioligand)	2.6	1.1	-	-	1.4
NK-1(*h*) (antagonist effect)	0.88	-	0.13	-	-
NK-3(*h*) (antagonist effect)	33	-	3.0	-	-
NK-3(*h*) (antagonist radioligand)	20	11	-	-	1
Metabolite M30/34					
NK-1(*h*) (agonist radioligand)	3.9	1.7	-	-	1.2
NK-1(*h*) (antagonist effect)	2.6	-	0.38	-	-
NK-3(*h*) (antagonist effect)	120	-	11	-	-
NK-3(*h*) (antagonist radioligand)	9.3	5.0	-	-	1.3

EC_{50}: effective concentration at 50% inhibition; *(h)*: human; IC_{50}: concentration required for 50 % inhibition; K_B: binding constant; K_i: inhibition constant; nH: slope factor; NK: neurokinin.
Source: Module 2.6.2 (Pharmacology written summary)
Note# Summary of studies R-13857, R-13859, R- 13858, R-13884, R-13886 , R-13879

Ex Vivo and In Vivo Receptor Occupancy Studies

Ex vivo receptor occupancy studies showed that elinzanetant occupied NK1Rs in the human putamen in a concentration-dependent manner with a pKi of 9.44 (Study R-13876).

The PET study in baboon following a single intravenous (IV) dose demonstrated a dose-dependent brain NK1R occupancy with an estimated half-maximal effective concentration (EC_{50}) of 9.93 ng/mL (Study R-13885).

Elinzanetant (HCl form) was found to penetrate the gerbil brain (dorsal striatum and cingulate cortex) following single oral dosing (1, 3, 10, and 30 mg/kg) and occupy both NK1R and NK3R. At 10 minutes after a single oral dose of 1 mg/kg, NK1R occupancy (~72%) was greater than NK3R occupancy (~31%). Daily dosing (4 to 5 days) did not result in elinzanetant accumulation in brain and blood and did not increase NK1R/NK3R occupancy (Study R-13860).

Ex vivo autoradiography in guinea pig brain was used to determine the effect of haloperidol (D2 antagonist) on elinzanetant exposure and receptor occupancy. Treatment of guinea pigs with haloperidol had no significant effect on NK1R occupancy by elinzanetant, and mean NK1R occupancy was >97% at all doses tested (30 mg/kg and 100 mg/kg). Mean NK3R occupancy by elinzanetant at 30 and 100 mg/kg was 37% and 78% in vehicle-treated guinea pigs, respectively, and 74% and 85% in haloperidol-treated guinea pigs, respectively. The apparently higher NK3R occupancy in guinea pigs treated with haloperidol at the lower dose of elinzanetant correlated with higher exposure of the haloperidol-treated animals to elinzanetant. The data suggest that NK1R/NK3R occupancy by elinzanetant was not affected by the dopamine D2 receptor antagonist haloperidol (Study R-13880).

In Vivo Primary Pharmacodynamic Studies

The Applicant investigated the in vivo pharmacodynamic activity of elinzanetant in a gerbil foot tapping model of NK1R activity and in the guinea pig wet-dog shake model of NK3R activity. Oral dosing of male gerbils with elinzanetant dose dependently reduced foot tapping induced by the NK1R agonist GR73632 (ID_{50} [dose resulting a 50% reduction in time spent foot tapping] =1.36 mg/kg). Similarly, elinzanetant doses of 8.5 and 25.5 mg/kg significantly reduced the wet-dog shake behavior induced by the NK3R agonist senktide in the guinea pigs. Both findings indicate a central NK3R antagonist activity of elinzanetant.

As noted earlier in Section 5, the Applicant did not conduct in vivo animal studies to demonstrate elinzanetant effects in reducing hot flash-like signs.

13.2.1.2. Secondary Pharmacology

Selectivity screens (b) (4) were performed for elinzanetant and the three principal human metabolites of elinzanetant (M27, M30/34, and M18/21). Elinzanetant was >100-fold more selective for the human NK3R and >300-fold for the human NK1R versus 88 other nontachykinin human receptors, enzymes, and transporters.

Radioligand binding assays produced equivocal results with elinzanetant-induced inhibition of radioligand binding to ER and PR. In the selectivity screen (Study R-13669), elinzanetant at

1μM had no significant effect on binding of the ER-ligand fluoromone ES (1nM) to recombinant human ERα and human ERβ ectopically expressed in insect Sf9 cells or on the binding of the progestin [^{3}H]R5020 to PR in human MCF-7 cells. However, in another radioligand binding assay (Study R-14343), elinzanetant inhibited [^{3}H]estradiol binding to ERα with an IC_{50} of 22.5μM and inhibited [^{3}H]progesterone binding to PR-B with an IC_{50} 0.64μM.

The metabolites M27, M30/34, and M18/21 inhibited [^{3}H]progesterone binding to PR-B with IC_{50}s of 1.34μM, 1.20μM, and 1.69μM, respectively (Study R-14016, Study R-14019, and Study R-14020). Inhibition of these receptors may be an important determinant of the uterine carcinogenic signals detected in rats treated orally with elinzanetant doses ≥60 mg/kg/day for 104 weeks. It could also contribute to the convulsions observed in a repeat-dose toxicity study in SD:Hsd rats treated with elinzanetant doses ≥20 mg/kg/day for 13 weeks and in the carcinogenicity study in female SD:Hsd rats treated with elinzanetant doses ≥60 mg/kg/day for 104 weeks. These findings are discussed earlier in this review in Section 7.

13.2.1.3. Safety Pharmacology

The Applicant conducted a complete battery of in vitro and in vivo safety pharmacology studies with elinzanetant and in vitro studies on the three principal metabolites. There were no major safety signals identified.

Key study findings and safety margins are summarized in Table 95.

Table 95. Safety Pharmacology Studies With Elinzanetant

Study	Effects of Elinzanetant/Metabolite	NOAEL	Safety Margin*
In vitro (elinzanetant)			
Study R-13675 in vitro hERG @ 1.91μM	• No inhibition of hERG tail current	-	-
Study R-13679 in vitro KCNH2 (hERG) assay@ 0.0228 – 50μM	• IC_{50}=31μM	-	~4,820X
In vitro (metabolites: M27, M30/34, M18/21)			
Study PH-42243 in vitro human cardiac ion channels# with M27 (BAY 3462932) @ 10μM	• No inhibitory effect on the hERG potassium channel, hNav1.5 sodium channel, thCav1.2 L-type calcium channel, hKvLQT1 potassium channel, hKv4.3 potassium channel, and hKir2.1 potassium channel	-	-
Study PH-42244 in vitro human cardiac ion channels# with M30/34 (BAY 3462933) @ 10μM		-	-
Study PH-42245 in vitro human cardiac ion channels# with M18/21 (BAY 3462934) @ 10μM		-	-

Study	Effects of Elinzanetant/Metabolite	NOAEL	Safety Margin*
In vivo (elinzanetant)			
Study R-13668 (GLP) Central nervous system (CNS) in rats @ 0, 5, 25, and 100 mg/kg elinzanetant (tosylate salt)	• 25 mg/kg increased defecation and urination at 4 and 24 h, respectively. • 100 mg/kg increased. response to finger approach and rearing at 24 h. • No seizures, tremors, or twitches. • No effect on body temperature.	100 mg/kg $C_{max, unbound}$ =98 µg/L in males on Day 1 in the 4-week rat Study [Study R-13595]	23X
Study R-13670 (GLP) Cardiovascular system (CVS) in monkeys @ 0, 6, 20, and 60 mg/kg elinzanetant (tosylate salt)	• Mild increase in heart rate (~15%), mild decrease in body temperature (~0.6°C), which was both reversible. No effect on ECG @ 60 mg/kg. • Mild decrease in body temperature (reversible) @ 20 mg/kg.	20 mg/kg $C_{max, unbound}$ =18 µg/L in males at 20 mg/kg on Day 1 in the 4-week monkey study [Study R-13639]	4X
Study R-13676 (GLP) Respiratory in rats @ 0, 5, 25, and 100 mg/kg elinzanetant (tosylate salt)	• No change in tidal volume, respiratory rate, minute volume, pulmonary resistance, or body temperature.	100 mg/kg $C_{max, unbound}$ =98 µg/L at 100 mg/kg in males on Day 1 in the 4-week rat study [Study R-13595]	23X

Source: Reviewer-generated table
*$C_{max, unbound}$ =4.3 µg/L at 120 mg, QD, obtained from Study No. B002427#. Specific human cardiac ion channels: the hERG potassium channel, hNav1.5 sodium channel, thCav1.2 L-type calcium channel, hKvLQT1 potassium channel, hKv4.3 potassium channel, and hKir2.1 potassium channel.
Abbreviations: C_{max}, maximum plasma concentration; ECG, electrocardiogram; heRG, human ether-a-go-go-related gene; IC_{50}, half-maximal inhibitory concentration; NOAEL, no-observed-adverse-effect level

13.2.2. Pharmacokinetics and Toxicokinetics

Absorption, distribution, metabolism, and excretion of elinzanetant were assessed in whole-body autoradiography studies rats and nonradiolabeled assays in rats, monkeys, and dogs. The key findings are noted below.

Absorption

- Oral bioavailability was moderate in male and female rats (77% and 47%) and low in monkeys and dogs (19%).
- Clearance differed between species. It was low in rats with differential clearance between male and female rats. Significant accumulation of elinzanetant was observed over the dose range tested in female rats, but not in male rats.
- High clearance of elinzanetant in dogs was associated with its low oral bioavailability in this species. Therefore, monkeys (also with low bioavailability of 19% but moderate clearance

compared to dog) were chosen as the second nonclinical species for chronic toxicity studies besides rats.

- No notable accumulation was observed in monkeys after repeat dosing.

Distribution

- In rat whole-body autoradiography studies, radioactivity showed high distribution in majority of the tissues.
  - Highest levels were noted in liver, kidney, adrenal gland, abdominal and brown fat, bulbo-urethral gland, pancreas, lacrimal glands, harderian gland and mucous gland; brain had lower levels which did not change with time (no accumulation).
  - After 35 days, radioactivity was noted in brown fat, uveal tract/retina, spleen. and adrenal cortex (Study R-13624).
    - The Applicant notes uveal tract/retina concentration indicates some long-term association of drug-related material with melanin.
    - The Applicant conducted an in vitro phototoxicity study, which is discussed under special toxicology studies (see Section 13.2.3).
    - The potential for elinzanetant to accumulate in melanin-rich tissues of the eyes and skin and be phototoxic in humans cannot be ruled out and is also discussed in Section 7.
- In pregnant rats, the organ distribution of elinzanetant was similar to nonpregnant rats. Fetal and associated tissue concentrations were generally much lower than maternal blood, except for amnion, placenta, and brain. The $AUC_{(0\text{-tlast})}$ ratio of placenta/maternal blood was 1.3, fetus average/amniotic fluid was 18.3, and fetal brain/maternal brain was 2.4 (Study R-14360).
- Plasma protein binding was high across all preclinical species tested (99.5 to 99.9%) and higher in human (>99.9%) for elinzanetant as well as the principal metabolites (M27, M30/34, and M18/21). No concentration dependence of the unbound fraction (fu) of elinzanetant was observed. These are summarized in Table 96.

Table 96. Plasma Protein Binding In Vitro for Elinzanetant and its Metabolites

Test compound:	[^{14}C]Elinzanetant	M27	M18/21	M30/34		
Batch no.:	PII 150-1-02 A	EB1182-73-P1	EB1740-14-P1	EB1182-86-P1	Method:	Transil®
Test system:	Plasma; *in vitro* incubation matrix				Assay:	LSC; LC-MS/MS

Analyte:	Elinzanetant		M27		M30/34		M18/21	
Species / Test system	**Conc. [µg/L]**	**Fraction unbound [%]**	**Conc. [µg/L]**	**Fraction unbound [%]**	**Conc. [µg/L]**	**Fraction unbound [%]**	**Conc. [µg/L]**	**Fraction unbound [%]**
Human (m)	711 - 6739	0.272	298 to 18204	0.0679	181 to 17514	0.475	467 to 1841 19768	0.181 0.322
Man (f)	706 - 6268	0.332	201 to 19374	0.0689	169 to 14843	0.514	371 to1786 19502	0.140 0.302
CD-1 mouse (m)	982 - 10735	2.30	247 to 17229	1.23	196 to 1537	0.699	355 to 25667	2.99
CD-1 mouse (f)	1005 - 10891	2.65	208 to 18762	2.00	171 to 16886	1.17	202 to 21786	2.84
SD rat (m)	989 - 10679	1.91	265 to 19000	1.44	242 to 14024	0.661	346 to 26371	2.37
SD rat (f)	976- 10734	0.843	201 to 19143	1.25	165 to 11879	0.510	385 to 26257	2.51
NZW rabbit (f)[a]	1031 - 10981	4.66	219 to 18286	3.35	1674 to 17114	3.44	340 to 15417	10.4
Cynomolgus monkey (m)	966 - 10318	2.96	193 to 16321	2.34	1611 to 17543	2.28	300 to 17375	10.2
Cynomolgus monkey (f)	977 - 10566	0.434	185 to 16229	0.537	169 to 13683	0.872	291 to 18300	6.69

Source: Pharmacokinetic tabulated summary [truncated table summarizing studies PH-42081 and PH-42138]
Abbreviations: LC-MS/MS, liquid chromatography with tandem mass spectrometry; LSC, liquid-solid chromatography; NZW, New Zealand White; SD, Sprague Dawley

- As noted in Table 97, elinzanetant distributes more into plasma than into the blood cells resulting in a blood-to-plasma concentration ratio (Cb/Cp) range of 0.574 to 0.663 in humans and of 0.6 to 0.7 in rats and monkeys.

Table 97. Binding of Elinzanetant to Plasma Proteins of Selected Species (In Vitro) and to In Vitro Matrices as Well as Blood to Plasma Concentration Ratio (Cb/Cp)

Species / Matrix	Concentration [µg-eq/L]	f_u[a] [%]	C_b/C_p
Human (m)	711 - 6739	0.272	0.574
Human (f)	706 - 6268	0.332	0.663
CD-1 mouse (m)	982 - 10735	2.30	0.6[b]
CD-1 mouse (f)	1005 - 10891	2.65	n.d.
Sprague Dawley rat (m)	989 - 10679	1.91	0.6[b]
Sprague Dawley rat (f)	976- 10734	0.843	n.d
NZW rabbit (f)	1031 - 10981	4.66	n.d.
Cynomolgus monkey (m)	966 - 10318	2.96	0.7 [b]
Cynomolgus monkey (f)	977 - 10566	0.434	n.d.

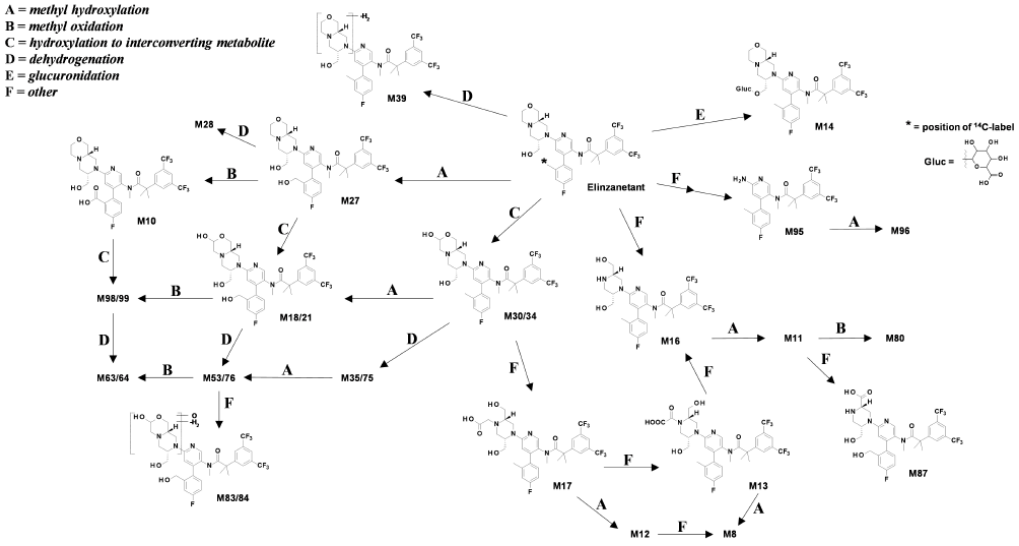
Source: Module 2.6.4 Pharmacokinetic written summary.
[a] fraction of free (unbound) drug in plasma; b = at a concentration of 10000 µg/L
Abbreviations: NZW, New Zealand White; SD, Sprague Dawley

- Elinzanetant was brain penetrant in the mouse, rat, and monkey with brain:blood ratios of 0.5:1, 0.1:1 to 0.5:1 and 0.6:1, respectively (Study R-13621).

Metabolism

- Elinzanetant is metabolized primarily by oxidation at the methyl-phenyl moiety as well as at the morpholine ring leading mainly to metabolites M27, M30/34, and M18/21. Figure 39 shows the main metabolic pathways.

Figure 39. Main Metabolic Pathways From In Vitro and In Vivo Studies



Source: Pharmacokinetic tabulated summary
M18/M21, M30/34, M35/75, M53/76, M63/64, M83/84 and M98/99 represent interconverting metabolites

- Based on clinical data, M30/34 (~11%) is considered as the major human metabolite. Human circulating metabolites M27, M30/M34, M18/21, M22 were observed in both rat and cynomolgus monkey plasma as shown in Table 98:

Table 98. In Vivo Metabolism of Elinzanetant in Different Species

ID	%oDRM[a]	Rat Day 91/Human Dosing Day 7		Cynomolgus Monkey Day 91 / Human Dosing Day 7
		Male (120 mg/kg)[b]	Female (50 mg/kg)[b]	Male and Female (80 mg/kg)[c]
Elinzanetant P	38	>equivalent	>equivalent	~equivalent
M18+M21 (Metabolites interconvert) Oxidation	7	~equivalent	<equivalent	<equivalent
M22 Oxidation	8	~equivalent	<equivalent	~equivalent
M27 Oxidation	12	~equivalent	<equivalent	<equivalent
M30+M34 (Metabolites interconvert) Oxidation	14	~equivalent	~equivalent	~equivalent
M31 Oxidation	5[d]	>equivalent	>equivalent	>equivalent
M75 Oxidation	5[d]	~equivalent	>equivalent	>equivalent

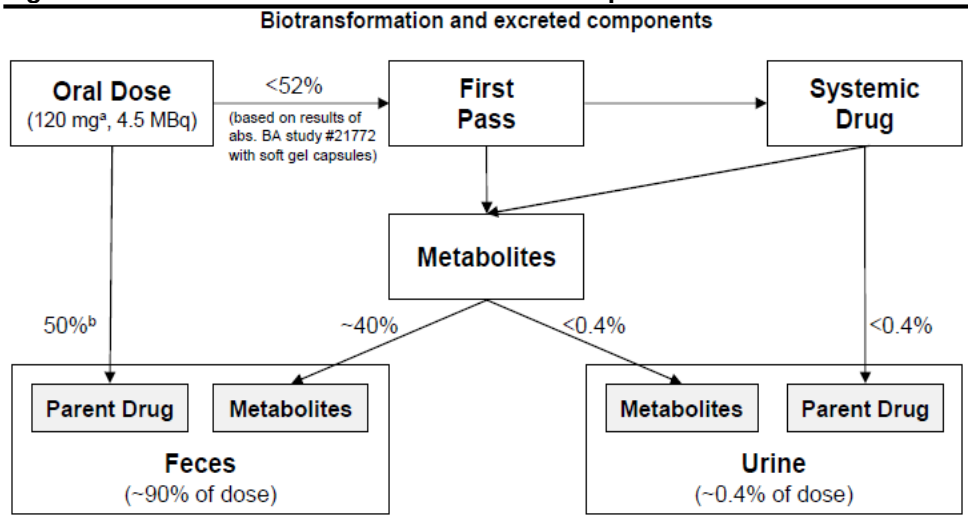
a = % of observed drug related material (oDRM) reported in M4.2.2.4 R-13659 after repeated dose of 90 mg to male subjects
b = MTD dose
c = NOAEL dose
d = as total for M31+M75
~ equivalent: 0.5 ≤ preclinical species/human exposure ≤3.0
> equivalent: preclinical species/human exposure >3.0
< equivalent: preclinical species/human exposure <0.5

Source: Pharmacokinetic tabulated summary

Excretion

Major route of elimination was via feces and bile in both rat and monkeys. Similarly in humans, metabolic profiling in plasma, feces, and urine demonstrated ~40% elinzanetant in plasma, ~90% of the administered dose was excreted via feces (about 50% unchanged and ~40% as metabolites) and negligible amount in urine (<0.5%).

Figure 40. Biotransformation and Excreted Components in Humans



a = nominal dose
b = absolute BA study #21772 (2) indicates mainly not absorbed drug, but excretion of absorbed drug to some extent cannot be excluded

Source: Figure from Study Report PH-42275

In Vitro Pharmacokinetic Drug Interaction Studies

A summary of in vitro pharmacokinetic studies with elinzanetant and its metabolites follows below. Refer to clinical pharmacology Section 14.2.4 for details on DDIs and their significance in clinical use.

Effects of Elinzanetant and Metabolites on Cytochrome P450 Isoforms

- Data from human liver microsomes with selective CYP inhibitors and from recombinant human CYP enzymes indicated that CYP3A4 is the primary CYP isoform involved in the oxidative metabolism of elinzanetant (Study R-13657, Report PH42629). Inhibition of CYP2E1 could not be determined (Study R-13658).
- Induction potential of elinzanetant and its metabolites M27, M30/34, and M18/21 towards human CYP isoforms was assessed at both messenger RNA (mRNA) and enzyme activity level, as summarized in Table 99 and Table 100 (summary from Study R-13656 and Study B003095).

Table 99. Induction Potential of Elinzanetant and its Metabolites Towards Human CYP Isoforms at the mRNA Level

CYP	Result for elinzanetant
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 21-fold
2B6	Concentration-dependent induction up to 9-fold
2C19	Concentration-dependent induction up to 4.5-fold
CYP	**Result for M27**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 21-fold
2B6	Concentration-dependent induction up to 17-fold
2C19	Concentration-dependent induction up to 8-fold
CYP	**Result for M30/34**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 16-fold
2B6	Concentration-dependent induction up to 8-fold
2C19	Concentration-dependent induction up to 3-fold
CYP	**Result for M18/21**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 16-fold
2B6	Concentration-dependent induction up to 12-fold
2C19	Concentration-dependent induction up to 4-fold

Source: Module 2.6.4 Pharmacokinetic written summary
Abbreviations: CYP, cytochrome; mRNA, messenger RNA; M, metabolite

Table 100. Induction Potential of Elinzanetant and its Metabolites M27, M30/34 and M18/21 Towards Human CYP Isoforms at the Enzyme Activity Level

CYP	Result for elinzanetant
1A2	No induction up to 90 000 µg/L
3A4	No induction up to 90 000 µg/L
2B6	Concentration-dependent induction up to 3-fold
2C19	Concentration-dependent induction up to 5-fold
CYP	**Result for M27**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 3-fold
2B6	Concentration-dependent induction up to 5-fold
2C19	Concentration-dependent induction up to 9-fold
CYP	**Result for M30/34**
1A2	No induction up to 90 000 µg/L
3A4	No induction up to 90 000 µg/L
2B6	Concentration-dependent induction up to 4-fold
2C19	Concentration-dependent induction up to 4-fold
CYP	**Result for M18/21**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 4-fold
2B6	Concentration-dependent induction up to 5-fold
2C19	Concentration-dependent induction up to 6-fold

Source: Module 2.6.4 Pharmacokinetic written summary
Abbreviations: CYP, cytochrome; M, metabolite

- In vitro evaluation of the potential of BAY 3427080 (elinzanetant) and its metabolites M30/M34, M18/M21, and M27 to act as direct-acting inhibitors of human CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2 and 3A4 showed no direct-acting inhibitory potency up to the highest test concentration (IC_{50}>5µM) except inhibitory potency on CYP3A4 (midazolam 1'-hydroxylation): BAY 3427080 (IC_{50}=0.77µM), M30/M34 (IC_{50}=0.98µM), M18/M21 (IC_{50}=1.1µM) and M27 (IC_{50}=1.2µM).
- No relevant metabolism-dependent (time-dependent) inhibitory potency of elinzanetant on biotransformation reactions catalyzed by these cytochrome P450 isoforms except a slight increase in the inhibitory potency after preincubation in the presence of NADPH was observed on CYP3A4 (PH-42451).
  - CYP3A4 inactivation kinetic parameters (half-maximal rate of inactivation [K_I] and maximal rate of inactivation [k_{inact}]) were as follows (Study B003014):
    - Elinzanetant (BAY 3427080): K_I=2.14µM, k_{inact}=0.0134 min^{-1}
    - M27 (BAY 3462932): K_I=1.66µM, k_{inact}=0.0150 min^{-1}
    - M30/34 (BAY 3462933): K_I=2.39µM, k_{inact}=0.0166 min^{-1}
    - M18/21 (BAY 3462934): K_I=3.37µM, k_{inact}=0.0218 min^{-1}
- The metabolic stability of GSK1144814 to aldehyde oxidase was determined by incubation with cynomolgus monkey and human cytosol at a concentration of 0.5µM and in the presence of isovanillin (known inhibitor of aldehyde oxidase). The data suggested that elinzanetant was not a substrate for aldehyde oxidase (Study R-13621)

Effects of Elinzanetant and its Metabolites on Transporters

The interaction of elinzanetant with various transporters was investigated in in vitro studies.

Elinzanetant as a Substrate

- Elinzanetant is classified as a substrate of P-gp, a transporter that removes substances from cells. IV coadministration of elinzanetant with elacridar (GF120918A) [a nonspecific inhibitor of P-gp efflux transporters] to rats increased by ~5X the elinzanetant brain:blood ratio and by ~2.5X the systemic exposure to elinzanetant (Study R-13621).
- Elinzanetant is not a substrate of the bidirectional transporter BRCP, the uptake transporters human OATP1A2 and human OATP2B1, and the MRP4 efflux transporters.
- Elinzanetant is not a substrate of the OATP1B1, OATP1B3, OATP1A2 and OATP2B1 uptake transporters.

Elinzanetant and its Metabolites as an Inhibitor

- Elinzanetant inhibited MATE1-, BSEP-, and OCT1-mediated metformin transport as well as OAT3-, OATP1B1-, OATP1B3-mediated transport. Elinzanetant is an inhibitor of BCRP with an IC_{50} value of 7.4μM (Study R-13631, Study R-13686, Study B002205, Study R-13635).
- OATP1B1 was inhibited by elinzanetant with an IC_{50} value of 0.7μM (Study R-13633).
- Elinzanetant inhibited the transport of digoxin via human P-gp in vitro with an IC_{50} of 14±6μM (corresponding to 9.6 μg/mL as free base) (Study R-13634).
- BAY 3427080 (elinzanetant), BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 3462934 inhibited OATP1B1 with IC_{50} values of 0.69μM, 0.59μM, 0.38μM and 1.21μM, respectively (Study B002050).
- BAY 3427080 (elinzanetant), BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 3462934 (M18/21) inhibited OATP1B3 with IC_{50} values of 0.25μM, 0.21μM, 0.19μM and 0.27μM, respectively (Study B002050).
- Elinzanetant, BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 3462934 (M18/21) inhibited human P-gp with IC_{50} values of 0.22μM, 1.51μM, 0.09μM and 2.94μM, respectively (Study B002191).
- Elinzanetant and the metabolites inhibited BCRP, with IC_{50} values of 0.08μM (elinzanetant), 0.48μM (M27) , 0.17μM (M30/34) and 1.38μM (M18/21) (Study B002163).
- Using nonspecific binding of elinzanetant to OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K, the Applicant predicted no in vivo DDI (Study R-14407).
- BAY 3427080 (elinzanetant), M27, M30/34, M22 directly inhibited UGT1A1 in the uridine diphosphate glucuronosyltransferases (UGTs) with IC_{50} values of 2.6μM., 0.46μM, 1.8μM and 2.6μM, respectively (Study B002074).

- Elinzanetant, BAY 3469432 (M27), BAY 3469433 (M30/34) and BAY 3469434 (M18/21) were classified as inhibitors of BSEP with IC_{50} values of 2.13µM, 5.91µM, 9.20µM and 16.7µM, respectively (Study B002085).

13.2.3. Toxicology

13.2.3.1. General Toxicology (Pivotal Studies)

Single-dose and repeat-dose toxicity studies with elinzanetant and metabolite M27, a disproportionate human metabolite, were conducted in rat and monkey. The key findings from all pivotal repeat-dose toxicity studies are described in Table 101 below. The GLP status of each study is also noted. For calculation of nonclinical safety or exposure margins, the clinical exposure at the MRHD of $AUC_{(0-24)}$=8572 µg.h/L (from the clinical study number CPM50130 [report number B002427]) was used for comparison unless otherwise noted.

Section 7 provides the nonclinical integrated summary for potential nonclinical signals of clinical concern observed in these studies.

For summary of all general toxicity studies refer to the nonclinical review in DARRTS (DARRTS°ID:°5623053 2025).

Table 101. Pivotal Repeat Dose Toxicity Studies With Elinzanetant

Repeat-Dose Toxicity Studies in Rat	
Study No./Design (NOAEL and Safety Margin*)	**Study Findings**
R-13595 (GLP) Sprague-Dawley Rat (Charles River, UK) [male (M) + female (F)], oral gavage, once daily for 4 weeks @ 0, 5, 25, 100 mg/kg/day; QD; elinzanetant (tosylate salt form) NOAEL =25 mg/kg/day (F), 100 mg/kg/day (M) Safety margin =10.0-fold (F), 10.5-fold (M) on AUC basis for MRHD*	Mortality • 1F @ 100 mg/kg euthanized on Day 12 due to severe clinical signs (piloerection, hunched posture, tiptoe gait, pale extremities, pinched flanks, and irregular/labored breathing). Clinical signs • Transient clinical signs noted in all groups included chewing, tense appearance (increasing in incidence in animals dosed at 100 mg/kg), rubbing chin on the cage floor, and vocalizing. Clinical chemistry • Higher group mean plasma total bilirubin concentration was observed in M @100 mg/kg (1.48X of control) and F at ≥25 mg/kg (1.78 to 1.54X of control). Organ weight • Liver- increased in M (1.1X control) and F (1.2X control) @ 100 mg/kg, no corresponding microscopic changes. • Adrenals- increased in M @100 mg/kg/day (1.2X control). Microscopic findings • 2F @ 100 mg/kg had abnormalities in the reproductive tract characterized by abnormal diestrus, mucification of the vaginal mucosa, atrophy of the uterus, and persistent corpora lutea in the ovary. • Minimal adrenal cortical hypertrophy in M @ 100 mg/kg Toxicokinetics • Systemic exposure was typically higher in F than M, with no relevant change in the absorption rate as dose increased. • There was some evidence of accumulation in F @ 25 and 100 mg/kg groups (1.7X and 3.5X, respectively).

Repeat-Dose Toxicity Studies in Rat

Study No./Design (NOAEL and Safety Margin*)	Study Findings
	Table 102. PK Parameters of Elinzanetant Following 4-Week Oral Repeat Dosing in SD Rats (Once Daily Dosing)

PK Parameters	5 mg/kg/Day	25 mg/kg/Day	100 mg/kg/Day
Male values on Day 1			
$AUC_{(0-24)}$ [µg·h/mL]	6.98	25.9	73.7
C_{max} [µg/mL]	0.777	2.57	5.15
T_{max} [h]	2	2	4
Male values on Day 28			
$AUC_{(0-24)}$ [µg·h/mL]	7.31	20.9	89.9
C_{max} [µg/mL]	0.741	2.75	6.36
T_{max} [h]	2	2	4
Female values on Day 1			
$AUC_{(0-24)}$ [µg·h/mL]	12.4	51.0	99.5
C_{max} [µg/mL]	1.02	3.38	5.37
T_{max} [h]	2	2	4
Female values on Day 28			
$AUC_{(0-24)}$ [µg·h/mL]	14.7	85.8	344
C_{max} [µg/mL]	1.09	5.07	18.9
T_{max} [h]	1	2	4

Source: Reviewer-generated table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; SD, Sprague-Dawley; T_{max}, time to maximum concentration

R-13596 (GLP)

Sprague-Dawley Rat (Charles River, Canada) (M+F), oral gavage, once daily, 13 weeks

@ 0, 5, 25, 100 mg/kg/day; QD; elinzanetant (free base)

NOAEL =100 mg/kg/day

Mortality and clinical signs

- None

Clinical chemistry

- Minimal decreases in lymphocyte counts (0.79X to 0.86X of control mean) for M and F @ 100 mg/kg, starting in F at Week 4 and for both sexes at Week 13.
- Increase in bilirubin (2.5X in M @ 100 mg/kg, 3.4X in F @ 100 mg/kg), urea (5.1X in F @ ≥25 mg/kg), creatinine (43.3X @ ≥25 mg/kg), and glucose (6.5X in M @ 100 mg/kg, 5.9 to 6.9X @ ≥25 mg/kg). Decreases in serum phosphorus (~2.5X) and potassium (~5X) @ 100 mg/kg in both M and F.

Repeat-Dose Toxicity Studies in Rat	
Study No./Design (NOAEL and Safety Margin*)	**Study Findings**
Safety margin =6.6-fold (M), 15.7-fold (F) on AUC basis for MRHD	Urine • Increases in glucose concentration per collection period (1.2X to 1.3X mean control) in Weeks 4 and 13, and minimal increases in urinary glucose (1.9X mean control) for F @ 100 mg/kg by Week 13. Toxicokinetics • No significant differences (<2-fold) in terms of C_{max} and $AUC_{(0-24)}$ were observed between Week 4 and Week 13. • No notable difference in exposure (in terms of $AUC_{(0-24)}$) was observed between M and F at the lowest dose (5 mg/kg). However, systemic exposures were significant higher (at least 2.4-fold) in F than in M at 25 and 100 mg/kg on both Week 4 and 13.

Table 103. PK Parameters of Elinzanetant Following 13-Week Oral Repeat Dosing in SD Rats (Once Daily Dosing)

PK Parameters	5 mg/kg/Day	25 mg/kg/Day	100 mg/kg/Day
Male values on Day 28			
$AUC_{(0-24)}$ [µg·h/mL]	4.57	7.73	30.7
C_{max} [µg/mL]	0.51	0.867	2.49
T_{max} [h]	2	2	2
Male values on Day 91			
$AUC_{(0-24)}$ [µg·h/mL]	5.8	12	56.7
C_{max} [µg/mL]	0.586	1.19	4.72
T_{max} [h]	2	2	2
Female values on Day 28			
$AUC_{(0-24)}$ [µg·h/mL]	8.05	27.5	116
C_{max} [µg/mL]	0.626	1.8	6.57
T_{max} [h]	1	1	2
Female values on Day 91			
$AUC_{(0-24)}$ [µg·h/mL]	7.06	32.2	135
C_{max} [µg/mL]	0.677	2.41	8.28
T_{max} [h]	1	1	2

Source: Review-generated table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; SD, Sprague-Dawley; T_{max}, time to maximum concentration

Repeat-Dose Toxicity Studies in Rat	
Study No./Design (NOAEL and Safety Margin*)	**Study Findings**
R-13628 (GLP) (amended report) Sprague-Dawley Rat (M+F) (Envigo, Netherlands), oral gavage, twice daily (BID), 6 hr apart 13 weeks with 4-week recovery M @ 0, 50, 120, 300 (175) mg/kg/day [0, 25, 60, 150 (87.5) mg/kg, BID] (Note: dose in HD males was reduced after 9 days of dosing from 300 mg/kg/day to 175 mg/kg/day because of marked intolerability and then discontinued altogether on the 11th day of dosing because of continued toxicity) F @ 0, 20, 50, 100 mg/kg/day [0, 10, 25, 50 mg/kg BID]	<u>Mortality</u>: • 300 mg/kg/day (M): 5 died prematurely, 3 on Day 9 and 2 on Day 11; 6 were euthanized on Day 9 or 11 due to clinical signs [dehydration, prostration or hunched back and body weight loss (between 3 and 14%)] • On Day 12, all surviving 7 M from 300 mg/kg/day were euthanized, with the exception of the 3 TK animals which were necropsied after a 28-day treatment-free recovery period (Day 40) • 100 mg/kg/day (F): 6 euthanized on Day 11 to 68 after showing prostration, decreased activity, hunched back, pallor, moderate to severe dehydration and rapid breathing. • 1 F @ 20 mg/kg/day and 2 F @ 50 mg/kg/day euthanized on Day 34 to 68 due to severe clinical signs [involuntary muscle contractions, spasms, rigidity, tremors, stiffness of the tail, salivation and in some animals, irritability and aggressive behavior for a short period after dosing] <u>Gross Pathology in unscheduled deaths</u>: • The histology showed muscle degeneration and necrosis in the tongue, the larynx and the skeletal muscles of the leg. Myotoxicity was also considered the cause of death for these animals @ 100 mg/kg/day F and @ 300 mg/kg/day M. • Alterations in the large intestine consisting of distended colon or cecum and/or hard content in the colon was noted in 3 M @ 300 mg/kg/day and 2 F @ 100 mg/kg/day suggesting alteration of food transport in the GI tract and may correlate with the decrease in food consumption noted in the first two weeks of treatment. • Histologic lesion associated with these findings in M was the depletion of secretions from the acinar cells in the salivary glands, which would possibly be associated with dry mouth, a difficulty in swallowing the food and corresponding appetite suppression. <u>Clinical signs</u>: • CNS: Tremors, rigidity, spasms (generally lasting 1-2 minutes and occasionally up to 3 minutes), abnormal involuntary muscle contractions (generally lasting 1-30 seconds and occasionally up to 2 minutes) and stiff tails in 1 M each from 50 and 120 mg/kg/day. F @ all doses had spasms, involuntary contractions, and convulsions. A few animals also appeared disoriented and showed irritability or aggressive behavior for a short period after dosing. • Body weight: 5% decrease in M @ 300 mg/kg/day during first 12 days. Transient weight loss in F.

Repeat-Dose Toxicity Studies in Rat

Study No./Design (NOAEL and Safety Margin*)	Study Findings
Study conduct details: Conducting lab = (b) (4) (b) (4) in 2018 Rats used: SD:Hsd obtained from Envigo RMS B.V.; Netherlands Conducting lab: (b) (4) (b) (4) NOAEL = not determined Multiple of exposure* for CNS-related signals: @ low dose of 20 mg/kg/day (F) and 50 mg/kg/day (M) =4-fold	Food consumption: • M @ 300 mg/kg/day had marked decrease (approximately half of the food consumption compared to controls) • F @ 100 mg/kg/day decrease intake (10%) during first 15 days Organ weight: • Heart (+23%), kidney (+28%), liver (+42%), lungs (+32%), and thymus (+110%) relative weights (compared to body weight) were elevated in the 7 M euthanized on Day 12. • After recovery phase, significant increases in heart, kidney, liver, and spleen weights (absolute and relative to body weight except for the spleen) were noted @ 120 mg/kg/day M. Histopathology: • Liver: Increase liver weight was accompanied by minimal hepatocellular atrophy • Lung: Alveolar macrophage infiltrates • Thymus: Minimal involution and atrophy • GI: Lumen of the colon was slightly dilated in 2/7 animals and the mandibular and parotid salivary glands showed minimal depletion of the secretory granules in the acinar cells in 3/7 animals.

Table 104. Incidence of Skeletal Muscle Degeneration in Male and Female Rats Euthanized Due to Overt Toxicity Induced by the Highest Test Doses of Elinzanetant

	Male Rats (300 mg/kg/Day)	Female Rats (100 mg/kg/Day)
Tissue/ Findings	**Number of Affected Rats/Total Number of Rats**	
Skeletal Muscle Degeneration/Myofiber	11/11	3/6
Larynx Degeneration/Necrosis, Muscle	9/11	1/6
Tongue Degeneration/Necrosis, Myofiber	11/11	1/6

Source: Reviewer-generated table using data from study report (page 54)

Repeat-Dose Toxicity Studies in Rat	
Study No./Design (NOAEL and Safety Margin*)	**Study Findings**
*MOE estimated using extrapolated AUC values for days when findings were first observed in male and female rats (For details, refer to Section 13.2.5). Multiple of exposure** for skeletal muscle findings: M =16-fold**, F =8-fold** @ 300 mg/kg/day for males and 100 mg/kg/day for females. [** taking AUC from day 1 since high-dose animals that had skeletal muscle findings did not survive to Week 13]	Skeletal muscle: • Moderate or severe degeneration/necrosis in the skeletal muscle in all 100 mg/kg F and 300 mg/kg M (or group 4) that died prematurely. • 7 M @ 300 mg/kg/day that were prematurely sacrificed also had degeneration/necrosis in the skeletal muscle of the leg (3 in 7), tongue (4 in 7), or larynx (2 in 7). Clinical chemistry: • M @ 300 mg/kg/day had increase in ALT, AST, CK plasma levels and decrease A/G ratio. • LDH, AST and CK increases in M correlated with histological findings of necrosis and degeneration in the skeletal muscles, suggesting that the cause of transaminases elevation is myotoxicity. • However, no increases in above parameters were seen in F. • F @ ≥50 mg/kg/day had increase in plasma creatinine, calcium, inorganic phosphorus, and sodium. Urinalysis: • Urine volume was increased, and urine creatinine values were decreased in a dose dependent fashion in both sexes and these changes were statistically significant in the F @ 100 mg/kg/day at Week 6 [150% increase in urine volume; 43% decrease in urine creatinine]. These effects disappeared at Week 13, suggesting an adaptation of the nephron. Toxicokinetics: • 2.6 to 4.3-fold accumulation in systemic exposure was observed (based on C_{max} and $AUC_{(tlast)}$ seen in F @ all doses between Day 1 and Week 13.

Repeat-Dose Toxicity Studies in Rat

Study No./Design (NOAEL and Safety Margin*)

Study Findings

Table 105. PK Parameters of Elinzanetant Following 13-Week Oral Repeat Dose in SD Rats (BID Dosing, 50 mg/kg/Day, 120 mg/kg/Day, 300 mg/kg/Day)

PK Parameters	50 mg/kg/Day	120 mg/kg/Day	300 mg/kg/Day
Male values at Day 1			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	29.460	54.68	140.6
C_{max} [µg/mL]	2.31	3.9	8.14
T_{max} [h]	12	3	3
Male values at Week 13			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	36.07	78.14	NA
C_{max} [µg/mL]	2.81	5.32	NA
T_{max} [h]	9	12	NA

Source: Reviewer-generated table
NA = not available (animals did not survive for TK analysis)
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetic; SD, Sprague-Dawley; T_{max}, time to maximum concentration

Table 106. PK Parameters of Elinzanetant Following 13-Week Oral Repeat Dose in SD Rats (BID Dosing, 20 mg/kg/Day, 50 mg/kg/Day, 100 mg/kg/Day)

PK Parameters	20 mg/kg/Day	50 mg/kg/Day	100 mg/kg/Day
Female values at Day 1			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	20.36	37.25	69.63
C_{max} [µg/mL]	1.12	2.06	3.93
T_{max} [h]	3	12	3
Female values at Week 13			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	59.84	152.5	297.5
C_{max} [µg/mL]	2.93	7.95	16
T_{max} [h]	3	12	12

Source: Reviewer-generated table
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetic; SD, Sprague-Dawley; T_{max}, time to maximum concentration

Repeat-Dose Toxicity Studies in Rat	
Study No./Design (NOAEL and Safety Margin*)	**Study Findings**
	FDA Analysis • Skeletal muscle findings: The Applicant does not provide any mechanistic basis for the findings of skeletal muscle degeneration and necrosis, but concludes that the findings, along with the CNS findings observed in this study, cannot be ruled out as treatment related. A follow up mechanistic study [R-13644 [QL24QG] failed to reproduce the results seen in this study. The findings from this study related to skeletal muscle necrosis is included in the integrated summary in Section 7 of this review. • CNS findings (tremors and convulsions): The Lowest Observed Adverse Effect Level (LOAEL) for these safety signals were 20 and 50 mg/kg/day in female and male rats, respectively. A NOAEL was not established. Exposure [$AUC_{(0-24)}$] data are available only for treatment Days 1 and 91, whereas convulsions were first noted around treatment Day 34 in female and male. Using the linear regression of the available $AUC_{(0-24)}$, it was estimated that exposures generated by the LOAELs on the first day when convulsions were noted are ~4-fold higher than the clinical exposure generated by the MRHD. The CNS-related effects of convulsions were observed in this study and in the 2-year carcinogenicity study in female rats. The integrated summary for this finding is included in Section 7 of this review. For details on exposure margin estimation for the CNS effects, refer to Section 13.2.5. • Liver findings: Increased liver weight accompanied by minimal hepatocellular atrophy was seen in this study. A nonpivotal 7-day study with elinzanetant (study R-13586) also noted liver toxicity characterized by hepatocyte necrosis. The liver findings are included in the integrated summary in Section 7 of this review.

Repeat-Dose Toxicity Studies in Rat	
Study No./Design (NOAEL and Safety Margin*)	**Study Findings**
Study R-13894 (GLP) Rat (M+F), oral gavage, BID (6 hr apart, 26 weeks M @ 0, 50, 120, 180 mg/kg/day [0, 25, 60, 90 mg/kg BID] F@ 0, 20, 50, 80 mg/kg/day [0, 10, 25, 40 mg/kg BID] NOAEL =120 mg/kg/day (M) [note# Applicant regards 180 as the NOAEL) and 80 mg/kg/day (F) Safety margin =8.8-fold (M) and 36.3-fold (F) on AUC basis for MRHD	Mortality: • 1 in control and 1 in 50 mg/kg/day males (difficulty breathing noted), not considered treatment related. Body weight: • The final body weight was marginally (1-5%) lower in treatment groups than in the respective controls, without a clear dose-effect. Hematology: • Lower hematocrit and red cell distribution width in both sexes @ 180 mg/kg/day M and 80 mg/kg/day F. • Higher mean cell hemoglobin concentrations in both sexes @ Week 13 and 26. • Low mean cell volume and low hemoglobin concentration in males @ Week 13 and 26. Clinical Chemistry: • Elevated ALT at Week 26 in M @ 180 mg/kg/day (2-fold). AST increase in F @ 50, 80 mg/kg/day at Week 26 (2-fold). Bilirubin levels increased in treatment groups in M @ both Week 13 and 26. Cholesterol levels decreased in M @ 120 and 180 mg/kg/day @ Week 13 and 26 (180 mg/kg/day only). Alterations of plasma electrolyte concentrations and markers of glomerular filtration rate. Urinalysis: • Increase in protein and glucose concentration in the urine from @ 180 mg/kg/day in M and 80 mg/kg/day in F. • Urine volume of male rats dosed at 120 and 180 mg/kg/day was higher than controls. • Increased incidence of white blood cells in the urine of male [consistent with mild kidney damage]. Gross pathology: • Depressions were noted in the kidneys of 2 M @ 50 mg/kg/day, 4M from the 120 mg/kg/day group and two males @ 180 mg/kg/day. • Pale areas were noted in the lungs of 1M @ 50 mg/kg/day, 3M @ 120 and 7M and 2F @ 180 and 80 mg/kg/day, respectively. Organ weight: • Dose-dependent increase in the relative weight of the adrenal gland, heart, kidney, liver, and decrease in thymus weight in M. • Relative weight of the adrenal, heart, kidney, and liver were statistically elevated @ 80 mg/kg/day in F.

Repeat-Dose Toxicity Studies in Rat	
Study No./Design (NOAEL and Safety Margin*)	**Study Findings**
	Histopathology: • Lung: Dose-related incidence of macrophage infiltrations in the alveoli was noted in both sexes, without increase in severity. Minimal infiltrates were noted in M and F @ 50 and 20 mg/kg/day respectively (low dose), and also @ higher dose groups. • Kidney: Tubular basophilia, hyaline casts and cortical scars were seen in males (no dose response), correlated with the increase relative kidney weights and kidney macroscopic observations. Additionally, the alterations of plasma electrolyte concentrations and markers of glomerular filtration rate suggest mild kidney toxicity. • Adrenal: Minimal hypertrophy of the adrenal cortex noted in 5/12 males and 4/12 females @ the high dose in M and F. • Thymus: Dose-related decrease in thymus weight in males was consistent with the dose-related increase in incidence and severity of the atrophy in the thymus in F (minimal severity, increased incidence with dose) and M (minimal to moderate severity, increased severity and incidence with dose). • Liver: No histopathological findings in the liver. Mild dose-related liver-related effects in M, manifested by elevated ALT and AST activity, higher bilirubin and a dose-related reduction in cholesterol concentration. These changes were not accompanied by correlating histopathology and were considered adaptive rather than toxicological. Toxicokinetics: • No accumulation occurred in M; however, notable accumulation was observed in F at all doses (2.4- to 3.0-fold) after 26 weeks of dosing. At the comparable dose for M and F (50 mg/kg/day), exposure in F was notably higher than in males and this difference was more pronounced with repeated administration.

Repeat-Dose Toxicity Studies in Rat

Study No./Design (NOAEL and Safety Margin*)

Study Findings

Table 107. PK Parameters of Elinzanetant Following 26-Week Oral Repeat Dose in SD Male Rats (BID Dosing)

PK Parameters	50 mg/kg/Day	120 mg/kg/Day	180 mg/kg/Day
Male values at Day 1			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	22.5	73.1	121
C_{max} [µg/mL]	1.98	5.70	8.06
T_{max} [h]	12	12	12
Male values at Week 26			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	36.2	76.1	108
C_{max} [µg/mL]	2.61	4.64	6.83
T_{max} [h]	9	9	12

Source: Reviewer-generated table
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetic; SD, Sprague-Dawley; T_{max}, time to maximum concentration

Table 108. PK Parameters of Elinzanetant Following 26-Week Oral Repeat Dose in SD Female Rats (BID Dosing)

PK Parameters	20 mg/kg/Day	50 mg/kg/Day	80 mg/kg/Day
Female values at Day 1			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	23.0	73.8	102.0
C_{max} [µg/mL]	1.42	4.64	6.33
T_{max} [h]	12	12	12
Female values at Week 26			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	67.4	194	311
C_{max} [µg/mL]	3.37	114	150
T_{max} [h]	9	9	12

Source: Reviewer-generated table
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetic; SD, Sprague-Dawley; T_{max}, time to maximum concentration

Repeat-Dose Toxicity Studies in Rat	
Study No./Design (NOAEL and Safety Margin*)	**Study Findings**
	FDA Analysis • No tremors, convulsions, or other CNS-related safety signals were noted in the present study. This contrasts with the findings of CNS-related safety signals (including rigidity, tremors, and convulsions) noted in rats were that were also treated twice daily with elinzanetant doses ≥20 mg/kg/day in the 13-week study R-13628. • The absence of CNS-related safety signals in the present study could not be accounted for by insufficient systemic exposures because, in the 13-week study R-13628 and the 2-year carcinogenicity study, convulsions were first noted in rats when systemic exposures reached ~35.1 µg.h/mL and ~150 µg.h/mL, respectively which are considerably lower than exposures measured in the present study [see Section 7 and Section 13.2.5 for a discussion of the apparently discrepant findings].

Source: Reviewer-generated table
Abbreviations: A/G, albumin-globulin; ALT, alanine Aminotransferase; AST, aspartate Aminotransferase; AUC, area under the concentration-time curve; CK, creatine kinase; C_{max}, maximum plasma concentration; CNS, central nervous system; GI, gastrointestinal; GLP, good laboratory practice; HD, high dose; LDH, lactate dehydrogenase; MOE, multiple of exposure; NOAEL, no-observed-adverse-effect level; MRHD, maximum recommended human dose; QD, once daily, ; SD, Sprague-Dawley; TK, toxicokinetic

Table 109. Repeat-Dose Toxicity Study for Metabolite (M27) in Rat

Study No. & Design	Study Findings
Study R-13953 (GLP) Sprague-Dawley Rat (M+F) (Charles River, UK), oral gavage, once daily @ 0, 5, 10, 20 mg/kg/day with M27 metabolite, QD, investigated at 13 (Interim) or 26 weeks (main study) NOAEL =20 mg/kg/day Safety margin =5.4-fold (M) and 15-fold (F)** **= based on $AUC_{(0-24)}$ of 2496.3 ng.h/mL (M27), obtained from clinical Study B002427	Mortality: • Two F @ 20 mg/kg (one main study at Day 83, one satellite on Day 64) euthanized for welfare reasons not considered related to M27 treatment. • Clinical Signs: • No treatment-related changes in clinical signs. Body weight: • Decreased BW gain compared to control @ 10 and 20 mg/kg in F from Week 13 to termination. Overall, body weight gain (Week 0-26) was unaffected by treatment. • Hematology: Increased leucocyte subpopulation counts in treated groups @ 20 mg/kg F in Week 13/14 and 26, @ 20 mg/kg M in Week 13 and 26 Clinical Chemistry: • Bilirubin concentration was increased in all treated female groups (up to 4x control at 20 mg/kg) in Week 13/14 and 26 and in the high-dose (20 mg/kg) male group (up to 2x control) in Week 13 and 26. There were no correlating findings of hemolysis, cholestasis, organ weight changes, macroscopic, or microscopic changes in the liver at 13 or 26 weeks.

Study No. & Design	Study Findings
	Histopathology: No treatment-related changes in histopathology. • Note @ 20 mg/kg/day: Slightly higher incidence and severity of myofiber regeneration, degeneration, and necrosis in the tongues of males and females administered 20 mg/kg/day for 13 weeks. In the study report, this finding was considered to be related to the sublingual blood sampling, rather than the test item, based on the location and character of this finding (Heimann et al. 2009). However, this finding was also observed in a 13-week toxicity study in rats with the parent compound (Study R-13628 [RH17GJ]) and cannot be ruled out as potentially treatment-related. M27 Toxicokinetics: • Exposure increased generally dose proportionally, tendency to be greater than dose proportional in both sexes on Day 1 and in females during Weeks 13 and 26. • Accumulation occurred after multiple doses, highest @ 5 mg/kg/day and lowest @ 20 mg/kg/day in both sexes. • Sex differences were generally greater than 2-fold, with increased exposure observed in F compared to M. • At Week 26, C_{max} (µg/mL) =1.740 (M) or 3.49 (F) and $AUC_{(0-24)}$ (µg·h/mL) =13.7 (M) or 38.3 (F). TK of M27 metabolites: • M18/21: Exposure increased proportional to M27 dose, accumulation was observed after repeat dosing in females, sex differences <2-fold • M30/34: low levels generated in all dosing groups, increased exposure observed in F compared to M (~2-fold higher in F).

Source: Reviewer-generated table; Clinical study number CPM50130 (report number B002427)
* Safety margins and multiples of exposures calculated based on clinical exposure at the Maximum Recommended Human Dose (MRHD) of $AUC_{(0-24)}$=8572.0 µg.h/L
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; F, female; GLP, good laboratory practice; M, male; NOAEL, no-observed-adverse-effect level; QD, once daily, SD, Sprague-Dawley; TK, toxicokinetic

Table 110. Repeat-Dose Toxicity Studies in Monkey

Study No./ Design (NOAEL and Safety Margin*)	Study Findings
Study R-13639; GLP Monkey (M+F), oral gavage, once daily, 4 weeks @ 0, 6, 20, 60 mg/kg/day elinzanetant (tosylate salt) NOAEL =20 mg/kg/day Safety margin =1-fold (based on average M and F exposure)	Mortality: • 1M and 1F @ 60 mg/kg were sacrificed prematurely on Day 6 and 22, respectively. • Euthanized monkeys had abnormal fecal consistency (loose/watery) and reduction in food intake. Dilation of distal nephron elements in the kidney was considered to be a test article-related primary adverse finding. • Other findings include acinar atrophy of the pancreas, cytoplasmic rarefaction in the liver, and hemorrhage in the adventitia and mucosa of multiple regions in the gastrointestinal tract. Increase in glucose to creatinine ratio in M @ 60 mg/kg. Toxicokinetics: • Exposures in M and F were similar.

Table 111. PK Parameters of Elinzanetant Following 28-Day Treatment in Monkey

PK Parameters	6 mg/kg/Day	20 mg/kg/Day	60 mg/kg/Day
Male values on Day 1			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	1.54	4.65	28.9
C_{max} [µg/mL]	0.371	0.607	2.24
T_{max} [h]	2	2	12
Male values on Day 28			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	1.7	6.86	40.2
C_{max} [µg/mL]	0.227	0.609	2.24
T_{max} [h]	4	4	5
Female values on Day 1			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	0.961	5.01	11.2
C_{max} [µg/mL]	0.199	0.794	0.916
T_{max} [h]	2	2	2
Female values on Day 28			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	1.15	9.88	31.1
C_{max} [µg/mL]	0.248	1.02	2.13
T_{max} [h]	2	4	14

Source: Reviewer-generated table
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetic; T_{max}, time to maximum concentration

Study No./ Design (NOAEL and Safety Margin*)	Study Findings
	FDA Analysis Gastrointestinal (GI) findings: GI findings of loose/watery fecal consistency with reduced food intake at 60 mg/kg/day (~4-fold the human therapeutic exposure on an AUC basis) was noted as potentially concerning findings as they led to premature sacrifice in monkeys. These animals also had hemorrhage in the adventitia and mucosa of multiple regions in the gastrointestinal tract. GI effects were also seen in the 13-week and 39-week studies as described below. Refer to Section 7 for the integrated summary for GI findings.
Study R-13629 (GLP) Monkey (M+F), oral, once daily, 13 weeks. @ 0, 6, 20, 40 mg/kg/day elinzanetant (free base form) NOAEL =40 mg/kg/day Safety Margin =2.9-fold (M), 1.2-fold (F)	Mortality: • None Clinical signs: • Thin appearance and dehydration were occasionally observed for females in all dose groups (including controls) but with greater frequency for females given ≥20 mg/kg (≥0.5-fold the human therapeutic exposure on an AUC basis). • Abnormal feces (liquid/soft) were noted in many animals across all dose groups at various points throughout the study. The incidence and severity of the findings were comparable between doses. Body weight and Food consumption: • Slight reduction in body weight or lack of body weight gain towards the end of the study was noted in some males and/or females across all dose groups, affecting 40 mg/kg animals more predominantly. • A reduction in food intake/appetite was observed throughout the study at all dose groups (including controls) for all males and females with the exception of a single animal. Hematology and Clinical chemistry: • Decrease in red blood cell count, hemoglobin, hematocrit and reticulocyte counts compared to controls @ 20 and/or 40 mg/kg. • Mild decrease in glucose and mild increase in triglycerides and urea @ 20 and/or 40 mg/kg. Organ Weight and Histopathology: • No test article-related changes in organ weight, macroscopic, or microscopic findings. Toxicokinetics: $AUC_{(0-t)}$ values increased from Day 28 to Day 91 at all doses, and systemic exposure to elinzanetant (mean AUC_{0-t} and C_{max} values) increased greater than dose proportionally, but the interanimal variability was large.

Study No./ Design (NOAEL and Safety Margin*)	Study Findings

Table 112. PK Parameters of Elinzanetant Following 91-Day (13-Week) Treatment in Monkey

PK Parameters	6 mg/kg/Day	20 mg/kg/Day	40 mg/kg/Day
Male values on Day 28			
$AUC_{(0-24)}$ [µg·h/mL]	0.266	2.21	9.207
C_{max} [µg/mL]	0.0569	0.211	0.642
T_{max} [h]	4	4	6
Male values on Day 91			
$AUC_{(0-24)}$ [µg·h/mL]	0.54	3.65	24.75
C_{max} [µg/mL]	0.037	0.25	1.77
T_{max} [h]	6	4	8
Female values on Day 28			
$AUC_{(0-24)}$ [µg·h/mL]	0.276	2.645	5.192
C_{max} [µg/mL]	0.0548	0.264	0.465
T_{max} [h]	4	4	3
Female values on Day 91			
$AUC_{(0-24)}$ [µg·h/mL]	0.64	4.19	10.33
C_{max} [µg/mL]	0.064	0.321	0.781
T_{max} [h]	7	6	6

Source: Reviewer-generated table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetic; T_{max}, time to maximum concentration

Study No./ Design (NOAEL and Safety Margin*)	Study Findings
Study R-13612 [as twice amended report] (GLP) Monkey (M+F), oral, BID dosing (6-hr apart), 13 weeks @ 0, 30, 60, 80 mg/kg/day [0, 15, 30, 40 mg/kg BID] elinzanetant (free base form) NOAEL =80 mg/kg/day Safety Margin =2.3-fold (based on average M and F exposure)	Mortality: None Clinical signs: • Thin appearance @ 40 mg/kg BID; Loose/liquid feces in M @ 30 mg/kg BID and F @ 15 mg/kg BID. • Mild and transient decrease in body temperature in 1 M @ 40 mg/kg BID. Body weight and food consumption: • Reduced body weight gain in M @ ≥15 mg/kg BID and in M and F @ ≥40 mg/kg BID. • Lower food consumption recorded occasionally in animals treated at 30 mg/kg BID and frequently in animals given 40 mg/kg BID when compared with control animals. Clinical chemistry: Reduced ALP and GGT in M and increased mean creatinine levels with reduced Cl in F @ 40 mg/kg BID, with no histopathological correlations.

Study No./ Design (NOAEL and Safety Margin*)	Study Findings
	Organ weight: • Increase liver weight (relative to body or brain weight) in both M and F @ 40 mg/kg BID, with no corresponding microscopic changes in the liver. • In M, dose-dependent decrease in epididymides and testes mean weight. The male animals were found to have varying degrees of sexual maturity that may have influenced organ weight differences (i.e., 2 controls were sexually mature, whereas all treated males were immature). FDA Analysis NK1R/NK3R inhibition in KNDy neurons in the hypothalamus reduces the activity of hypothalamic neurons that secrete gonadotropin-releasing hormone (GnRH). The reduced GnRH release suppresses the release of gonadotropins (luteinizing hormone [LH] and follicular stimulating hormone [FSH]) from the anterior pituitary gland. A reduction of the LH and FSH levels due to elinzanetant-induced inhibition of NK1R/NK3R could explain the dose-dependent reduction of the mean weight of epididymides and testes. Histopathology: • No test article-related changes in microscopic findings. Toxicokinetics: • High interanimal variability and some overlap in exposure between doses. Mean exposure in M was higher than in F on both Days 1 and 91 @ 15 mg/kg BID whereas on Day 1 the mean exposure in F @ 30 mg/kg BID was higher than in M.

Study No./ Design (NOAEL and Safety Margin*)	Study Findings

Table 113. PK Parameters of Elinzanetant Following 91-Day (13-Week) Treatment in Monkeys Dosed BID

PK Parameters	15 mg/kg BID	30 mg/kg BID	40 mg/kg BID
Male values on Day 1			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	7.370	7.340	30.40
C_{max} [µg/mL]	0.609	0.603	1.96
T_{max} [h]	3	24	12
Male values on Day 91			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	8.440	10.7	16.30
C_{max} [µg/mL]	0.671	0.885	1
T_{max} [h]	7	9	9
Female values on Day 1			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	2.99	20.5	24.9
C_{max} [µg/mL]	0.313	1.41	1.79
T_{max} [h]	9	24	7
Female values on Day 91			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	1.670	16.2	24
C_{max} [µg/mL]	0.178	1.370	1.690
T_{max} [h]	1	9	9

Source: Reviewer-generated table
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetic; T_{max}, time to maximum concentration

Study No./ Design (NOAEL and Safety Margin*)	Study Findings
Study R-13895(GLP) Monkey (M+F), oral, BID dosing (6hr apart), 39 weeks @ 0, 30, 60 and 80 mg/kg/day [0, 15, 30 and 40 mg/kg BID] NOAEL =80 mg/kg/day (40 mg/kg BID) for M; 30 mg/kg/day (15 mg/kg BID) for F Safety margin =1-fold (M), 0.35-fold (F)	Mortality: None Clinical signs: • Loose and/or liquid feces in M @ 15 and 40 mg/kg BID and F @ 30 and 40 mg/kg BID. • Diarrhea accompanied by additional GI disturbances signs including distended and gassy abdomen and signs of dehydration in some animals. • 2 F @ 40 mg/kg BID had diarrhea that led to dehydration, weight loss and general ill-health. Minimal inflammatory cell infiltrate in the mucosa of the large intestine was also seen. • 1 F @ 30 mg/kg BID had muscle fasciculation during 2 consecutive days towards the end of the treatment period. • Occasional contracted muscles in toes and associated abnormal locomotion observed for animals in each treated group with a dose-related incidence during the first 2 weeks of treatment. • Body weight and food consumption: • Mean body weight gain ~48% lower than controls in F @ 40 mg/kg BID which correlated with GI-related effects (loose stool/diarrhea). Food consumption information was not provided. Clinical chemistry: • Increased ALT activity in F @ 40 mg/kg BID at Week 13 and 26 (2.5-fold) and 39 (3.6-fold) and in M @ 30 mg/kg BID at Week 39 (1.8-fold). • Increased plasma urea in F @ 40 mg/kg BID at end of treatment period. • Increased triglycerides in both M and F @ 30 and 40 mg/kg BID Organ weight: • Dose-related increase in liver weights in M (up to 68% @ 40 mg/kg, BID) and F (up to 38% increase @ 40 mg/kg, BID). Decreased absolute and relative (to body weight) female reproductive organ weights in F @ 40 mg/kg, BID (ovaries: -55%, uterus and cervix: -43%) and ovary weights (-67%) @ 30 mg/kg, BID.

Study No./ Design (NOAEL and Safety Margin*)	Study Findings
	Histopathology: • Liver: Sinusoid compression in liver, presenting as narrowing of the sinusoidal space in M and @ 40 mg/kg, BID and F @ 30 mg/kg BID. • Large Intestine: Minimal inflammatory cell infiltrate was present in the mucosa of the cecum or colon of F @ 40 mg/kg, BID. • Ovaries: Corpora lutea and/or follicular activity was absent in the ovaries of F @ 30 and 40 mg/kg, BID, correlating with a reduction in ovary weight. These changes are consistent with an observed lack of menstrual cycling; however, menstrual status was not monitored for females during the in-life phase of this study. These findings are consistent with the expected pharmacological effects of elinzanetant. Toxicokinetics: • High inter animal variability was noted, which may impact dose proportionality, dose accumulation and gender differences and therefore evaluations should be interpreted with caution. Of note, 1 F @ 60 mg/kg/day female (No. 470) showed notably higher systemic exposure than other females of the same group, likely causing higher AUC compared to M at that dose. • Excluding the 1 F @ 60 mg/kg/day (No. 470), systemic exposure (C_{max} and AUC) increased in a dose proportional manner from 30 to 60 mg/kg/day in both males and females. • Exposure was notably higher (2.5X) in M @ 80 mg/kg/day on Day 1 compared to Week 39. • Metabolites M27, M22, M18/21, and M30/34 systemic exposures were measured in this study. Refer to the nonclinical review in DARRTS (DARRTS°ID:°5623053 2025) for details.

Study No./ Design (NOAEL and Safety Margin*)	Study Findings

Table 114. PK Parameters of Elinzanetant Following 39-Week Treatment in Monkey

PK Parameters	15 mg/kg, BID	30 mg/kg, BID	40 mg/kg, BID
Male values on Day 1			
$AUC_{(0-24)}$ [µg·h/mL]	2.67	6.46	21
C_{max} [µg/mL]	0.256	0.475	1.450
T_{max} [h]	9	9	9
Male values on Week 39			
$AUC_{(0-24)}$ [µg·h/mL]	2.4	5.690	8.370
C_{max} [µg/mL]	0.221	0.494	0.793
T_{max} [h]	7	7	8
Female values on Day 1			
$AUC_{(0-24)}$ [µg·h/mL]	2.730	6.2	13.4
C_{max} [µg/mL]	0.222	0.491	1.1
T_{max} [h]	8	9	14
Female values on Week 39			
$AUC_{(0-24)}$ [µg·h/mL]	3.0	16.90	9.490
C_{max} [µg/mL]	0.332	1.300	0.771
T_{max} [h]	7	4	4

Source: Reviewer-generated table
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetic; T_{max}, time to maximum concentration

Source: Reviewer-generated table; clinical study number CPM50130 (report number B002427)
*Safety margins calculated based on clinical exposure at the Maximum Recommended Human Dose (MRHD) of $AUC_{(0-24)}$=8572.0 µg.h/L
Abbreviations: ALT, alanine Aminotransferase; ALT, alkaline phosphatase; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; F, female; GGT, Gamma-glutamyltransferase; GLP, good laboratory practice; KNDy, kisspeptin/NKB/dynorphin; M, male; NK1R. neurokinin 1 receptor; NK3R, neurokinin 3 receptor; NOAEL, no-observed-adverse-effect level; QD, once daily; TK, toxicokinetic

13.2.3.2. Genetic Toxicology

In vitro and in vivo genotoxicity studies with elinzanetant and in vitro genotoxicity studies with its three principal metabolites (M27, M30/34, and M18/21) showed **negative results**. The assay conditions and results are further described in the Table 115 below:

Table 115. Genetic Toxicology Studies With Elinzanetant and its Metabolites

Study	Study Findings
Genotoxicity Studies–Elinzanetant	
R-13577 Ames assay up to 1500 µg/plate (limit of solubility)	Elinzanetant did not induce mutations in the presence or absence of S9.
R-13579 Mutagenicity assay in cultured mouse lymphoma L5178Y cells (up to 80 µg/mL for 3 h and 50 µg/mL for 24 h)	Elinzanetant was not mutagenic in mouse lymphoma L5178Y cells under treatment conditions (3 h with or without S9 or 24 h without S9 followed by a 2-day expression period).
R-13576 Micronucleus assay in rats @ 0, 1000, 2000 mg/kg/day, males, oral gavage, for two days	Elinzanetant did not induce micronuclei formation in vivo in male rats. Piloerection and hunched posture were observed on Day 2. @ 2000 mg/kg: Systemic exposure mean: 17200 ng/mL, range: 14600 to 19200 ng/mL
Metabolite Genotoxicity Studies - Metabolites	
R-13888 Ames assay @ 0, 5, 16, 50, 160, 500, 1600 and 5000 µg/plate M27 (BAY 3462932)	M27 metabolite of elinzanetant did not induce gene mutations at concentrations up to 5000 µg/plate (precipitation observed ≥1600 µg/plate) in the absence of S9. No testing was performed in the presence of S9.
R-13874 Micronucleus assay in cultured human lymphocytes. M27 (BAY 3462932)	M27 metabolite of elinzanetant did not induce micronuclei formation in the absence of S9 at 3+21 hour (up to 80 µg/mL) and 24+0 hour (up to 30 µg/mL) No testing was performed in the presence of S9.
R-13867 Ames assay @ 5, 16, 50, 160, 500, 1600 and 5000 µg/plate M30/M34 (BAY 3462933)	M30/M34 metabolites of elinzanetant did not induce mutations at concentrations up to 5000 µg/plate (precipitation observed ≥1600 µg/plate) in the absence of S9. No testing was performed in the presence of S9.
R-13866 Micronucleus assay in cultured human lymphocytes. (up to 60 µg/mL) M30/34 (BAY 3462933)	M30/M34 metabolites of elinzanetant did not induce micronuclei formation at 3+24h up to 60 µg/mL and 24 h up to 30 µg/mL in the absence of S9. No testing was performed in the presence of S9.
PH-42069 M18/21 Salmonella/microsome Test up to 5000 µg/plate M18/21 (BAY 3462934)	M18/21 metabolites of elinzanetant did not induce gene mutations in the salmonella microsome assay up to 5000 µg/plate with or without S-9. (precipitation observed ≥1600 µg/plate).

Study	Study Findings
PH-42100 Micronucleus assay in Chinese hamster V79 cells M18/21 (BAY 3462934)	M18/21 metabolites of elinzanetant did not induce micronuclei formation in vitro (up to 30 µg/mL for 4 h +20 h recovery or 24 h treatment without S9, and up to 45 µg/mL for 4 h +20 h recovery with S9).

Source: Reviewer-generated table

13.2.3.3. Carcinogenicity

The nonclinical integrated summary for the rat carcinogenicity findings as a potential nonclinical signal of clinical concern is described in Section 7. Also refer to the carcinogenicity review in DARRTS dated February 4, 2025 (DARRTS°ID:°5523839 2025) and FDA's statistical review in DARRTS dated December 12, 2024 (DARRTS°ID:°5494197 2024). A brief summary of both studies is noted below.

13.2.3.3.1. Carcinogenicity Study in Rat (104-Week; B003186)

The rat carcinogenicity study was conducted in female Sprague Dawley rat (Envigo, IN, United States) at 0, 7, 20, 60, 80 mg/kg/day [0, 3.5, 10, 30, 40 mg/kg BID] via oral gavage. The overall study conduct was considered adequate.

Key Study Findings

- Oral treatment of female Sprague Dawley rats with elinzanetant doses ranging from 7 to 80 mg/kg/day compared to vehicle for 104 weeks dose-dependently reduced body weight gain but had no effect on overall survival.
- Elizabethan treatment resulted in neoplastic findings. The effects were statistically significant with respect to the dose-response relationships and pairwise group comparisons with the vehicle control. The neoplastic findings are noted below and in Table 116:
  - Malignant lymphoma in the hematolymphoid system at 80 mg/kg/day.
  - Malignant endometrial adenocarcinoma of the uterus at ≥60 mg/kg/day.
  - Combined malignant and benign endometrial tumors at ≥60 mg/kg/day.
  - Combined malignant and benign endometrial tumors and malignant squamous cell carcinoma of the uterus at ≥60 mg/kg/day.

Table 116. Statistically Significant Dose-Response Relationships and Pairwise Comparisons in Elinzanetant-Treated Female Rats

		Elinzanetant Dose (mg/kg/day)				
		0 Control (VC)	7 Low dose (LD)	20 Low-Mid Dose (LMD)	60 Mid Dose (MD)	80 High Dose (HD)
Organ Name	**Tumor Name**	**p - Trend**	**p - C vs. LD**	**p - C vs. LM**	**p - C vs. MD**	**p - C vs. HD**
Hematolymphoid System	M-Lymphoma	1/100 (72) 0.0020 *	3/100 (67) 0.2831	3/100 (71) 0.3046	6/100 (71) 0.0557	9/100 (72) 0.0087**
Uterus	M-Adenocarcinoma, Endometrium	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	22/100 (75) 0.00001**
	M-Carcinoma, Squamous Cell	0/100 (72) 0.0206 *	0/100 (66) NC	1/100 (71) 0.4965	1/100 (69) 0.4894	3/100 (70) 0.1172
	C_Endometrium (B+M)	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	23/100 (75) 0.00001**
	C_Endometrium (B+M)/ Carcinoma, Squamous Cell	2/100 (72) 0.00001 *	3/100 (67) 0.4658	6/100 (71) 0.1330	16/100 (72) 0.0003 **	25/100 (75) 0.00001**

Source: FDA Statistical Reviewer Report
Note: X/ZZ (YY): X = number of tumor-bearing animals; YY = mortality weighted total number of animals; ZZ = unweighted total number of animals observed; NC = Not calculable. The p-values marked with an asterisk * indicate statistically significant dose-response relationships at p<0.005 and p<0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparisons at p<0.01 and p<0.05 for a common tumor and a rare tumor, respectively.
Abbreviations: NC, not calculated

- The oral dose of 20 mg/kg/day was the highest test dose not associated with carcinogenic signals in female rats. Based on AUCs, the clinical exposure margins (safety margin) provided by the highest noncarcinogenic dose to the MRHD is 7.5X for elinzanetant.
- The oral dose of 60 mg/kg/day was the lowest test dose associated with carcinogenic signals in female rats. Based on AUCs, the clinical exposure margin provided by this dose to the MRHD is 29X for elinzanetant.

13.2.3.3.2. Carcinogenicity Study in Transgenic Mice (26-Week; B003184)

The mouse carcinogenicity study was conducted in male and female transgenic ras H2 mice at 0, 10, 30, 85 mg/kg/day in males (0, 5, 15, 42.5 mg/kg BID) and at 0, 10, 20, 70 mg/kg/day in females (0, 5, 10, 35 mg/kg BID) via oral gavage. N-methyl-N-nitrosourea single intraperitoneal dose on Day 1 as used as the positive control. The overall study was considered adequate.

Key Study Findings

- Elinzanetant did not affect the overall survival and induced no adverse clinical signs up to the high dose of 85 mg/kg/day in males and 70 mg/kg/day in females.
- Oral treatment with elinzanetant doses ranging from 10 to 85 mg/kg/day in males and 10 to 70 mg/kg/day in females compared to vehicle for 26 weeks resulted in no statistically significant neoplastic findings.

13.2.3.4. Reproductive and Developmental Toxicity

A full battery of reproductive and developmental toxicity studies was conducted in rats and rabbits. The studies are summarized below. Also refer to Section 8 for details on findings from these studies used to support labeling.

13.2.3.4.1. Fertility and Early Embryonic Development; R-13611

In the fertility and early embryonic development (FEED) study conducted in rat [Study R-13611], female rats were treated with 0, 5, 25, or 100 mg/kg/day of elinzanetant via oral gavage for 22 days before cohabitation with untreated males and Days 1 to 14 during cohabitation with untreated males and on postcoital Days 0 to 6. The major study findings are noted in Table 117:

Table 117. Fertility and Early Embryonic Development Study in Elinzanetant-Treated Female Rats

Study No. & Design (NOAEL and Safety Margin)	Key Findings
Female rats @ 0, 5, 25 and 100 mg/kg/day Dosing: once daily for 22 days before cohabitation, during cohabitation with untreated males (1 to 14 days) and on Day 0 to 6 postcoitum (pc). NOAEL (maternal and fetal) =25 mg/kg/day (corresponds to $AUC_{(0-24)}$ of 27500 µg.h/L)* Safety margin based on maternal and fetal NOAEL =3X Multiple of Exposure (MOE) for increased pre- and postimplantation loss @ 100 mg/kg/day =14X	• Decreased body weight gain and food consumption @ 100 mg/kg/day during the premating and gestation treatment periods and @ 25 and 100 mg/kg/day during the gestation treatment period. • Increased pre- and postimplantation losses and decreased number of implantations @100 mg/kg. • Decreased number of live fetuses, uterus weight, and fetal body weights @ 100 mg/kg/day. Toxicokinetics: (not conducted)* **Table 118. Elinzanetant Exposure in Nonpregnant Female Rats (Relevant to the FEED Study in Female Rats)** Exposure in Female on Day 28 / Dose (mg/kg/Day): 5 / 25 / 100 $AUC_{(0-tlast)}$ (µg·h/mL): 8.05 / 27.5 / 116 C_{max} (µg/mL): 0.626 / 1.8 / 6.57 T_{max} (h): 1 / 1 / 2 *Source: Reviewer-generated table using TK values at 4-week from 13-week repeat dose toxicity study in nonpregnant rats [R-13596] Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration; TK, toxicokinetic

Source: Reviewer-generated table
Clinical $AUC_{(0-24)}$=8572.0 µg.h/L [from the clinical study number CPM50130 (report number B002427)
Abbreviations: AUC, area under the concentration-time curve; NOAEL, no-observed-adverse-effect level

13.2.3.4.2. Embryo–Fetal Development

Embryo-fetal development (EFD) studies were conducted in rats and rabbits. The pivotal studies along with their key findings are described below.

Table 119. Embryo-fetal Development Studies in Elinzanetant-Treated Female Rats and Rabbits

Study No. & Design	Key Findings
Study R-13610 Female rat @ 0, 5, 25 or 100 mg/kg/day Dosing: once daily from gestation day (GD) 6 to 17 NOAEL (maternal) =25 mg/kg/day (corresponds to $AUC_{(0-24)}$ of 57200 µg.h/L) NOAEL (fetal) =100 mg/kg/day (corresponds to $AUC_{(0-24)}$ of 197000 µg.h/L) Safety Margin* based on maternal NOAEL =7X	• There was a statistically significant decrease in mean maternal body weight gain @ 100 mg/kg/day along with a statistically significant decrease in mean food consumption. • There was no test article-related effect on placenta morphology or on mean numbers of corpora lutea, implantations, resorptions, pre- or postimplantation losses, live or dead fetuses, percent live males, or on gravid uterus weight at any dose. • No test article-related effect on fetal body weights at any dose level. • The increased number of fetuses @ 100 mg/kg/day dose group with variations (visceral and skeletal). These were not considered test article related due to: (i) inconsistent pattern of variations in the affected litters, (ii) incidence of variations in elinzanetant-exposed litters being well below the incidence in historical controls in the same facility, and (iii) lack of dose responsiveness.

Study No. & Design	Key Findings
Safety Margin* based on fetal NOAEL =23X	Toxicokinetics: (not conducted) **Table 120. Elinzanetant Exposure in Pregnant Female Rats in EFD Study** Exposure on GD 17 / Dose (mg/kg/day): 5 / 25 / 100 $AUC_{(0\text{-}last)}$ (µg·h/L): 8610 / 57200 / 197000 C_{max} (µg/L): 758 / 3630 / 15300 T_{max} (h): 4 / 2 / 6 Source: Reviewer-generated table with TK values from dose-range finding PPND study (study B003162), which uses the same doses as this study (from table 1 on page 465 of study report). Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; EFD, embryo-fetal development; GD, gestation day; PPND, pre- and postnatal development; T_{max}, time to maximum concentration; TK, toxicokinetic; $_{tlast}$, time of the last quantifiable concentration
Study R-13597 Female rabbits @ 0, 60, 90, or 140 mg/kg/day [0, 30, 45, 70 mg/kg BID] Dosing: twice daily (BID); from GD 7 to GD19 NOAEL (maternal) =90 mg/kg/day NOAEL (fetal) =140 mg/kg/day Safety margin* (maternal) =0.25X Safety margin* (fetal) =1.2X	• Maternal toxicity (marked body weight loss and decreased food consumption) @ 140 mg/kg/day which led to premature sacrifice in four females after 7 to 11 days of treatment. • 3 of four females that were euthanized early were determined to be pregnant and 1 of the females had a trichobezoar observed in the stomach. • No test article-related effects on developmental or fetal growth parameters at any dose and no test article-related effect on mean fetal body weight, fetal malformations, or variations at any dose. Toxicokinetics: **Table 121. Elinzanetant Exposure in Pregnant Female Rabbits in EFD Study** Exposure on GD 19 / Dose (mg/kg/day): 60 / 90 / 140 $AUC_{(0\text{-}tlast)}$ (µg·h/L): 1250 / 2160 / 10600 C_{max} (µg/L): 110 / 206 / 953 T_{max} (h): 9 / 9 / 10 Source: Reviewer-generated table Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; EFD, embryo-fetal development; GD, gestation day; T_{max}, time to maximum concentration; $_{tlast}$, time of the last quantifiable concentration

Source: Reviewer-generated table
*Clinical $AUC_{(0\text{-}24)h}$ =8572.0 µg.h/L [from the clinical study number CPM50130 (report number B002427)
Abbreviations: AUC, area under the concentration-time curve; NOAEL, no-observed-adverse-effect level

13.2.3.4.3. Pre- and Postnatal Developmental

A pre- and postnatal developmental study was conducted in the rat. The key findings from the dose-range finding and pivotal study are described below.

Table 122. Pre- and Postnatal Development Study in Elinzanetant-Treated Female Rats

Study No. & Design	Key Findings
Study B003162 or T105436-9/8500238; DRF study; GLP Female rats @ 0, 5, 25, 100 mg/kg/day once daily and 50 mg/kg BID Dosing: once daily or BID from GD 6 to lactation day (LD) 4 Maternal NOAEL =25 mg/kg/day Fetal NOAEL = not determined (decrease in pup viability index at lowest dose tested)	• Maternal mortality: @ 100 mg/kg/day QD group and 50 mg/kg BID group. • Clinical observations: dystocia (e.g., piloerection, rough pelage, hunched posture, and decreased activity), decreased body weight and body weight gain, and decreased food consumption in dams found in moribund condition. • Litters: Increase in total litter loss and decreased pup viability (by PND 5) in all elinzanetant-treated groups. • Gestational outcomes: Increased gestation length, postimplantation loss, decreased number of liveborn pups delivered, decreased pup body weights, and pups found with no milk in stomach. **Table 123. Elinzanetant Exposure in Pregnant Rats on GD 17** Dose (mg/kg/day) Exposure on GD 17 | 5 | 25 | 100 $AUC_{(0\text{-}tlast)}$ (µg·h/L) | 8610 | 57200 | 197000 C_{max} (µg/L) | 758 | 3630 | 15300 T_{max} (h) | 4 | 2 | 6 Source: Reviewer-generated table from Bioanalytical and TK Analyses report in appendix 10.4 of the study report Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; GD, gestation day; T_{max}, time to maximum concentration; $_{tlast}$, time of the last quantifiable concentration
Study B003187 [T105437-0/ 8500239]; Pivotal Study; GLP Female rats @ 1.5, 5, 15 mg/kg/day Dosing: once daily from GD 6 to LD 21 NOAEL (maternal and fetal) =1.5 mg/kg/day Safety margin*=0.2X (no safety margin) Note#: During review of the study report, the Nonclinical team noted several discrepancies in summary tables throughout the report.	Dams (F_0) • No effects seen on maternal mortality, clinical observations, or other outcomes. • Higher number of dams with still born pups in elinzanetant treatment groups. Litters (F_1) • Increase in total litter deaths and stillborn pups @ 5 and 15 mg/kg/day. • There was a decrease in viability index, i.e., % alive on postnatal (PND) Day 4 versus PND 0 (83% @ 5 and 15 mg/kg/day compared with 96% in controls and 1.5 mg/kg/day). • Increased incidence of neonatal pups with no milk band or milk in the stomach was observed both by clinical observation and at necropsy, respectively, @ 5 and 15 mg/kg/day.

Study No. & Design	Key Findings
The raw data were used to recreate tables, interpret the findings, and derive the Nonclinical review team's final conclusions from the study.	

Table 124. Natural Delivery and Litter Data Summary

Dose (mg/kg/day)	0	1.5	5	15
F_0 females				
No. pregnant	22	19	21	22
No. sacrificed moribund due to total litter loss	1	1	3	3
F_1 Litters				
No. pups delivered	289	230	279	285
Liveborn	267	225	263	273
Stillborn	22*	5	16	12
No. pup deaths - PND 0 to 4	10	10	45	48
Viability Index (%)	96.3	95.6	82.9	82.4
No. pup deaths - PND 4 to 22	10	17	9	13
Weaning Index (%)	94.3	89.4	94.0	92.1

Source: Reviewer-generated table
*The high number of stillbirths in the control group is due to 1 control dam (R0001) that had 18 stillborn pups (complete litter).
Abbreviation: PND, postnatal day

Table 125. Summary of Pup Clinical Observations (F_1 Generation) in the Rat PPND Study

Dose (mg/kg/day)	0	1.5	5	15
Number of litter/pups evaluated	21/233	18/206	20/226	20/236
No milk band present (physical appearance)	Pups: 0/233 Litters: 0/21	Pups: 0/206 Litters: 0/18	Pups: 17/226 Litters: 3/20	Pups: 13/236 Litters: 3/20
Cool to touch (temperature)	Pups: 0/233 Litters: 0/21	Pups: 1/206 Litters: 1/18	Pups: 25/226 Litters: 3/20	Pups: 14/236 Litters: 2/20

Source: Reviewer-generated table
Abbreviation: PPND, pre- and postnatal development

- Increase in female pup body weight was observed and considered test-article related but not adverse.
- No effects on developmental markers or sexual maturation in the F_1 generation pups were noted.
- Increased sensitivity to touch was noted in F_1 generation female pups with an incidence of 2/21, 2/21, 5/20 and 6/20 in control, LD, MD, and HD, respectively.

FDA Analysis:

Although no neurobehavior findings were noted, the dose-dependent increase in sensitivity to touch in female pups could be an adaptive behavior change in response to decrease maternal care or a CNS-related effect. More studies would be necessary to fully elucidate the mechanistic basis of this finding.

Metabolites in pup plasma: Metabolites M27 (BAY 3462932), and M18/21(BAY 3462934) were detected in the F1 pup plasma at 24-hour postdosing of the dams with elinzanetant doses ≥5 mg/kg/day on lactation

Study No. & Design	Key Findings
	Day 4. Major human metabolite M30/34 (BAY 3462933) was detected in the plasma of pups from dams treated with elinzanetant doses ≥1.5 mg/kg/day.

Table 126. Elinzanetant Exposure in Pregnant Rats on GD 20

	Dose (mg/kg/day)		
Exposure on GD 20	**1.5**	**5**	**15**
$AUC_{(0\text{-}24)}$ (µg·h/L)	2000	8960	36200
C_{max} (µg/L)	134	700	2940
T_{max} (h)	6	4	6

Source: Reviewer-generated table from Bioanalytical and TK Analyses report in appendix 10.4 of the study report
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; GD, gestation day; T_{max}, time to maximum concentration; $_{tlast}$, time of the last quantifiable concentration; TK, toxicokinetic

Source: Reviewer-generated table
*Clinical $AUC_{(0\text{-}24)}$=8572.0 µg.h/L [from the clinical study number CPM50130 (report number B002427)
Abbreviations: BID, twice daily; DRF, dose range finding; GD, gestation day; GLP, good laboratory practice; NOAEL, no-observed-adverse-effect level; PND, postnatal day; QD, once daily

13.2.3.5. Other Toxicology Studies

Table 127. Mechanistic Study: Effect on Muscle Disposition in Male Rats

Study No & Designs	Study Findings
Study R-13644 [QL24QG] – non GLP Male rats @ 200 mg/kg/day (once daily) and 25 mg/kg ,100 mg/kg BID for 14 days Note #Envigo rats used, study conducted in (b) (4)	• Piloerection and red staining around nose were observed at all doses with no dose dependent severity. • Multifocal, minimal degeneration of the skeletal muscle observed @ 200 mg/kg once daily (1 in 10 rats) and @ 100 mg/kg BID (3 in 10 rats). • Minimal, focal fibrosis in 1 in 10 rats @ 100 mg/kg BID. (Applicant notes that this could be early signs of skeletal muscle pathology [degeneration/ necrosis]) • Elinzanetant accumulation was noted in skeletal muscle (8 to 10-fold compared to plasma) FDA Analysis: The Applicant notes that the purpose of this study was to reproduce, in an accelerated time window of 14 days, the skeletal muscle findings recorded in the 13-week oral toxicity study in rat [Study R-13628] and to explore the mechanistic basis of the finding. However, the skeletal muscle severe degeneration seen @ 150 mg/kg BID or 300 mg/kg/day (300 mg/kg/day up to Day 9 followed by 175 mg/kg/day for remaining dosing phase) in the 13-week repeat-dose toxicity study could not be reproduced in this study. Refer to Section 7 for integrated summary of this finding.

Study No & Designs	Study Findings
Study R-13578 [8382675]; GLP In vitro 3T3 Neutral Red Uptake phototoxicity assay in mouse Balb/c 3T3 clone A31 cells @ 0.316, 1, 3.16, 20, 31.6, 100 µg/mL ± UV-A light	Elinzanetant is noted to absorb light in the visible part of the spectrum (290-700 nm); hence, an in vitro 3T3 NRU (Neutral Red Uptake) phototoxicity assay was performed. Key findings • Cytotoxicity was observed at the highest 4 concentrations of elinzanetant analyzed (1.00 to 31.6 µg/mL) in presence of UV irradiation, resulting in an IC_{50} of 0.845 µg/mL and a no-observed-effect-concentration (NOEC) of 0.316 µg/mL. • The MPE (mean photo effect) value for the positive control, chlorpromazine, was 0.662 and that for elinzanetant was 0.442; as the MPE value was ≥0.15 elinzanetant was phototoxic in this assay. • Detailed multiple of exposure (MOE) calculations taking into account the exposures in eye and skin and the % unbound of elinzanetant are noted in the full nonclinical review archived in DARRTS (DARRTS°ID:°5623053 2025). The most conservative multiple of exposure for phototoxicity was approximately 7-fold. FDA Analysis: In two whole-body autoradiography studies conducted in rats [study WD2008-00842-00 (study report R-13624) and study KINE 220019-EXT (study report R-14368)], elinzanetant distributed to and accumulated in melanin-rich tissues. Although the MOEs calculated by the Applicant and by the Pharm/Tox review team appear reasonable, they should be interpreted with caution because elinzanetant concentrations in human pigmented tissues are derived based on the distribution of elinzanetant to rat pigmented tissues (eyes and skin). Overall, elinzanetant has several characteristics that, per the *S10 Photosafety Evaluation of Pharmaceuticals* guidance (January 2015), make it a potential phototoxicant. Refer to Section 7 for an integrated review of this finding.

Source: Reviewer-generated table
Abbreviations: BID, twice daily; GLP, good laboratory practice; IC_{50}, half-maximal inhibitory concentration

13.2.4. Safety Margins From Pivotal Toxicology Studies

Table 128. Safety Margins to the Maximum Recommended Human Dose (MRHD) from the Pivotal Toxicology Stuties

Study	Sex/Age	NOAEL (mg/kg/day)	Exposure (µg.h/L)	Safety Margin[a]
26-week repeat dose study in rats	Female	80	311000	36X
	Male	120	76100	8.8X
26-week repeat dose study in rats (with metabolite M27)	Female	20	38300	15X
	Male	20	13700	5.4X
39-week repeat dose study in monkeys	Female	30	3000	0.35X
	Male	80	8370	1X
2-year carcinogenicity study in female rats	Female	20	64000	7.5X
Fertility and early embryonic development in rats	Maternal and Fetal	25	85800	3X
Embryofetal development in rats	Maternal	25	57200	6.7X
	Fetal	100	197000	23X

Study	Sex/Age	NOAEL (mg/kg/day)	Exposure (µg.h/L)	Safety Margin[a]
Embryofetal development in rabbits	Maternal	25	2160	0.25X
	Fetal	100	10600	1.2X
Pre- and postnatal development in rats	Maternal and Fetal	1.5	2000	0.2X

Source: Reviewer-generated table
[a] Safety margins calculated based on clinical exposures at the elinzanetant MRHD of 120 mg/day: Elinzanetant $AUC_{(0-24)}$ =8572.0 µg.h/L; M27 $AUC_{(0-24)}$ =2496.3 µg.h/L [from the clinical study number CPM50130 (report number B002427)]..
Abbreviations: AUC, area under the concentration-time curve; M, metabolite; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level

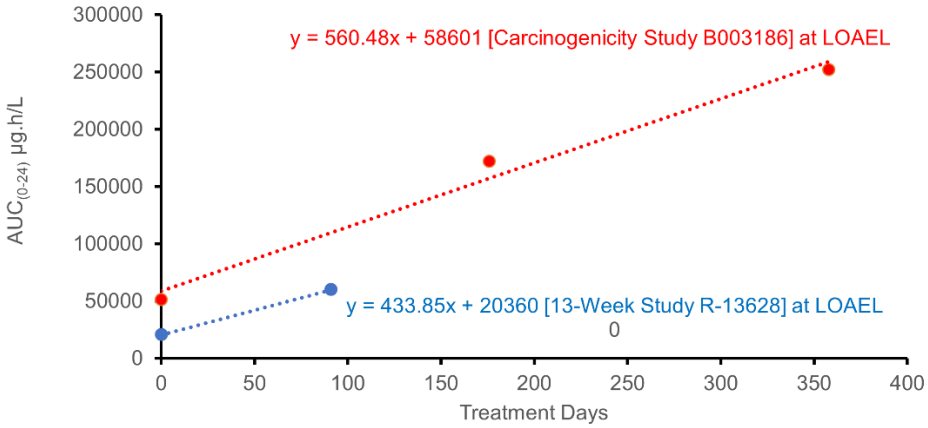
13.2.5. Multiples of Exposure for Convulsions

CNS-related safety signals, including convulsions, were noted in the 13-week repeat-dose toxicity Study R-13628 conducted in male and female rats and in the 2-year carcinogenicity study conducted in female rats Study B003186. As discussed in this section, multiples of exposure at the time convulsions induced by elinzanetant were first noticed in these studies were estimated based on extrapolated $AUC_{(0-24)}$ for each study as compared to the exposure of 8572 µg•h/L generated by the MRHD.

In the 13-week repeat-dose toxicity Study R-13628, convulsions were observed at all tested doses (≥20 mg/kg/day in female rats and ≥50 mg/kg/day in male rats) and were first noted around treatment Day 34. In the carcinogenicity Study B003186, which was conducted in female rats only, the incidence of convulsions was markedly higher in rats treated with elinzanetant doses ≥60 mg/kg/day compared with vehicle. In this study, convulsions in rats treated with the doses of 60 and 80 mg/kg/day were first noted around treatment Days 162 and 106, respectively. For female rats, the oral LOAELs for convulsions were 20 mg/kg/day in the 13-week study and 60 mg/kg/day in the carcinogenicity study.

In the 13-week repeat-dose toxicity Study R-13628, exposures ($AUC_{(0-24)}$) were measured on treatment Days 1 and 91. Using the linear regression of the time-dependent increase in $AUC_{(0-24)}$ Figure 41, the $AUC_{(0-24)}$ generated in female rats treated with the LOAEL (20 mg/kg/day) when convulsions were first observed (treatment Day 34) was estimated to be approximately 35111 µg•h/L. Using the same approach, the $AUC_{(0-24)}$ generated in male rats treated with the LOAEL (50 mg/kg/day) on treatment Day 34 was estimated to be approximately 31930 µg•h/L. Within the study, elinzanetant exposures capable of inducing convulsions were relatively consistent between sexes and were ~4-fold higher than the clinical exposure of 8572 µg•h/L generated by the MRHD of elinzanetant (120 mg/day) in women.

Figure 41. Linear Regressions of Systemic Exposures in Female Rats Treated Orally With the Elinzanetant Dose of 20 mg/kg/Day, BID, for 13 Weeks in Study R-13628 or 60 mg/kg/Day, BID, for 2 Years in the Carcinogenicity Study, Study B003186

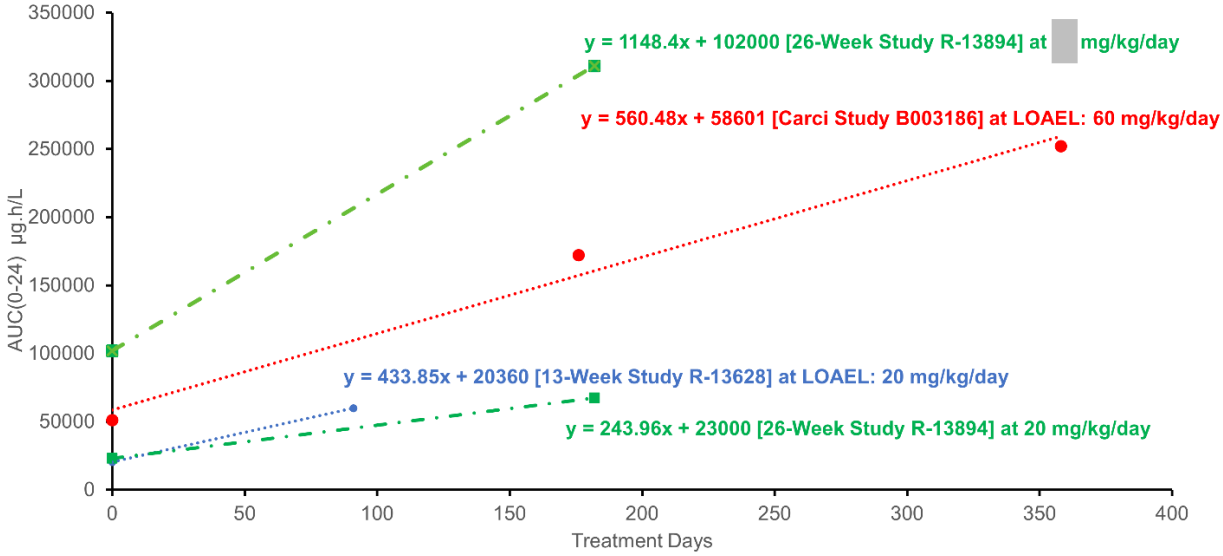


Source: Reviewer-generated graph, using data from Study R-13628 and Study B003186
The dotted lines represent the linear regressions of the $AUC_{(0-24)}$ measured in the two studies. For the linear regression, the first treatment day is considered as Day 0. In the regression equations shown in the graph, y represents $AUC_{(0-24)}$ and x represents treatment days.
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; LOAEL, lowest-observed-adverse-effect level

In the 2-year carcinogenicity study, exposures were assessed on treatment Days 1, 176, and 358. Using the linear regression of the time-dependent increase in AUC_{0-24} at the oral LOAEL for convulsions in this study (60 mg/kg/day) (Figure 41), systemic exposure was estimated to be ~149399 µg•h/L at the time when convulsions were first noted in elinzanetant-treated female rats (treatment Day 162). Using the same approach, the $AUC_{(0-24)}$ generated in female rats treated for 2 years with the elinzanetant dose of 80 mg/kg (Figure 42) was estimated to be ~150076 µg•h/L at the time convulsions were first noted at this dose (treatment Day 106).

Thus, within the 2-year carcinogenicity study, exposures needed to induce convulsions in female rats were relatively consistent between doses and were ~17-fold higher than the clinical exposure of 8572 µg•h/L generated by the MRHD of elinzanetant (120 mg/day) in women.

Figure 42. Linear Regressions of Systemic Exposures in Female Rats Treated by Oral Gavage Twice Daily



Source: Reviewer-generated graph
Doses: Elinzanetant 60 and 80 mg/kg/day for 2 years in the carcinogenicity Study B003186 and 20 mg/kg/day for 13 weeks in Study R-13628 and for 26 weeks in Study R-13894
The dotted lines represent the linear regression of the $AUC_{(0-24)}$ measured in the two studies. For the linear regressions, the first treatment day was considered Day 0. In the regression equations shown in the graph, y represents $AUC_{(0-24)}$, and x represents treatment days.
Abbreviations: AUC, area under the concentration-time curve; LOAEL, lowest-observed-adverse-effect level

Considering the estimated $AUC_{(0-24)}$ generated by the LOAELs in the 13-week toxicity study and the carcinogenicity study and the exposure of 8572 µg•h/L generated by the MRHD, multiples of exposure for convulsions were estimated to be ~4X and ~17X the MRHD, respectively.

Convulsions were not observed in the 26-week repeat-dose toxicity Study R-13894 in which male and female rats were treated twice daily with elinzanetant doses ranging from 50 to 180 mg/kg/day and 20 to 80 mg/kg/day, respectively. However, the apparently inconsistent CNS effects could not be fully accounted for by insufficient systemic exposures. As noted above, at the time when convulsions were first noted, systemic exposures generated by the oral LOAELs were ~35111 µg•h/L in female rats in the 13-week study and ~149399 µg•h/L in female rats in the 2-year carcinogenicity study. In the 26-week study, systemic exposures were as high as 311000 µg•h/L in female rats treated twice daily with the oral dose of 80 mg/kg/day. Considering the time-dependent increase in $AUC_{(0-24)}$ observed in females treated with the dose of 80 mg/kg/day in the 26-week study, $AUC_{(0-24)}$s in these animals exceeded 149399 µg•h/L after treatment Day 42. Yet, convulsions were not observed throughout the entire duration of the 26-week study (182 days).

The studies differed with respect to the SD rat substrains and their sources. Specifically, the SD rats used in the 13-week study, the 2-year carcinogenicity, and the 26-week studies were from the same substrain (SD:Hsd). However, they were sourced from Envigo, United States, Envigo, Netherlands, and Envigo, United Kingdom, respectively. Convulsions were also not observed in the 13-week repeat-dose toxicity study R-13596 in which rats were treated once daily for 13 weeks with elinzanetant doses generating exposures as high as 56700 µg•h/L in male rats and

135000 µg•h/L in female rats. The substrain of rats used in the 13-week study R-13596 was SD:Crl, and the animals were sourced from Charles River, Canada.

Although not conclusively established, the apparently discrepant findings could be related to differential seizure susceptibility of the rat substrains from difference sources. According to a published study (Langer et al. 2011), SD:Crl rats are less susceptible than SD:Hsd rats to developing seizures in response to electrical stimulation of the BLA. In addition, SD:Hsd rats from the Netherlands are less susceptible than SD:Hsd rats from Germany to developing seizures in response to BLA electrical stimulation.

13.3. Excipients, Impurities and Degradation Products

The excipients and their amounts in the elinzanetant drug product are acceptable from the nonclinical perspective. The drug substance and drug product impurity release specification and shelf-life specification are set either as per the ICH guidance for industry *Q3A(R) Impurities in New Drug Substances* (June 2008) and the ICH guidance for industry *Q3B(R2) Impurities in New Drug Products* (August 2006) or qualified based on Permissible Daily Exposure/Total Daily Intake (PDE/TDI) calculation utilizing NOAEL derived from nonclinical studies. Overall, the specifications are acceptable from nonclinical perspective.

13.3.1. Excipients

The elinzanetant drug product has no novel excipients for the oral route of administration. Table 129 lists the maximal daily exposures (MDEs) to the excipients considering the maximal recommended human dose of 120 mg elinzanetant.

Qualification of Excipients

The maximal daily doses of two excipients (glyceryl monocaprylocaprate and glyceryl monooleate) exceed the maximal daily exposures (MDEs) in previously approved oral drug products per the FDA Inactive Ingredient Report (IIR) (Table 129).

Table 129. Drug Product Composition and Assessment of Maximal Daily Doses of Excipients in the MRHD of Elinzanetant (120 mg/Day)

Composition	Amount per Capsule (mg)	Maximal Daily Dose (mg)	MDE per FDA IIR (mg)
Elinzanetant	60.0	120.0	NA
All-rac-α-tocopherol		(b) (4)	246
Caprylocaproyl macrogoglycerides			3623
Glyceryl monocaprylocaprate			501.9
Glyceryl monooleate			2.0
Polysorbate 80			233.0

Source: Reviewer-generated table
Abbreviations: IIR, inactive ingredient report; MDE, maximum daily exposure; MRHD, maximum recommended human dose; NA, not applicable

Glyceryl Monooleate

Api et al. (2021) reported that the oral NOAEL for glyceryl monooleate in a repeat-dose toxicity study in rats was 1,000 mg/kg/day (the highest test dose). In this GLP-compliant, combined repeat-dose and reproductive study, Sprague Dawley rats were administered glyceryl monooleate via oral gavage (0, 100, 300, or 1000 mg/kg/day; n=12 rats/sex/dose). Males were dosed for 42 days (starting 14 days prior to mating and continuing through the mating period); females were dosed up to lactation Day 4. An additional 5 Sprague Dawley rats/sex/dose were maintained for 2 weeks after dosing as a recovery group. No mortality occurred throughout the study period. There were no treatment-related effects on general condition, clinical observations, sensory reflex function test, landing leg width, grip strength, locomotor activity, body weight, food consumption, urinalysis (male only), hematology, organ weight, organ function, clinical chemistry, necropsy, or histopathology.

A permitted daily exposure (PDE) for glyceryl monooleate is estimated using the NOAEL of 1,000 mg/kg/day in rats and the formula:

Equation 5. Formula for Permitted Daily Exposure (PDE)

$$PDE = \frac{NOAEL\ x\ 50}{F1\ x\ F2\ x\ F3\ x\ F4\ x\ F5}$$

$$PDE = \frac{1000\ x\ 50}{5\ x\ 10\ x\ 1\ x\ 1\ x\ 1} = 1000\ mg/day$$

F1=5 (extrapolation from rat to human), F2=10 (variability between individuals), F3=1 for reproductive study covering the whole period of organogenesis, F4=1 (fetal toxicity associated with maternal toxicity), F5=1 (determined NOAEL)
Abbreviations: NOAEL, no-observed-adverse-effect level; PDE, permissible daily exposure

The estimated PDE is (b) (4) x the maximal daily dose of glyceryl monooleate in the Applicant's product.

Per the CFR, 21 CFR §184.1323, glyceryl monooleate of a purity suitable for its intended use is an ingredient generally recognized as safe, as a direct human food ingredient. In addition, as described in a 1986 publication (CIR Expert Panel 1986), federal regulations also allow the use of glyceryl oleate as a prior-sanctioned food ingredient (21 CFR§181.27) and as both an indirect (21 CFR §175.300, 21 CFR§75.320) and direct (21 CFR 175.515) food additive.

Thus, based on the totality of the information, glyceryl monooleate is considered adequately qualified as an excipient in the Applicant's product.

Glyceryl Monocaprylocaprate

The MDE for glyceryl monocaprylocaprate in previously approved oral products is only 501.9 mg (~(b) (4)% the maximal daily dose of this excipient in the MRHD of elinzanetant). However, a glyceryl mono- and dicaprylocaprate mix is an excipient in a previously approved oral drug product at an MDE of 13,770 mg per the FDA IIR. According to the U.S.

Pharmacopeia, no less than 75% of the glyceryl mono- and dicaprylocaprate mix (a product also referred to as glyceryl monoprylocaprate Type I (USP 2020) is the monoester (USP).With this consideration, the MDE to glyceryl monocaprylocaprate in the previously approved oral drug product is no less than ~10,328 mg. Therefore, glyceryl monocaprylocaprate at the amount in the Applicant's product is considered adequately qualified.

13.3.2. Impurities and Degradants of Concern

Drug Substance

Table 130 lists the drug substance specification provided in the electronic common technical document (eCTD) Section 3.2.S.4. The red box highlights the specification for organic impurities.

Table 130. Drug Substance Specification

(b) (4)



Table 131 lists all the potential organic impurities in the drug substance.

Table 131. Potential Organic Impurities in Elinzanetant Drug Substance

Short name / code no.	Structural formula	Origin
Chemical name (IUPAC)	(b) (4)	

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Reference ID: 5682958

Assessment and Summary

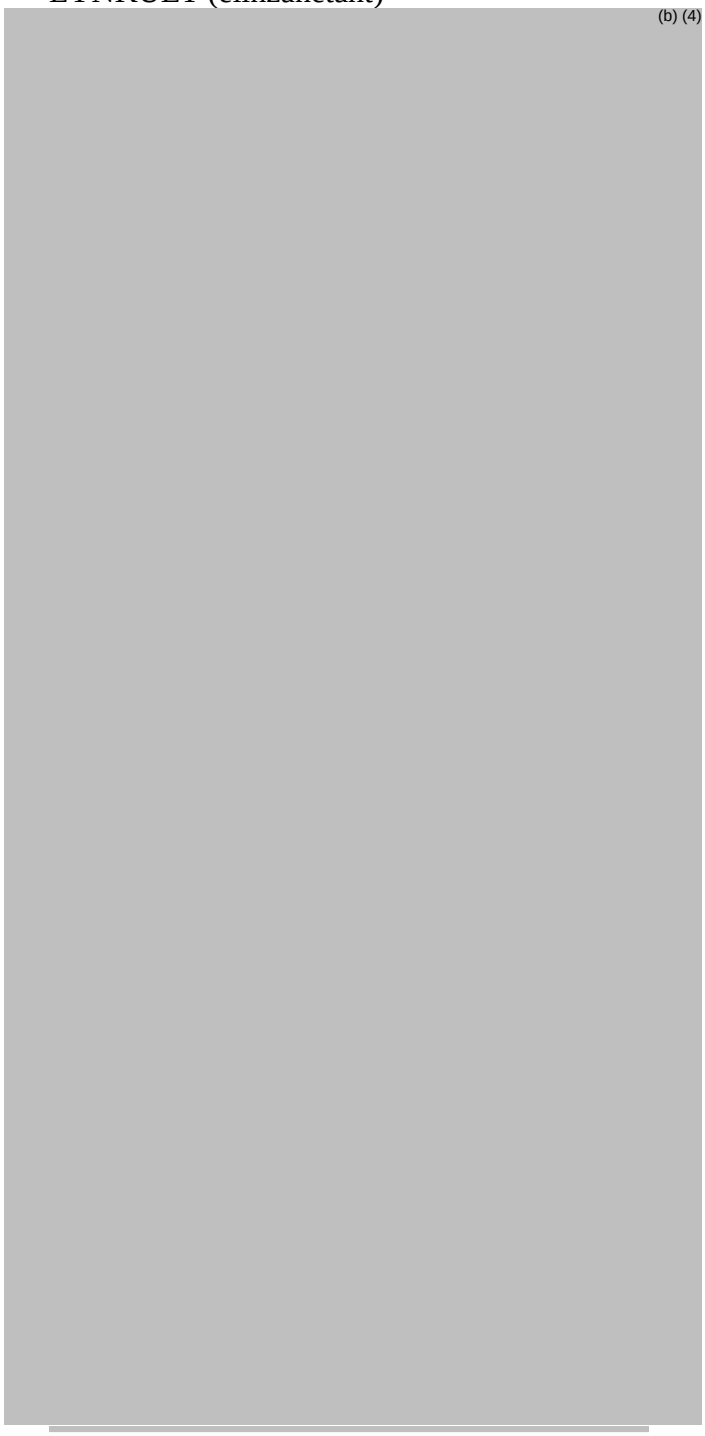
The qualification threshold of (b) (4)% set for the organic impurities and (b) (4)% for any unspecified impurities (b) (4) is acceptable. The Applicant identified the organic impurities to have no structural alerts and designated as class 5 impurities as per ICH guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023). The nonclinical team consulted the CDER Computational Toxicology team (CDER/OTS/OCP/DARS Computational Toxicology Consultation Service) for a (Q)SAR analysis and all the seven potential organic impurities of the drug substance listed by the Applicant were predicted to be negative. For a more detailed review refer to the nonclinical review in DARRTS (DARRTS°ID:°5623053 2025) which also includes the appended (Q)SAR consult report.

Drug Product

The Applicant has proposed a shelf life of 30 months based on available stability data (Module 3.2.P.8). Drug product-related impurities have been detected and characterized as degradation products and are described below.



(b) (4)



Source: module 3.2.P.5.5.

Drug Product Specification

The drug product release and shelf-life specification for the degradation products is shown in Table 132.

Table 132. Drug Product Specification for Degradation Products of Elinzanetant

Test	Release Specification	Shelf Life Specification
(b) (4)		

Source: Extracted from module: 3.2.P.5.6

Qualification of Degradation Products

The release specifications for (b) (4) are set at ≤(b) (4)% as (b) (4) Qualification for the higher release specification limit for APPEARS THIS [≤(b) (4)%] and for shelf-life specifications set at higher limits [(b) (4)%] for all degradation products and are described below:

(b) (4) Qualification

(b) (4)
(b) (4) (b) (4)
Based on the NOAELs, the PDE/TDI calculation for 50-kg women is described in Equation 6 and Equation 7.

Equation 6. Permissible Daily Exposure/Total Daily Intake Calculation for (b) (4) (as Described in the (b) (4)), Rat Study

(b) (4)

Equation 7. Permissible Daily Exposure/Total Daily Intake Calculation for (b) (4) (as Described in the (b) (4)), Monkey Study



Conclusion

At the maximal recommended human dose of elinzanetant (120 mg), (b) (4)% of shelf-life specification limit for the (b) (4) corresponds to a daily intake of (b) (4) mg, which is (b) (4)-fold lower than the TDI based on the more conservative PDE/TDI of (b) (4) mg/day based on the NOAEL from the monkey. Considering the stability data provided for the clinical batches in the eCTD Module 3.2.P.8.3, the highest level of (b) (4) is within specification and the specified limit appears reasonable.

(b) (4) Qualification

(b) (4)

A 4-week oral repeat-dose toxicity study (Study PH-42298/T105216-5) was conducted in rats using (b) (4) at doses up to (b) (4) mg/kg/day. The high dose of (b) (4) mg/kg/day was identified as the NOAEL. This corresponds to (b) (4) mg/kg based on batch purity of 96%. Based on the NOAEL, the PDE/TDI calculation for 50-kg women is described in Equation 8.

Equation 8. Permissible Daily Exposure/Total Daily Intake Calculation for (b) (4)



Conclusion for (b) (4)

The shelf-life specification limit for the (b) (4) of up to (b) (4)% at the maximal recommended human elinzanetant dose of elinzanetant (120 mg) corresponds to a daily intake of

(b) (4) mg, which is (b) (4) fold lower than the TDI. Considering the stability data provided for the clinical batches in the eCTD Module 3.2.P.8.3, the highest level of (b) (4) is within specification and the specified limit appears reasonable.

(b) (4)

The Applicant notes (b) (4)
.

As a note, the Applicant mentions that data from a single-dose toxicokinetic study in rats using (b) (4) (Study PH-42303) indicated that the (b) (4) (b) (4) was not measured). Considering the theoretical cumulative shelf-life specification limits for (b) (4) (b) (4)%, the total (b) (4) exposure would result in a (b) (4) mg daily dose, which is similar to the TDI of (b) (4) mg/day derived for (b) (4)

Conclusion for (b) (4)

The Applicant's justifications for the proposed specifications for (b) (4) and (b) (4) are considered acceptable. It's likely that the (b) (4) will break down in vivo, and it is reasonable to expect (b) (4) to be less toxic relative to the (b) (4) Applying the NOAEL for (b) (4) to (b) (4) and (b) (4) is therefore considered acceptable. Based on the stability data provided for the clinical batches in Module 3.2.P.8.3 the highest level of (b) (4) (b) (4) is within specification and the specified limit appears reasonable.

Any Unspecified Degradation Product

The limit is set at (b) (4)% for both release and shelf-life (b) (4) is considered acceptable.

Sum of All Degradation Products

The limit is set at (b) (4)% for release and (b) (4)% for shelf-life. Based on the stability data provided for the clinical batches in Module 3.2.P.8.3, the highest level of total degradation products is (b) (4)% at 36 months for batch 4308531, and thus the limit appears reasonable.

(b) (4)

The risk assessments for (b) (4) in drug substance (Module 3.2.S.3.2; risk assessment on (b) (4) and drug product (Module 3.2.P.5.5; risk assessment on (b) (4) were

evaluated by the CMC team and noted to be adequate. No further evaluation was necessary from the Pharm/Tox perspective.

Residual Solvents

Residual solvents in the drug substance (b) (4) controlled per ICH guidance for industry *Q3C(R8) Impurities: Guidance for Residual Solvents Guidance for Industry* (December 2021), as described in the eCTD Module 3.2.S.3.2 (Impurities–Residual solvents) (b) (4)

Elemental Impurities

All the elemental impurities, considering the administration route, are controlled as per ICH guidance for industry *Q3D(R2) – Guideline for Elemental Impurities* (September 2022) as described in the eCTD Module 3.2.P.5.5 (Risk of elemental impurities).

14. Clinical Pharmacology

14.1. In Vitro Studies

Elinzanetant is also referred to as GSK1144814, BAY 3427080, and NT-814.

14.1.1. Distribution

Plasma Protein Binding (Module 4.2.2.3, PH-42081 for Parent, PH-42138 for Metabolites)

The protein binding of elinzanetant and its metabolites is high in female human plasma. The mean fu values of elinzanetant, M27, M30/34, M18/21 were 0.332%, 0.0689%, 0.514%, and 0.140%, respectively, in plasma of females.

Blood Plasma Partitioning (Cb/Cp) (Module 4.2.2.3, Report PH-42081)

The measured Cb/Cp was less than 1 and amounted to 0.574 in man and 0.663 in woman. Since the Cb/Cp was less than 1, more substance distributed into plasma than into the blood cells.

The distribution between blood cells and plasma was investigated in the concentration range of 536 µg/L to 47549 µg/L. No concentration dependent Cb/Cp binding in the tested concentration range was observed.

14.1.2. Metabolism Studies

Elinzanetant is Primarily Metabolized by CYP3A4 (Module 4.2.2.6, Report R-13657)

The enzymes responsible for the oxidative metabolism of elinzanetant were investigated with human liver microsomes and recombinant CYP enzymes. [^{14}C] elinzanetant at 5µM was metabolized in human liver microsomes to oxidized metabolites M18/M21, M24, and M30&M32/M34 and dehydrogenated metabolite M39 as the major metabolites. M18/M21, M24, M30&M32/34 and M39 formation, which constituted 7.8%, 9.0%, 29% and 12%, respectively, of the metabolites generated by human liver microsomes, was inhibited by azamulin, a selective

CYP3A4 inhibitor. M27, M30&M32/M34 and M39 were also formed in recombinant CYP3A4 incubations as major metabolites. Incubations with recombinant CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 showed little or no metabolism. Data from human liver microsomes with selective inhibitors and results from recombinant CYP enzyme incubations suggest that CYP3A4 is the primary CYP enzyme involved in the oxidative metabolism of elinzanetant in vitro.

Minor Contribution of CYP3A5 and UGT Pathways (Module 4.2.2.6, Report PH-42629)

Oxidation via CYP3A was observed in vitro and in vivo as dominant human biotransformation route of elinzanetant, while direct glucuronidation of parent drug was a minor pathway. To estimate the fraction metabolized via UGT and CYP3A from human hepatocytes, reaction phenotyping experiments were performed applying cobicistat as a potent CYP3A inhibitor and cyp3cide as a selective CYP3A4 inhibitor. Complete inhibition of all oxidative pathways was observed in the presence of cobicistat, and the fraction metabolized via CYP3A was calculated to be in the range of ~88 to 94%, while ~5 to 12% were assigned to the UGT pathway. CYP3A5 contribution to total clearance was in the range of ~6 to 15%. Therefore, a clinically relevant impact of the CYP3A5 polymorphism on the total clearance of elinzanetant is considered unlikely.

Elinzanetant is not a Substrate for Aldehyde Oxidase (Module 4.2.2.2, Report 13621)

Metabolic stability of elinzanetant to aldehyde oxidase was evaluated. Following incubation with human cytosol at a concentration of 0.5μM elinzanetant and in the presence of isovanillin (known inhibitor of aldehyde oxidase), the rate constants (k) values under both conditions were less than 0.0055, indicating that elinzanetant is not a substrate for aldehyde oxidase.

14.1.3. In Vitro Metabolism-Mediated Drug Interaction Studies

CYP and UGT Inhibition

Module 4.2.2.6, PH-42451

The potential of elinzanetant and its metabolites M30/M34, M18/M21 and M27 to act as direct-acting inhibitors of human cytochrome P450 isoforms (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2 and 3A4) was evaluated in vitro with pooled human liver microsomes or recombinant CYP1A1 and 2J2. No direct-acting inhibitory potency up to the highest tested concentrations (IC_{50}>5μM) for elinzanetant and metabolites M30/M34, M18/M21 and M27 was observed for CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2 and 3A4 (testosterone 6β-hydroxylation). Applying a rank order approach, elinzanetant (IC_{50}=0.77μM), M30/M34 (IC_{50}=0.98μM), M18/M21 (IC_{50}=1.1μM) and M27 (IC_{50}=1.2μM) showed inhibitory potency on CYP3A4 (midazolam 1'-hydroxylation).

The potential to act as metabolism-dependent (time-dependent) inhibitors of human cytochrome P450 isoforms (CYP1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) was evaluated in vitro with pooled human liver microsomes or recombinant CYP1A1 after 30 minutes preincubation with and without NADPH-regenerating system. No clinically relevant metabolism-dependent (time-

dependent) inhibitory potency of elinzanetant on biotransformation reactions catalyzed by CYP1A1, 1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 was observed. A slight increase in the inhibitory potency after preincubation in the presence of NADPH was observed on CYP3A4 (midazolam 1'-hydroxylation, elinzanetant: IC_{50}=0.40µM; M30/M34: IC_{50}=0.31µM; M18/M21: IC_{50}=0.28µM and M27: IC_{50}=0.51µM) and (testosterone 6β-hydroxylation, elinzanetant: IC_{50}=1.8µM; M30/M34: IC_{50}=1.7µM; M18/M21: IC_{50}=1.6µM and M27: IC_{50}=1.9µM) compared to those data after coincubation, indicating a time-dependent inhibition effect by elinzanetant and its metabolites M30/34, M18/21, and M27.

Module 4.2.2.6, B003014

Irreversible inhibitory potency for elinzanetant and its metabolites towards human CYP3A4 were tested in duplicate up to a concentration of 10µM. Inactivation kinetic parameters for elinzanetant (BAY 3427080) were determined to be K_I =2.14µM, k_{inact} =0.0134 min^{-1}, for M27 (BAY 3462932) K_I =1.66µM, k_{inact} =0.0150 min^{-1}, for M30/34 (BAY 3462933) K_I =2.39µM, k_{inact} =0.0166 min^{-1} and for M18/21 (BAY 3462934) K_I =3.37µM, k_{inact} =0.0218min^{-1}.

Module 4.2.2.6, B002074

To evaluate elinzanetant (BAY 3427080), M27 (BAY 3462932), M30/34 (BAY 3462933) and M18/21 (BAY 3462934) as direct inhibitors of UGT activity, pooled human liver microsomes were incubated with marker substrates in the presence or absence of the test compound.

BAY 3427080 directly inhibited UGT1A1 with an IC_{50} value of 2.6µM. Less than 50% direct inhibition by BAY 3427080 (up to concentrations of 5µM) was observed for UGT2B7. BAY 3427080 (up to concentrations of 5µM) was not a direct inhibitor (<20% maximal inhibition) of UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B15 or UGT2B17.

BAY 3462932 directly inhibited UGT1A1 with an IC_{50} value of 0.46µM. Less than 50% direct inhibition by BAY 3462932 (up to concentrations of 5µM) was observed for UGT1A4 and UGT2B7. BAY 3462932 (up to concentrations of 5µM) was not a direct inhibitor (<20% maximal inhibition) of UGT1A3, UGT1A6, UGT1A9, UGT2B15 or UGT2B17.

BAY 3462933 directly inhibited UGT1A1 with an IC_{50} value of 1.8µM. Less than 50% direct inhibition by BAY 3462933 (up to concentrations of 5µM) was observed for UGT2B7. BAY 3462933 (up to concentrations of 5µM) was not a direct inhibitor (<20% maximal inhibition) of UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B15 or UGT2B17.

BAY 3462934 directly inhibited UGT1A1 with an IC_{50} value of 2.6µM. Less than 50% direct inhibition by BAY 3462934 (up to concentrations of 5µM) was observed for UGT1A6. BAY 3462934 (up to concentrations of 5µM) was not a direct inhibitor (<20% maximal inhibition) of UGT1A3, UGT1A4, UGT1A9, UGT2B7, UGT2B15 or UGT2B17.

CYP Enzyme Induction

Module 4.2.2.6, R-13656

The effects of elinzanetant on mRNA levels of CYP genes (CYP1A2, 2B6 and 3A4) were evaluated at concentrations from 0.1 to 100µM in cultured human hepatocytes from three donors.

The mRNA level for each specific CYP was determined using quantitative real-time polymerase chain reaction technology (TaqMan™). Following exposure of cultured human hepatocytes to elinzanetant for 48 hours, no notable increases in the mRNA levels of CYP1A2 were observed.

At 10μM elinzanetant, maximal increases in CYP2B6 mRNA levels to a mean ratio of treated over control of 13 were observed, corresponding to a 66% increase relative to the prototypic inducer phenytoin.

At 3μM elinzanetant, maximal increases in CYP3A4 mRNA levels to a mean ratio of treated over control of 8.5 were observed, corresponding to a 45% increase relative to the prototypic inducer rifampicin.

Module 4.2.2.6, B003095

The objective of this in vitro study in human hepatocytes was to investigate the inductive potential of elinzanetant and its metabolites M18/21, M27, M30/34 (up to 90000 μg/L) on the expression of CYP3A4, CYP2B6, CYP2C19, and CYP1A2.

Elinzanetant and its metabolites M18/21, M27 and M30/34 did not induce CYP1A2 mRNA or activity.

Elinzanetant and its metabolites M18/21, M27 and M30/34 caused concentration-dependent induction of CYP3A4 mRNA in hepatocytes from all three donors. However, at the enzyme activity level, elinzanetant and M30/34 did not induce CYP3A4 activity in any of three donors; for M18/21 and M27, up to 3.5-fold (25% of rifampicin effect) and 3.4-fold (24% of rifampicin effect) induction was observed, respectively.

In addition, induction of the coregulated CYP isoforms CYP2B6 and CYP2C19 was observed for elinzanetant and its metabolites M18/21, M27 and M30/34 at both mRNA and enzyme activity level.

FDA analysis: Based on M12 Drug Interactions Studies guidance, elinzanetant and its metabolites M18/21, M27, M30/34 have low induction potential on CYP enzymes.

Identification of Transporter Substrate

Passive Membrane Permeability (Module 4.2.2.6, R-13631)

The passive membrane permeability of [^{14}C]-GSK1144814 was determined at pH 7.4 and the absorptive membrane permeabilities were determined at both pH 5.5 and pH 7.4, using a biorelevant buffer (FaSSIF, fasted state intestinal fluid), in MDCKII-MDR1 cells, in presence of the potent P-gp inhibitor, GF120918. [^{14}C]-GSK1144814 was determined to have moderate passive membrane permeability of 74 nm/s at pH 7.4. The absorptive membrane permeability of [^{14}C]-GSK1144814 in the presence of FaSSIF was moderate at both pH 7.4 and 5.5 with a $P_{7.4[abs]}$ value of 28 nm/s and a $P_{5.5[abs]}$ value of 18 nm/s.

Substrate for P-gp (Module 4.2.2.6, R-13687)

The purpose of this study was to evaluate NT-814 as substrate of the human MDR1 (also named as P-gp or ABCB1) efflux transporter (Table 133).

Table 133. Summary of the Obtained Results, ABC Transporter Assays

	NT-814			
Transporter and assay type	Bidirectional permeability assessment of NT-814 for the MDR1 transporter			
	Maximum net ER	Substrate	K_M*	V_{max}*
MDR1 ML	8.98 at 18.5 µM	Yes	3.526 µM	0.793 pmol/min

* Data from the 10 µM concentration were excluded from the K_M and V_{max} calculations as they were not in line with the other data points. Kinetic parameters were calculated using nominal, total concentrations of NT-814.

Source: CSR-13631, table 2
Abbreviations: ABC, ATP-binding cassette; CSR, clinical study report; K_M, Michaelis constant; MDR1, multidrug resistance 1; ML, monolayer assay; net ER, net efflux ratio; V_{max}, maximal rate of metabolism

FDA analysis: Clinical studies (Study 21679 and Study R-21667) were conducted to investigate DDI risk related to elinzanetant being a substrate for P-gp.

Not a Substrate for OATP1A2, OATP2B1 or MRP4 (Module 4.2.2.6, B002205)

In vitro, elinzanetant was shown not to be a substrate for uptake transporters human OATP1A2 and human OATP2B1 as well as for the efflux transporter hMRP4 at the concentrations tested between 20 and 5000nM.

Not a Substrate for BCRP, OATP1B1 or OATP1B3 (Module 4.2.2.6, R-13686)

Based on data from an uptake transporter substrate assay, NT-814 is likely not a substrate of OATP1B1 and OATP1B3 transporter. Based on a monolayer substrate assay, NT-814 is likely not a substrate of BCRP transporter.

Transporter Inhibition

P-gp Inhibition (Module 4.2.2.6, B002191)

In transfected LLC-PK1 cells over-expressing human P-gp (L-MDR1 cells), BAY 3427080 showed a concentration dependent inhibition of the efflux of digoxin in the concentration range from 0.1µM to 10µM with an IC_{50} of 2.23µM. After correction of the nominal test concentrations for nonspecific binding (NSB), the IC_{50} was calculated at 0.22µM.

Additionally, the metabolites BAY 3462932 (M27), BAY 3462933 (M30/34) and BAY 3462934 (M18/M21) inhibited the efflux of P-gp probe substrates digoxin or dipyridamole with IC_{50} values of 6.28µM, 1.22µM and 10.7µM in the concentration range from 0.1µM to 10µM, respectively. After correction of the test concentrations for NSB, the IC_{50s} were calculated to be lower, amounting to 1.51µM, 0.09µM and 2.94µM, respectively.

In summary, BAY 3427080 and its metabolites BAY 3462932, BAY 3462933 and BAY 3462934 are all inhibitors of P-gp, with IC_{50} values of 0.22μM, 1.51μM, 0.09μM and 2.94μM, respectively.

FDA Analysis

Based on M12 Drug Interactions Studies guidance, a clinical DDI study is warranted to assess the DDI potential related to P-gp inhibition by elinzanetant. Study 22081 was conducted to investigate clinical DDI risk related to elinzanetant being an inhibitor for P-gp.

BCRP Inhibition (Module 4.2.2.6, B002163)

In transfected MDCKII cells over-expressing human BCRP (BCRP-MDCKII cells), elinzanetant showed a concentration dependent inhibition of the efflux of topotecan in the nominal concentration range from 0.1μM to 10μM with an IC_{50} of 0.88μM. After correction of the test concentrations for NSB, the IC_{50} was calculated at 0.08μM.

Additionally, the metabolites BAY 3462932, BAY 3462933, and BAY 3462934 inhibited the efflux of BCRP probe substrate topotecan with IC_{50} values of 2.31μM, 1.99μM and 5.33μM in the nominal concentration range from 0.1μM to 10μM, respectively. After correction of the test concentrations for NSB, the IC_{50s} were calculated to be lower, amounting to 0.48μM, 0.17μM, and 1.38μM, respectively.

In summary, elinzanetant and its metabolites BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 3462934 (M18/M21) are inhibitors of BCRP, with IC_{50} values of 0.08μM, 0.48μM, 0.17μM, and 1.38μM, respectively.

FDA Analysis

Based on M12 Drug Interactions Studies guidance, a clinical DDI study is warranted to assess the DDI potential related to BCRP inhibition by elinzanetant. Study 21666 were conducted to investigate clinical DDI risk related to elinzanetant being an inhibitor for BCRP. The substrate drug evaluated in Study 21666 is rosuvastatin, a substrate for BCRP, OATP1B1/1B3, and OAT3.

OATP1B1/1B3 Inhibition

Module 4.2.2.6, R-13633

Elinzanetant was evaluated as an inhibitor of the human hepatic uptake transporter OATP1B1 in vitro. Inhibition of uptake of the probe substrate [^{3}H]-Estradiol 17β-D-glucuronide ([^{3}H]-EG) by elinzanetant (concentration range 0.1 to 100μM) was investigated using the stable transfected cell line CHO-OATP1B1. Elinzanetant inhibited human OATP1B1 in vitro with a calculated IC_{50} value of 0.7μM (corresponding approximately to 0.6 μg/mL as free base).

Module 4.2.2.6, R-13686

In an uptake transporter inhibition assay, elinzanetant inhibited the OATP1B1-mediated E217ßG transport (34% at 7μM) and elinzanetant inhibited the OATP1B3-mediated CCK-8 transport (IC_{50}: 7.63μM).

FDA Analysis

Based on M12 Drug Interactions Studies guidance, the risk of clinical DDI related to OATP1B1/1B3 inhibition is low. No clinical DDI study was warranted. However, Study 21666 were conducted to investigate clinical DDI risk related to elinzanetant being an inhibitor for BCRP. The substrate drug for BCRP used in Study 21666 (rosuvastatin) is also a substrate for OATP1B1/1B3. Data from Study 21666 confirmed that the risk of clinical DDI related to OATP1B1/1B3 inhibition is low.

BSEP Inhibition

Module 4.2.2.6, B002085

Potential BSEP inhibition by elinzanetant and its metabolites was investigated in the concentration range from 0.05µM to 20µM. Elinzanetant and its metabolites BAY 3469432, BAY 3469433, and BAY 3469434 were classified as inhibitors of BSEP with IC_{50} values of 2.13µM, 5.91µM, 9.20µM, and 16.7µM, respectively.

Module 4.2.2.6, R-13686

In a vesicular transport inhibition assay, elinzanetant inhibited the BSEP-mediated taurocholate transport (20% at 4.5µM).

Inhibiting MATE1 but not MATE2K

Module 4.2.2.6, R-14407

Table 134. Percentage Inhibition of MATE1 and MATE2K in the Presence of Test Article

Test article (µM)	Percentage inhibition toward MATE1	Percentage inhibition toward MATE2K
BAY 3427080		
(1)	34.1	3.32
(10)	69.3	3.58
BAY 3462932		
(1)	36.0	0
(10)	87.4	0
BAY 3462933		
(1)	23.1	0
(8)	73.7	0
BAY 3462934		
(1)	55.2	0
(10)	91.1	0

Source: Applicant's submitted pharmacokinetic drug interaction report R-14407, table 31
Abbreviations: MATE1, multidrug and toxin extrusion protein 1; MATE2K, multidrug and toxin extrusion protein 2 splice variant K

Table 135. MATE1 Activity Remaining and IC_{50} of BAY 3427080

In-well concentration of BAY 3427080 (µM)	MATE1 activity remaining (%)
0.0196	90.0
0.0941	84.4
0.205	71.1
0.871	35.3
1.74	25.8
4.97	18.1
IC_{50} of BAY 3427080 (µM)	0.546

Source: Applicant's submitted pharmacokinetic drug interaction report R-14407, page 8
Abbreviation: IC_{50}, half-maximal inhibitory concentration; MATE1, multidrug and toxin extrusion protein 1

Table 136. MATE1 Activity Remaining and IC_{50} of BAY 3462932

In-well concentration of BAY 3462932 (µM)	MATE1 activity remaining (%)
0.0102	93.5
0.0264	88.3
0.153	71.7
0.951	37.0
2.48	21.1
5.76	8.86
IC_{50} of BAY 3462932 (µM)	0.491

Source: Applicant's submitted pharmacokinetic drug interaction report R-14407, page 8
Abbreviation: IC_{50}, half-maximal inhibitory concentration; MATE1, multidrug and toxin extrusion protein 1

Table 137. MATE1 Activity Remaining and IC_{50} of BAY 3462933

In-well concentration of BAY 3462933 (µM)	MATE1 activity remaining (%)
0.0193	102
0.0409	101
0.157	87.1
0.765	49.5
1.63	37.9
2.40	27.4
IC_{50} of BAY 3462933 (µM)	0.824

Source: Applicant's submitted pharmacokinetic drug interaction report R-14407, page 8
Abbreviation: IC_{50}, half-maximal inhibitory concentration; MATE1, multidrug and toxin extrusion protein 1

Table 138. MATE1 Activity Remaining and IC_{50} of BAY 3462934

In-well concentration of BAY 3462934 (µM)	MATE1 activity remaining (%)
0.00473	104
0.0167	104
0.0553	94.7
0.147	89.0
0.803	36.7
3.77	10.0
IC_{50} of BAY 3462934 (µM)	0.542

Source: Applicant's submitted pharmacokinetic drug interaction report R-14407, page 8
Abbreviation: IC_{50}, half-maximal inhibitory concentration; MATE1, multidrug and toxin extrusion protein 1

Module 4.2.2.6, R-13686

In an uptake transporter inhibition assay, elinzanetant inhibited the MATE1-mediated metformin transport (IC_{50}: 3.19µM). NT-814 did not inhibit the MATE2K probe substrate transport at concentrations up to 7µM.

FDA Analysis

Based on M12 Drug Interactions Studies guidance, the risk of clinical DDI related to MATE1 inhibition is low. No clinical DDI study was conducted.

Not an Inhibitor for OAT1, OAT3, OCT1, OCT2, or MRP2 (Module 4.2.2.6, R-14407)

The inhibitor assessment of each test article towards OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K was performed with the vector control- and transporter transfected HEK cells. A summary of the percentage inhibition of each transporter is shown in the following tables. Based on the initial assessment (two concentrations of the test article), the IC_{50} assessment of all test articles toward MATE1 was performed.

Table 139. Percentage Inhibition of OAT1, OAT3, OCT1, and OCT2 in the Presence of Test Article

Test article (μM)	Percentage inhibition toward OAT1	Percentage inhibition toward OAT3	Percentage inhibition toward OCT1	Percentage inhibition toward OCT2
BAY 3427080				
(1)	0	5.39	0	0
(8)	0	0	0	0
BAY 3462932				
(1)	0	0	6.65	0
(10)	0	0	20.6	0
BAY 3462933				
(1)	0	22.0	4.64	4.64
(10)	0	6.05	14.7	3.44
BAY 3462934				
(1)	0	0	5.44	0
(10)	0	0	30.4	0

Source: Applicant's submitted pharmacokinetic drug interaction report R-14407, page 6
Abbreviation: OAT, organic anion transporter

The inhibitor assessment of each test article towards MRP2 was conducted in the presence of ATP (or AMP) in MRP2 vesicles. A summary of the percentage inhibition of each test article is shown in Table 140.

Table 140. Percentage Inhibition of MRP2 in the Presence of Test Article

Test article (μM)	Percentage inhibition toward MRP2
BAY 3427080	
(1)	0
(8)	0
BAY 3462932	
(1)	8.43
(10)	0
BAY 3462933	
(1)	0
(10)	0
BAY 3462934	
(1)	0
(10)	0

Source: Applicant's submitted pharmacokinetic drug interaction report R-14407, page 8
Abbreviations: MRP2, multidrug resistance-associated protein 2

14.2. In Vivo Studies

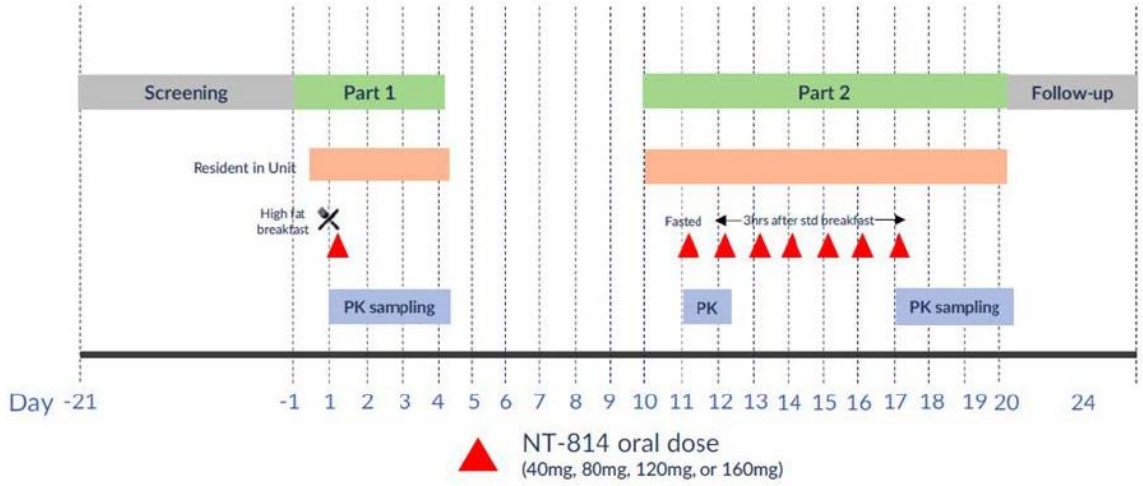
Elinzanetant is also referred to as GSK1144814, BAY 3427080, NT-814.

14.2.1. Clinical PK and/or PD Studies in Healthy Subjects

14.2.1.1. Healthy Female Subject Multiple Dose Pharmacokinetics and Single Dose Food Effect, Study 21678

This was a Phase 1, open-label, single-sequence, crossover study in healthy female volunteers, designed to evaluate the pharmacokinetics of repeated doses of NT-814 (40, 80, 120, and 160 mg soft gel capsules) across four parallel cohorts. It also assessed the effect of food on NT-814 pharmacokinetics following a single dose at each level. In Part 1, subjects received a single dose of NT-814 30 minutes after a high-fat breakfast (800 to 1000 kcal, with 500 to 600 kcal from fat and 250 kcal from carbohydrates) on Study Day 1. In Part 2, subjects received a single dose of NT-814 in a fasting state on Study Day 11, followed by once-daily dosing from Study Day 12 to Study Day 17, administered three hours after a regular breakfast (approximately 400 to 500 kcal, with 150 kcal from fat). The overall study design is provided in Figure 47.

Figure 47. Study Design, Study 21678



Source: CSR, figure 9-1
Abbreviations: CSR, CSR, clinical study report; PK, pharmacokinetic

Results

Pharmacokinetic Results

Assessment of Food Effect

A high-fat, high-calorie breakfast on Day 1 reduced the C_{max} of NT-814 by approximately 70% and the AUC_{0-24} by 30 to 40% compared to the fasted state on Day 11, as shown in Table 141. Additionally, food intake delayed the median T_{max} by 2.0 to 2.5 hours.

Table 141. Assessment of Food Effect on NT-814, PK Subset, Study 21678

Dose Level	PK Parameter	Statistic	Study Day 1 (Fed)[a]	Study Day 11 (Fasted)[a]	Ratio/ Difference[b]	90% CI[c]
40 mg (N = 12)	C_{max} (ng/mL)	Adj geo mean	198	549	0.36	0.279, 0.464
	AUC_{24} (ng*h/mL)	Adj geo mean	1070	1510	0.71	0.617, 0.814
	t_{max} (h)[d]	Median	3.000	1.000	1.50	1.000, 3.000
80 mg (N = 13)	C_{max} (ng/mL)	Adj geo mean	413	1440	0.29	0.224, 0.366
	AUC_{24} (ng*h/mL)	Adj geo mean	2390	3780	0.63	0.553, 0.722
	t_{max} (h)[d]	Median	4.000	1.000	2.75	2.250, 3.000
120 mg (N = 11)	C_{max} (ng/mL)	Adj geo mean	768	2540	0.30	0.232, 0.394
	AUC_{24} (ng*h/mL)	Adj geo mean	4250	7390	0.58	0.497, 0.665
	t_{max} (h)[d]	Median	3.000	1.500	1.25	0.500, 2.000
160 mg (N = 12)	C_{max} (ng/mL)	Adj geo mean	937	3090	0.30	0.235, 0.391
	AUC_{24} (ng*h/mL)	Adj geo mean	6310	10400	0.61	0.527, 0.695
	t_{max} (h)[d]	Median	4.000	1.500	2.00	1.000, 2.750
Overall (N = 48)	C_{max} (ng/mL)	Adj geo mean	492	1580	0.31	0.275, 0.354
	AUC_{24} (ng*h/mL)	Adj geo mean	2880	4580	0.63	0.586, 0.673
	t_{max} (h)[d]	Median	NC	NC	NC	NC

Source data: Table 14.2.3.3.1 and Table 14.2.3.3.2
Adj Geo Mean = adjusted geometric mean; AUC_{24} = area under concentration versus time curve from time of dosing to 24 hours after dosing; AUC_{inf} = area under concentration versus time curve from time of dosing extrapolated to infinity; CI = confidence interval; C_{max} = maximum concentration; NC = not calculated; PK = pharmacokinetics; t_{max} = time after dosing of C_{max}.
[a] Adjusted geometric mean from model.
[b] Ratio of adjusted geometric mean for Fed/Fasted (Study Day 1/Study Day 11) for C_{max} and AUC_{24}. Hodges-Lehmann median difference calculated as Fed-Fasted (Study Day 1-Study Day 11) for t_{max}.
[c] Confidence interval for ratio of adjusted geometric means for C_{max} and AUC_{24}, and for Hodges-Lehmann estimate for t_{max}. Analysis was not performed on AUC_{inf} as the number of subjects with reliable estimates for both days was less than six.
[d] Results for t_{max} obtained from non-parametric Wilcoxon signed-rank test.
Source: Study 21678 report, table 11-2

Assessment of Dose Proportionality

Following single dose administration of elinzanetant under fasted and fed conditions, C_{max} and AUC was increased greater than dose proportional manner (20% to 50%) over the dose range 40 to 160 mg QD which is 0.33 to 1.33 times the recommended dose of 120 mg elinzanetant QD as shown in Table 142.

Table 142. Assessment of Dose Proportionality of NT-814, Study 21678

Parameter/Category		NT-814			
		40 mg (N = 12)	80 mg (N = 13)	120 mg (N = 11)	160 mg (N = 12)
Study Day 1					
C_{max} (ng/mL)	n	12	13	11	12
	Geometric mean	198	413	768	937
	ß (90% CI)[a]	1.16 (0.94, 1.38)			
	2^ß (90% CI)[b]	2.23 (1.92, 2.60)			
AUC_{24} (ng*h/mL)	n	12	13	11	12
	Geometric mean	1070	2390	4250	6310
	ß (90% CI)[a]	1.28 (1.15, 1.41)			
	2^ß (90% CI)[b]	2.43 (2.23, 2.66)			
Study Day 11					
C_{max} (ng/mL)	n	12	13	11	12
	Geometric mean	549	1440	2540	3090
	ß (90% CI)[a]	1.28 (1.10, 1.46)			
	2^ß (90% CI)[b]	2.43 (2.14, 2.75)			
AUC_{24} (ng*h/mL)	n	12	13	11	12
	Geometric mean	1510	3780	7390	10,400
	ß (90% CI)[a]	1.42 (1.27, 1.56)			
	2^ß (90% CI)[b]	2.67 (2.42, 2.95)			
AUC_{inf} (ng*h/mL)	n	4	6	7	7
	Geometric mean	1360	4310	7620	10,500
	ß (90% CI)[a]	1.47 (1.24, 1.69)			
	2^ß (90% CI)[b]	2.77 (2.37, 3.23)			
Study Day 17					
C_{max} (ng/mL)	n	12	12	11	12
	Geometric mean	525	1300	2050	2990
	ß (90% CI)[a]	1.25 (1.07, 1.42)			
	2^ß (90% CI)[b]	2.37 (2.11, 2.68)			
AUC_{tau} (ng*h/mL)	n	12	12	11	12
	Geometric mean	2000	4950	9080	14,100
	ß (90% CI)[a]	1.41 (1.25, 1.57)			
	2^ß (90% CI)[b]	2.65 (2.37, 2.96)			

Source data: Table 14.2.3.1.
AUC = area under the concentration versus time curve; AUC_{24} = AUC from time of dosing to 24 hours after dosing; AUC_{inf} = AUC from time of dosing extrapolated to infinity; AUC_{tau} = AUC over a dose interval; CI = confidence interval; C_{max} = maximum concentration.
[a] ß is the slope parameter and its 90% CI is a measure of dose proportionality.
[b] 2^ß represents the increase in exposure for a 2-fold increase in dose.

Source: CSR, table 11-3

Assessment of Dose Accumulation

The analysis of dose accumulation on Study Day 17 compared to Study Day 11 (final day versus first day of repeat dosing) is presented in Table 143. On Study Day 17, C_{max} showed a 10 to 20% decrease compared to Study Day 11, with an overall geometric mean ratio of 0.91 (90% CI:

0.833, 0.992). In contrast, AUC_{tau} values were approximately 30% higher on Study Day 17, with a geometric mean ratio of 1.31 (90% CI: 1.229, 1.391).

Table 143. Assessment of Dose Accumulation of NT-814, PK Subset, Study 21678

Dose Level	PK Parameter	Adjusted Geometric Mean[a]		Ratio[b]	90% CI[c]
		Study Day 17	Study Day 11		
40 mg (N = 12)	C_{max} (ng/mL)	525	549	0.96	0.805, 1.135
	AUC_{tau} (ng*h/mL)	2000	1510	1.33	1.172, 1.499
80 mg (N = 13)[d]	C_{max} (ng/mL)	1300	1420	0.91	0.770, 1.085
	AUC_{tau} (ng*h/mL)	4950	3720	1.33	1.177, 1.506
120 mg (N = 11)	C_{max} (ng/mL)	2050	2540	0.81	0.675, 0.967
	AUC_{tau} (ng*h/mL)	9080	7390	1.23	1.081, 1.398
160 mg (N = 12)	C_{max} (ng/mL)	2990	3090	0.97	0.815, 1.149
	AUC_{tau} (ng*h/mL)	14,100	10400	1.35	1.192, 1.524
Overall (N = 48)	C_{max} (ng/mL)	1430	1570	0.91	0.833, 0.992
	AUC_{tau} (ng*h/mL)	5960	4560	1.31	1.229, 1.391

Source data: Table 14.2.3.2
AUC = area under the concentration versus time curve; AUC_{tau} = AUC from time zero over a dose interval; CI = confidence interval; C_{max} = maximum concentration; PK = pharmacokinetic
[a] Adjusted geometric mean from model.
[b] Ratio of adjusted geometric mean for (Study Day 17/Study Day 11).
[c] Confidence interval for the ratio of adjusted geometric means.
[d] n=12.

Source: Study 21678 report, table 11-4

14.2.1.2. Mass Balance Study in Healthy Male Subjects, Study 21664

This study is a single dose study to assess the mass balance recovery, absorption, metabolism, and excretion of [^{14}C]-NT-814 in six healthy male subjects after a single dose of 120 mg [^{14}C]-NT-814 oral suspension under fasting condition. The overall mean recovery of drug-derived radioactivity ($\%A_{E,\ ur+fec}$ ($0\text{-}t_{last}$)) was 90.4±1.04% (range 88.3 to 91.4%) of the administered dose up to 480 hours (20 days). Including toilet tissue (0.48±0.31%), the recovery was 90.8±0.97% (range 89.2 to 92.0%). The amount of radioactivity excreted into feces was $\%A_{E,\ fec}$ ($0\text{-}t_{last}$) =89.9±1.04% (range 88.0 to 91.2%). The amount of radioactivity excreted into urine was $\%A_{E,\ ur}$ ($0\text{-}t_{last}$) =0.436±0.214% (range 0.215 to 0.848%). The arithmetic mean values (±SD) of cumulative recovery (%) of total radioactivity (TR) in urine and feces are shown in Table 144.

Table 144. Excretion of Radioactivity for up to 480 Hours After a Single Oral Administration of 120 mg [^{14}C]elinzanetant, Study 21664

Subject No.	(b) (6)												arithmetic mean	
Samples analyzed[a]	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces
Collection interval [h]	0-384	0-336	0-336	0-336	0-384	0-408	0-384	0-432	0-384	0-480	0-336	0-336		
%A_E(0-t_{last}) [% of dose] (± standard deviation)	0.480	90.5	0.282	91.2	0.511	89.9	0.215	88.0	0.848	89.3	0.281	90.7	0.436 (± 0.214)	89.9 (± 1.04)
%$A_{E,ur+fec}$(0-t_{last}) [% of dose][b] (± standard deviation)	91.0		91.4		90.4		88.3		90.1		91.0		90.4 (± 1.04)	
Identification	[% of dose]													
Elinzanetant		42.1		62.7		50.4		60.4		19.9		67.3		50.5
M8+M87		4.86		2.99		3.57		-		5.67		1.73		3.14
M10		0.268		0.178		0.261		-		0.403		0.0797		0.198
M11		1.86		1.28		1.89		1.11		3.34		0.815		1.71
M12		2.92		1.70		2.49		1.58		5.18		0.983		2.47
M13		4.22		2.30		3.22		2.66		6.10		1.99		3.41
M16		-		-		-		-		0.00		0.0917		0.0153
M17		5.15		3.07		4.44		3.13		9.63		2.62		4.67
M18/M21		3.25		2.28		3.31		2.58		3.49		1.50		2.73
M27		2.45		2.27		3.47		2.76		5.69		2.13		3.13
M30/M34		1.37		0.854		1.58		1.42		1.88		1.26		1.39
M39		-		-		-		-		0.0868		-		0.0145
M53/M76		0.369		0.172		0.111		0.0370		0.653		0.0613		0.234
M80		9.92		5.53		6.72		3.73		9.56		2.06		6.25
M83/M84		0.430		0.167		0.275		-		0.387		-		0.210
M96		1.05		0.451		0.670		0.270		1.22		0.257		0.654
M98/M99>M63/M64		-		0.743		1.74		-		4.11		1.67		1.38
Other		10.4		4.50		4.29		6.84		10.6		4.21		6.80
Not balanced	0.480	-	0.282	-	0.511	1.40	0.215	1.49	0.848	1.39	0.281	1.94	0.436	1.04
Calculated	0.480	90.5	0.282	91.2	0.511	89.9	0.215	88.0	0.848	89.3	0.281	90.7	0.436	89.9
Calculated total[c]	**91.0**		**91.4**		**90.4**		**88.3**		**90.1**		**91.0**		**90.4**	

Source: Mass Balance PH-4227 report, table 6-8
a = urine samples were not investigated (e.g., due to low radioactivity concentrations)
b = AE, AE,ur and AE,fec were calculated based on the individual dose administered
c = difference to 100% is the sum of unknown metabolites and not excreted or balanced radioactivity

PK Analysis

Elinzanetant was extensively metabolized following oral dosing. Key PK parameters of TR in whole blood and plasma for elinzanetant, M27, M30/34, and M18/21following a single dose of 120 mg [^{14}C]elinzanetant are summarized in Table 145. Exposure to elinzanetant, M27, M30/34, and M18/21 accounted for approximately 31%, 5.9%, 11% and 5.3% of circulating plasma TR. The sum of these analytes measured accounted for approximately 53% of the circulating plasma TR.

Table 145. Key PK Parameters of Total Radioactivity of Elinzanetant and its Metabolites, Study 21664

Analyte Matrix	TR Plasma	TR Whole Blood	NT-814 Plasma	M27 Plasma	M30/34 Plasma	M18/21 Plasma
No. of Subjects	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6
t_{max} (hours)	1.500 (1.00-4.00)	2.000 (1.00-4.00)	1.500 (0.75-48.02)	1.750 (1.00-4.00)	2.008 (1.50-4.00)	2.008 (1.50-6.00)
C_{max} (ng/mL)[a]	960 (105.79)	527 (118.15)	521 (143.55)	55.2 (85.22)	128 (74.23)	91.3 (47.21)
AUC(0-t_{last}) (ng.h/mL)[a]	19400 (52.11)	4160 (195.42)	6540 (45.33)	1250 (44.86)	2380 (44.18)	1140 (45.27)
AUC(0-inf) (ng.h/mL)[a]	21700 (50.49)	6630, 28000 [n=2]	6620 (44.75)	1320 (42.68)	2450 (43.58)	1200 (43.43)
%AUCextrap (%)	10.51 (12.98)	16.5, 18.1 [n=2]	1.11 (55.99)	5.29 (38.35)	2.55 (27.22)	4.67 (46.01)
$t_{1/2}$ (hours)	46.258 (36.46)	11.591 (139.20) [n=4]	37.101 (25.26)	41.185 (23.75)	34.245 (35.39)	31.343 (35.71)
CL/F (mL/min)	NA	NA	302 (44.75)	NA	NA	NA
Vz/F (L)	NA	NA	970 (43.73)	NA	NA	NA
MRT(0-t_{last}) (hours)	43.944 (29.38)	10.851 (101.41)	39.704 (35.34)	51.267 (34.46)	37.012 (40.49)	32.613 (44.71)
MRT(0-inf) (hours)	62.229 (25.70)	20.50, 49.59 [n=2]	42.589 (33.81)	62.003 (30.39)	41.929 (38.45)	39.705 (45.17)
MPR C_{max}	NA	NA	NA	0.1034 (35.71)	0.2393 (44.51)	0.1672 (80.43)
MPR AUC(0-inf)	NA	NA	NA	0.1949 (14.00)	0.3608 (14.67)	0.1735 (24.58)

Source: CSR synopsis
Data shown are geometric mean (geometric coefficient of variation [CV%]) except for t_{max}, which is median (range),
[a] Units for TR are expressed as nanograms equivalent(s) (ng equiv) (free base).
MPR is calculated based on molar concentrations.
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; MPR, metabolite to parent ratio; n, number of subjects with an observation, N: number of subjects in the dataset, NA: not applicable, TR: total radioactivity

Metabolic Profiling in Plasma

Elinzanetant covered 39.1% of the total radioactivity AUC_{0-144} in human plasma. Metabolites M30/M34 (BAY 3462933), M27 (BAY 3462932), and M18/M21 (BAY 3462934) accounted for 13.7%, 7.6% (including traces of M28), and 4.9% of the total radioactivity AUC_{0-144}, respectively. All other identified metabolites (M11, M14, M16, M28, M39, M35/M75, M53/M76, M95, M96) covered, in sum, 14.3% of the total radioactivity AUC_{0-144} (each less than 3.5%). Metabolite profiling in urine was not performed due to the low amount of radioactivity excreted.

The geometric mean apparent terminal half-life for plasma TR and NT-814 were approximately 46 hours and 37 hours, respectively. The geometric mean plasma half-life values for M27,

M30/34, and M18/21 were comparable to the half-life of NT-814, at 41 hours, 34 hours, and 31 hours, respectively.

The geometric mean of AUC_{inf} whole blood to plasma TR concentration ratios is 0.31, indicating that there is little distribution of TR into the cellular components of whole blood. The Applicant reported that there was no time-dependent difference in the concentration ratios.

FDA Analysis

Following a single dose administration of 120 mg [^{14}C] elinzanetant oral suspension to healthy male subjects, on average, 90.8% of the radioactivity administered was recovered, with 90.4% in feces and 0.44% in urine. This indicates that renal clearance of elinzanetant and its metabolites plays a limited role in the elimination of elinzanetant (Table 144).

M30/34 was the most abundant circulating metabolite of elinzanetant in plasma.

The ratio of metabolites to the parent compound is 0.39.

14.2.1.3. Healthy Female Subjects Multiple Dose PK Study for Elinzanetant and Its Metabolites, Study 21703

This is an open-label study to investigate the pharmacokinetics, safety, and tolerability of repeated 120 mg doses of NT-814 (elinzanetant) and its metabolites in 12 healthy female volunteers. On the first and last days of dosing, NT-814 was administered after a minimum of 10 hours of fasting. For the intervening days (Days 2 to 13), the drug was given approximately three hours after consuming a standard breakfast. Plasma samples for NT-814 and its metabolites were obtained within 15 minutes before dosing and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 168 hours postdose. Urine PK data were also collected.

Study Results

Study results showed that elinzanetant was rapidly absorbed following single and multiple doses with a range of median T_{max} of 1.2 to 1.5 hours. Primary PK parameters (AUC and C_{max}) of elinzanetant and its metabolites are shown in Table 146. Modest accumulation of elinzanetant and its metabolites M18/21, M27, and M30/34 was observed at Day 14 compared to Day 1, as shown in Table 147. Mean apparent terminal elimination half-life ($t_{1/2}$) was estimated to be 37.4 hours on Day 14. NT-814 accounted for a mean of 41.5% of the total drug-related exposure (sum of $AUC_{(0-24)}$ of NT-814 and metabolites M27, M30/34, M18/21 and M22) on Study Day 1 and 49.3% on Study Day 14.

The study showed that mean trough elinzanetant plasma concentrations on Study Day 14 (310 ng/mL) were higher than on Days 5 (134 ng/mL) and 11 (164 ng/mL) but were comparable to on Study Day 15 suggesting that steady state was reached by Study Day 14.

Table 146. Summary Statistics of Noncompartmental PK Parameters of Elinzanetant and Metabolites in Plasma, Study 21703

Compound	Parameters (Unit)	Day 1 (N=12)	Day 14 (N=9)
Elinzanetant	C_{max} (µg/L)	2170 / 30.9 (1510 – 3880)	3520 /28.5 (2210 – 5120)
	AUC(0-24) (µg·h/L)	7080 / 28.9 (4830 – 11200)	14500 / 27.3 (9160 – 20500)
M30/M34	C_{max} (µg/L)	769 / 17.0 (608 – 1050)	954 / 21.2 (745 – 1340)
	AUC(0-24) (µg·h/L)	5270 / 20.3 (3270 – 6920)	7370 / 23.5 (5310 – 10900)
M27	C_{max} (µg/L)	476 / 23.4 (339 – 722)	628 / 26.6 (436 – 947)
	AUC(0-24) (µg·h/L)	2270 / 26.2 (1360 – 3480)	4240 / 30.1 (2810 – 7050)
M18/M21	C_{max} (µg/L)	528 / 17.8 (387 – 714)	515 / 17.8 (423 – 686)
	AUC(0-24) (µg·h/L)	2700 / 21.5 (1620 – 3520)	3600 / 24.1 (2660 – 5240)
M22	C_{max} (µg/L)	6.51 / 26.3 (4.25 – 10.0)	8.69 / NC (7.06 – 12.5)
	AUC(0-24) (µg·h/L)	25.9 / 28.9 (14.1 – 38.1)	37.6 / 22.2 (28.7 – 49.1)

Source: Applicant's clinical pharmacology summary, table 2-15 Geom. Mean/CV [Range]
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Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geom., geometric; M, metabolite; N, number of subjects; PK, pharmacokinetic

Table 147. Geometric Mean Ratios (Day 14/Day 1) of C_{max} and $AUC_{(0-24)}$ of Elinzanetant and its Metabolite M18/21, M27 and M30/34, Study 21703

	Elinzanetant		M27		M30/34		M18/21	
Statistics	C_{max}	$AUC_{(0-24)}$	C_{max}	$AUC_{(0-24)}$	C_{max}	$AUC_{(0-24)}$	C_{max}	$AUC_{(0-24)}$
Adj geometric mean	1.56	2.11	1.26	1.88	1.23	1.44	0.97	1.36
90% CI	1.34, 1.80	1.95, 2.29	1.07, 1.48	1.68, 2.11	1.11, 1.37	1.29, 1.60	0.85, 1.11	1.19, 1.56

Source: Applicants CSR for Study 21703, table 11-1
Abbreviations: Adj, adjusted; AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; M, metabolite

FDA Analysis

This study showed an accumulation ratio of 2.11 for elinzanetant, which is higher than the accumulation ratio of 1.23 (1.081 to 1.398) observed in Study 21678 (Table 143) following multiple doses of 120 mg elinzanetant for 7 days. The Applicant did not provide an explanation for the difference observed across the studies. A possible explanation could be the administration conditions: in this study, the drug was taken on Day 14 (the last of treatment) under fasting conditions, whereas in Study 21678, it was administered on Day 17 (the last day of treatment), three hours after breakfast. Nonetheless, in both cases, the accumulation was modest (accumulation ratio ~2).

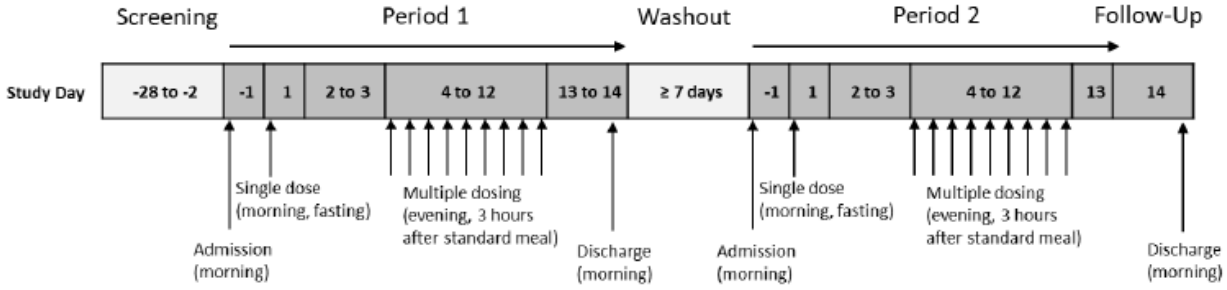
In this study, elinzanetant was the major component in human plasma accounting for an average of 49.3% of the total exposure. This proportion is notably higher than the total radioactivity observed for elinzanetant in plasma (39.1%), as observed in mass-balance Study 21664.

In this study, metabolite M30/34 accounted for approximately 24.5% of the total drug-related material, while metabolites M27 and M18/21 contributed 14.2% and 11.8% of the total drug-related material, respectively. However, in the mass-balance Study 21664, the total radioactivity in plasma for metabolites M30/34, M27, and M18/21 were much lower, accounting for 13.7%, 7.6% (including traces of M22), and 4.9% of the total radioactivity, respectively. The reasons for these discrepancies in exposure remain unexplained.

14.2.1.4. Relative Bioavailability Study (Soft Gel Capsule: 60 mg and 40 mg), Study 21665

This study was a single- and multiple-dose, open-label, randomized, 2 × 2 crossover study conducted in 18 healthy subjects to evaluate the PK and relative bioavailability of elinzanetant following a single dose of either 2 × 60 mg soft gel capsules (the to-be-marketed formulation and the formulation evaluated in Phase 3 studies) or 3 × 40 mg soft gel capsules (an earlier formulation evaluated in Phase 1 and 2 studies) (Figure 48). The multiple-dose regimen was included to investigate PK comparison and bioavailability between the two formulations under clinically relevant conditions. A 120 mg once-daily dose of elinzanetant was selected, as this dose was tested in Phase 3 studies. Additionally, the multiple doses were administered in the evening, three hours after a standard meal, aligning with the intended administration scheme (i.e., at bedtime) for clinical use.

Figure 48. Study Design, Study 21665



Source: Applicant's submitted Study 21665 report

Results

In the PK analysis, data from 17 subjects were included out of the original 18 subjects. This exclusion was due to one male subject not completing the study because of an AE related to COVID-19.

The geometric LS mean ratios for C_{max} and AUC of elinzanetant (3 × 40 mg capsules compared to 2 × 60 mg capsules) were determined to be within the bioequivalence acceptance range of 0.8 to 1.25 following both single dosing under fasted conditions and multiple dosing administered 3 hours after a standardized meal (Table 148).

For C_{trough} at Day 13 (C_{trough}, D13), the treatment ratio of elinzanetant 3 x 40 mg (A)/ elinzanetant 2 x 60 mg (B) was 1.1698 (1.0361; 1.3208) with the upper 90% CI slightly exceeding the upper bioequivalence range of 1.25. C_{trough} at Day 10, Day 11, Day 12, and Days 10 to 13 (model-based average) were also investigated, resulting in the treatment ratios A/B of 1.0350 (0.9480; 1.1300), 1.0942 (0.9662; 1.2392), 1.0873 (0.9863; 1.1986), and 1.0955 (1.0136; 1.1841), respectively, with all values close to 1 and all 90% CIs within the bioequivalence acceptance range.

Table 148. Point Estimate (LS Means) and 90% CI for Treatment Ratio of Elinzanetant 3x40 mg / Elinzanetant 2x60 mg, Study 21665

Parameter	Unit	Ratio	N	Geom. CV (%)	Estimated ratio	90% confidence limits lower / upper
AUC	µg·h/L	A/B	17	17.15	0.9913	0.8946 / 1.0984
C_{max}	µg/L	A/B	17	27.52	0.9892	0.8406 / 1.1641
$AUC(0\text{-}24)_{md}$	µg·h/L	A/B	17	11.92	1.0183	0.9480 / 1.0939
$C_{max,md}$	µg/L	A/B	17	21.45	1.0289	0.9055 / 1.1691
C_{trough} (Day 10)*	µg/L	A/B	17	14.65	1.0350	0.9480 / 1.1300
C_{trough} (Day 11)*	µg/L	A/B	17	20.89	1.0942	0.9662 / 1.2392
C_{trough} (Day 12)*	µg/L	A/B	17	16.29	1.0873	0.9863 / 1.1986
C_{trough} (Day 13)	µg/L	A/B	17	20.36	1.1698	1.0361 / 1.3208
C_{trough} (Day 10-13)*	µg/L	A/B	17	17.99	1.0955	1.0136 / 1.1841

Source: Applicant's Summary of biopharmaceutics, table 2-8
*Post hoc analyses
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{trough}, trough concentration; CV, coefficient of variation; LS, least squares; N, number of subjects

FDA Analysis

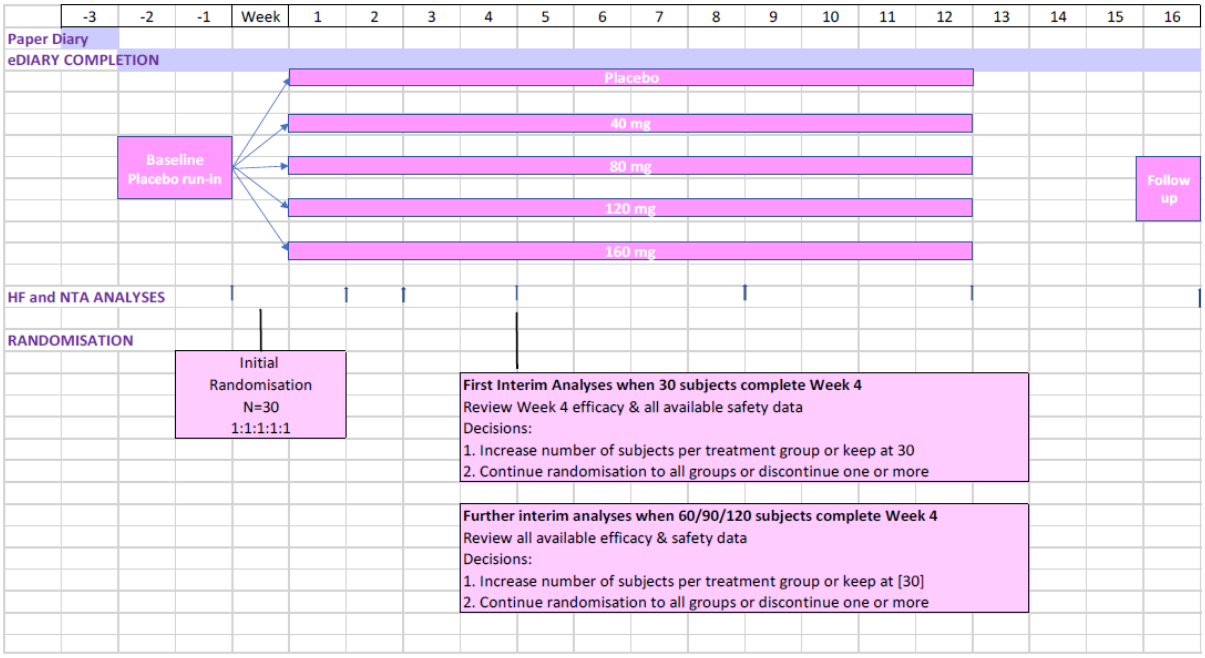
The results of the study indicate that the systemic exposure of elinzanetant between the to-be-marketed formulation and the earlier formulation used in Phase 1 and Phase 2b studies are similar under both single and multiple dosing conditions.

14.2.2. Clinical PK and/or PD Studies in Intended Patient Population, SWITCH-1

This study was designed as a dose-finding investigation to evaluate the safety and efficacy of elinzanetant soft-gel capsules at doses of 40 mg, 80 mg, 120 mg, and 160 mg. The study employed a double-blind, randomized, placebo-controlled design with female subjects experiencing moderate to severe VMS associated with menopause. The study utilized an adaptive design, allowing for modifications to the total number of subjects recruited and/or the number of subjects randomized to each treatment group based on emerging safety and efficacy data.

The study duration for each subject was approximately 19 weeks, comprising a 3-week formal screening and baseline period. This period included a single-blind (subjects only) placebo run-in phase for the final 2 weeks, during which subjects received placebo once daily. This was followed by a 12-week double-blind treatment phase and a final follow-up visit 4 weeks after the end of the treatment period. During the treatment phase, subjects were randomized in a 1:1:1:1:1 ratio to one of five parallel groups to receive either NT-840 at doses of 40 mg, 80 mg (2 x NT-814 40 mg capsules), 120 mg (3 x NT-814 40 mg capsules), or 160 mg (4 x NT-814 40 mg capsules), or a matching number of placebo capsules for each group, administered QD in the evening. The study design is depicted in Figure 49.

Figure 49. Study Design, SWITCH-1



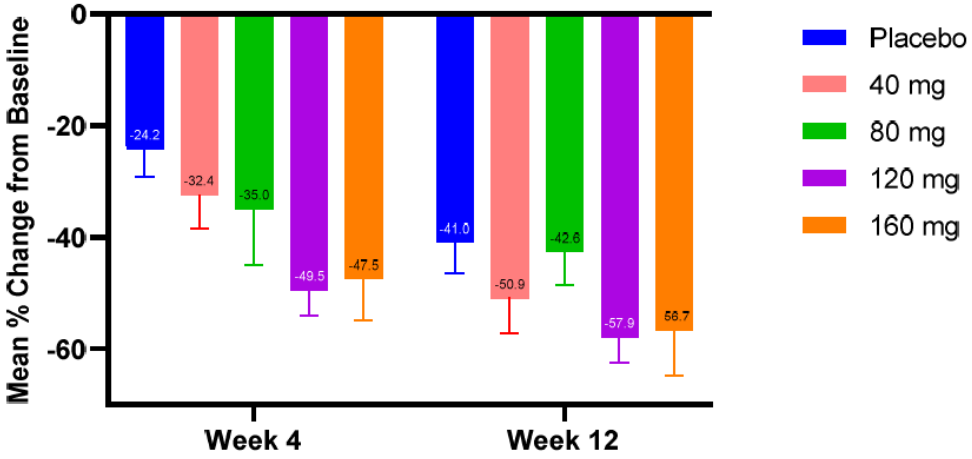
Source:
Abbreviations: HF, hot flash; N, number of subjects; NTA, night time awakening

Results

Efficacy assessment was conducted using two coprimary endpoints: the mean change from baseline in the mean daily frequency and severity of moderate and severe HFs at Weeks 4 and 12. Efficacy with respect to hot flash frequency and severity was evaluated using diaries completed daily throughout the study period. A reduction of at least two moderate to severe HFs per day (equivalent to 14 per week) compared to placebo was deemed clinically meaningful to establish efficacy in treating VMS. Additionally, a statistically significant decrease in the frequency and severity of HFs from baseline compared to placebo at Weeks 4 and 12 was also assessed.

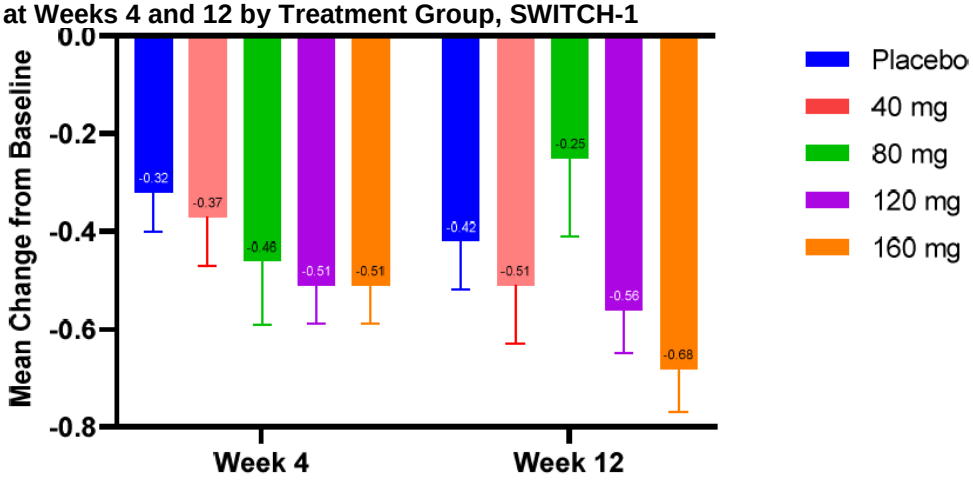
In general, reductions in both frequency and severity from baseline were observed across all treatment groups, with more substantial reductions noted in the NT-814 treatment groups compared to the placebo. Overall, the 120 mg and 160 mg doses demonstrated a greater extent of reduction in both frequency and severity than the 40 mg and 80 mg doses (Figure 50 and Figure 51).

Figure 50. Mean (SE) Percent Change in Moderate and Severe HFs Frequency at Weeks 4 and 12 by Treatment Group, SWITCH-1



Source: Applicant's End of Phase 2 (EOP2) meeting package figure 19
Abbreviations: HFs, hot flashes; SE, standard error

Figure 51. Least Squares Mean (SE) Change From Baseline in Moderate and Severe HFs Severity at Weeks 4 and 12 by Treatment Group, SWITCH-1



Source: Applicant's end of phase 2 (EOP2) meeting package figure 19
Abbreviations: HFs, hot flashes; SE, standard error

For the 120 mg treatment group, the reduction in hot flash frequency from baseline was statistically significant compared to placebo at both Weeks 4 and 12 (p=0.0002 and p=0.0116, respectively). The 160 mg treatment group showed a significant reduction compared to placebo at Week 4 (p=0.0115), but this reduction was not sustained at Week 12.

Additionally, prespecified nonparametric analyses demonstrated statistically significant differences from placebo for both the 120 mg and 160 mg groups at both time points (p<0.005). These results are summarized in Table 149, which displays the percentage change from baseline in moderate and severe hot flashes at Weeks 4 and 12.

Table 149. Percentage Change From Baseline of Moderate and Severe HFs at Week 4 and 12 by Treatment Group, SWITCH-1

		Placebo (N=47)	NT-814 40 mg (N=31)	NT-814 80 mg (N=17)	NT-814 120 mg (N=52)	NT-814 160 mg (N=52)
Percentage Change from Baseline of Moderate and Severe Hot Flashes by Week						
Week 4	Mean (SD)	-24.16 (34.22)	-32.43 (34.19)	-34.97 (41.32)	-49.46 (32.69)	-47.52 (50.10)
	Median (range)	-21.05 (-98.1, 36.0)	-36.11 (-100.0, 48.7)	-34.31 (-100.0, 85.8)	-48.22 (-100.0, 28.6)	-56.34 (-100.0, 186.4)
Week 12	Mean (SD)	-41.00 (36.59)	-50.85 (35.81)	-42.62 (25.28)	-57.92 (32.95)	-56.66 (53.11)
	Median (range)	-37.54 (-100.0, 29.0)	-55.76 (-100.0, 28.9)	-43.49 (-78.4, 35.0)	-63.49 (-100.0, 47.6)	-70.69 (-100.0, 198.5)
Statistical Analysis of Change from Baseline versus Placebo (MMRM)						
Change from Baseline to Week 4						
LS mean (95% CI)		-2.80 (-4.26, -1.34)	-4.32 (-6.10, -2.54)	-4.09 (-6.50, -1.68)	-6.73 (-8.11, -5.35)	-5.43 (-6.83, -4.02)
Difference in LS means (95% CI)		NA	-1.52 (-3.83, 0.78)	-1.29 (-4.11, 1.53)	-3.93 (-5.94, -1.92)	-2.63 (-4.66, -0.60)
p-value		NA	0.1946	0.3682	0.0002	0.0115
Wilcoxon p-value		NA	0.1677	0.0164	<0.0001	<0.0001
Change from Baseline to Week 12						
LS mean (95% CI)		-4.81 (-6.48, -3.15)	-6.48 (-8.49, -4.46)	-5.58 (-8.32, -2.85)	-7.76 (-9.31, -6.21)	-6.59 (-8.24, -4.95)
Difference in LS means (95% CI)		NA	-1.67 (-4.28, -0.95)	-0.77 (-3.97, 2.44)	-2.95 (-5.22, -0.67)	-1.78 (-4.12, 0.56)
p-value		NA	0.2097	0.6369	0.0116	0.1346
Wilcoxon p-value		NA	0.3084	0.1756	0.0043	0.0023

Source: CSR, Table 11-1
Abbreviations: CSR, clinical study report; HFs, hot flashes; LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of subjects in treatment arm; NA, not applicable; SD, standard deviation

For the coprimary endpoint of weekly severity of moderate and severe hot flashes, statistically significant differences from placebo were observed at specific time points for the 160 mg and 120 mg groups. The 160 mg group exhibited a significantly greater reduction from baseline at Week 12, as determined by MMRM analysis (p=0.0479). Conversely, the 120 mg group showed a significant reduction from baseline at Week 4, as indicated by nonparametric analyses (p=0.0436), as detailed in Table 150.

Table 150. Weekly Severity and Change From Baseline of Moderate and Severe HFs at Week 4 and 12 by Treatment Group, SWITCH-1

			NT-814			
		Placebo (N=47)	40 mg (N=31)	80 mg (N=17)	120 mg (N=52)	160 mg (N=52)
Weekly Severity and Change from Baseline of Moderate and Severe Hot Flashes by Week						
Baseline	Mean (SD)	2.54 (0.20)	2.51 (0.26)	2.63 (0.24)	2.54 (0.24)	2.54 (0.26)
	Median (range)	2.54 (2.1, 3.0)	2.51 (2.0, 3.0)	2.68 (2.1, 3.0)	2.52 (2.0, 3.0)	2.52 (2.0, 3.0)
Week 4	Mean (SD)	2.24 (0.50)	2.13 (0.61)	2.19 (0.69)	2.03 (0.66)	2.01 (0.73)
	Median (range)	2.38 (1.0, 3.0)	2.15 (0.0, 3.0)	2.16 (0.0, 3.0)	2.20 (0.0, 3.0)	2.14 (0.0, 3.0)
Week 12	Mean (SD)	2.13 (0.57)	1.97 (0.69)	2.37 (0.52)	1.99 (0.71)	1.80 (0.81)
	Median (range)	2.22 (1.0, 3.0)	2.07 (0.0, 3.0)	2.41 (1.3, 3.0)	2.17 (0.0, 3.0)	2.06 (0.0, 3.0)
Change from baseline to Week 4	Mean (SD)	-0.31 (0.41)	-0.38 (0.54)	-0.44 (0.56)	-0.51 (0.57)	-0.54 (0.67)
	Median (range)	-0.15 (-1.5, 0.2)	-0.21 (-2.5, 0.2)	-0.38 (-2.3, 0.1)	-0.36 (-2.5, 0.4)	-0.38 (-2.6, 0.3)
Change from baseline to Week 12	Mean (SD)	-0.41 (0.50)	-0.53 (0.64)	-0.26 (0.45)	-0.56 (0.68)	-0.73 (0.78)
	Median (range)	-0.25 (-1.6, 0.4)	-0.38 (-2.5, 0.4)	-0.07 (-1.1, 0.2)	-0.39 (-2.5, 0.4)	-0.51 (-2.8, 0.2)
Statistical Analysis of Change from Baseline versus Placebo (MMRM)						
Change from Baseline to Week 4						
LS mean (95% CI)		-0.32 (-0.48, -0.17)	-0.37 (-0.57, -0.18)	-0.46 (-0.73, -0.20)	-0.51 (-0.66, -0.36)	-0.51 (-0.67, -0.36)
Difference in LS means (95% CI)		NA	-0.05 (-0.30, 0.20)	-0.14 (-0.45, 0.17)	-0.19 (-0.41, 0.03)	-0.19 (-0.41, 0.03)
p-value		NA	0.7033	0.3724	0.0896	0.0900
Wilcoxon p-value		NA	0.6268	0.3811	0.0436	0.0916
Change from Baseline to Week 12						
LS mean (95% CI)		-0.42 (-0.60, -0.23)	-0.51 (-0.73, -0.28)	-0.25 (-0.57, 0.06)	-0.56 (-0.74, -0.39)	-0.68 (-0.87, -0.50)
Difference in LS means (95% CI)		NA	-0.09 (-0.39, 0.21)	0.16 (-0.20, 0.52)	-0.15 (-0.41, 0.11)	-0.27 (-0.53, -0.00)
p-value		NA	0.5511	0.3822	0.2606	0.0479
Wilcoxon p-value		NA	0.4058	0.2287	0.4074	0.0796

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Source:
Abbreviations: HFs, hot flashes; LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of subjects in treatment arm; NA, not applicable; SD, standard deviation

Significant improvements were also observed for other secondary efficacy endpoints, such as sleep, mood, and quality of life. The magnitude of the benefits observed compared to placebo was clinically meaningful across all assessments.

In most efficacy measures, a clear dose-response relationship was evident, with a plateau of effect achieved at the 120 mg and 160 mg doses. Overall, these data suggest that 120 mg is the lowest effective dose, with no appreciable advantage observed for the 160 mg dose.

14.2.3. Studies Investigating the Effect of Intrinsic Factors in Healthy Subjects

14.2.3.1. Pharmacokinetics and Safety of Elinzanetant in Subjects With Impaired Renal Function, Study 21669

The study was a Phase 1, multicenter, open-label, nonrandomized, single-dose investigation designed to evaluate the pharmacokinetics of elinzanetant following a single 120 mg administration. This dose was administered as two 60 mg soft gel capsules to both male and female subjects. The study comprised four parallel groups: subjects with renal impairment classified as mild, moderate, and severe, as well as normal healthy subjects.

In the original submission of this application, the Applicant classified subjects with renal impairment based on eGFR values expressed in mL/min/1.73 m². To align with the Agency's current guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing* (March 2024) which recommends considering eGFR values expressed in mL/min, the Applicant conducted a reanalysis of the study results as a response to the clinical pharmacology review team's information request. This section of this review discusses the study results based on the Applicant's reanalysis.

In this study, a cohort of 31 subjects were initially enrolled. However, one subject was excluded from the PK analysis due to the use of a forbidden concomitant medication, leaving 30 subjects eligible for inclusion in the PK calculations. The reanalysis of the study results incorporated data from these 30 subjects, who were subsequently categorized into four distinct groups based on the Agency's current renal impairment guidance. These groups consisted of 5 individuals with mild renal impairment (eGFR 60 to 90 mL/min), 6 with moderate renal impairment (eGFR 30 to 60 mL/min), 8 with severe renal impairment (eGFR <30 mL/min), of whom at least four were undergoing hemodialysis, and 11 subjects with normal renal function (eGFR >90 mL/min).

Results

Plasma concentration of elinzanetant and its metabolite M18/21, M27, and M30/34 were measured up to 120 hours following single dose administration. C_{max} and AUC of elinzanetant and its metabolites are shown in Table 151.

Table 151. Assessment of Effect of Renal Function on Elinzanetant in Plasma, Study 21669

	Geometric Mean Ratio (90% CI)					
PK	Mild/Normal		Moderate/Normal		Severe/Normal	
Parameter	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}
Elinzanetant	1.61 (1.05;2.48)	1.86 (1.24;2.80)	1.73 (1.15;2.61)	1.84 (1.25;2.70)	1.12 (0.77;1.62)	1.2 (0.81;1.64)
M18/21	1.03 (0.74;1.43)	1.13 (0.89;1.44)	1.29 (0.94;1.76)	1.01 (0.81;1.26)	1.16 (0.87;1.54)	0.92 (0.75;1.14)
M27	1.28 (0.92;1.78)	1.34 (1.05;1.70)	1.62 (1.19;2.21)	1.25 (0.99;1.57)	1.24 (0.94;1.65)	1.02 (0.83;1.26)

PK Parameter	Geometric Mean Ratio (90% CI)					
	Mild/Normal		Moderate/Normal		Severe/Normal	
	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}
M30/34	1.35	1.40	1.41	1.32	0.99	1.00
	(0.95;1.93)	(1.10;1.78)	(1.01;1.96)	(1.05;1.65)	(0.73;1.34)	(0.82;1.24)

Source: Applicant's IR response dated January 10, 2025, table 2-5 and appendix 4, table 8.4/11-16
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; IR, information request; M, metabolite; PK, pharmacokinetic

The Applicant reported that the GMR values for unbound elinzanetant indicated that for AUCu, mean exposures increased by 1.48-fold in subjects with mild impairment compared to controls, and by 2.73-fold and 1.77-fold in those with moderate and severe impairment, respectively. Similarly, for C_{max},u, mean maximum exposures increased by 1.71-fold in subjects with mild impairment compared to controls, and by 2.89-fold and 1.82-fold in those with moderate and severe impairment, respectively. The geometric mean of fu of elinzanetant in plasma was 0.110% (range: 0.0632 to 0.245) in the moderate renal impairment group and 0.144% (range: 0.0719 to 0.201) in the severe renal impairment group, compared to 0.0851% (range: 0.0525 to 0.160) in subjects with normal renal function.

14.2.3.2. Pharmacokinetics and Safety of Elinzanetant in Subjects With Impaired Liver Function, Study 21668

This open-label study aimed to evaluate the pharmacokinetics, safety, and tolerability of elinzanetant in subjects with impaired hepatic function, classified as Child-Pugh A (mild) or B (moderate), compared to matched controls with normal hepatic function. Both unbound and total concentrations of elinzanetant were measured following single and multiple doses of elinzanetant in the study to evaluate the effects of liver impairment on the pharmacokinetics of elinzanetant.

A total of 33 subjects were divided into four groups: Group A, comprising 8 subjects with mild hepatic impairment, and their matched Control A group with 8 individuals with normal hepatic function; and Group B, consisting of 9 subjects with moderate hepatic impairment, and their matched Control B with 8 individuals with normal hepatic function. Each subject received 120 mg of elinzanetant (two 60 mg soft gel capsules) orally once daily on Day 1 and subsequently from Days 3 to 8. The multiple dose design was selected to accommodate potential drug exposure increase due to accumulation and a potential time-dependent pharmacokinetic profile following multiple dosing.

Results

The total elinzanetant C_{max} and $AUC_{(0\text{-}tlast)}$ after a single dose, as well as C_{max} at steady state ($C_{max,\,md}$) and AUC over 24 hours at steady state ($AUC_{0\text{-}24,\,md}$) after multiple doses across all treatment groups are presented in Table 152.

Table 152. Assessment of Effect of Hepatic Functions on Elinzanetant Total Concentration in Plasma, Study 21668

Parameter	Comparison	N	Geom. LS Mean	90% CI for the ratio	Geom. CV(%)
AUC(0-t_{last}) (µg·h/L)	A/B	16	1.2953	[0.9567; 1.7537]	36.83
	C/D	17	2.1262	[1.5839; 2.8541]	
$AUC(0\text{-}24)_{md}$ (µg·h/L)	A/B	16	1.4533	[1.0362; 2.0381]	41.39
	C/D	17	2.3422	[1.6701; 3.2848]	
C_{max} (µg/L)	A/B	16	1.0580	[0.7643; 1.4645]	39.72
	C/D	17	1.8643	[1.3591; 2.5571]	
$C_{max,md}$ (µg/L)	A/B	16	1.1635	[0.8086; 1.6741]	44.81
	C/D	17	2.3192	[1.6118; 3.3371]	

(A): Group A – Child-Pugh A; (B): Control A; (C): Group B – Child-Pugh B; (D): Control B.
Source: Applicant's clinical pharmacology summary, table 2-24
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo., geometric; LS, least squares; md, multiple dose; N, number of subjects; t_{last}, time of the last quantifiable concentration

The Applicant reported that the unbound exposure of elinzanetant was marginally increased in subjects with mild or moderate hepatic impaired function compared to those with normal hepatic function (Table 153).

Table 153. Assessment of Effect of Hepatic Impairment on Elinzanetant Unbound Concentration in Plasma, Study 21668

Parameter	Comparison	Geom. LS Mean	90% CI for the Ratio
$C_{max,md,u}$ (µg/L)	A/B	1.08	0.72; 1.62
	C/D	1.07	0.71; 1.63
$AUC_{(0\text{-}24)md,u}$ (µg.h/L)	A/B	1.35	0.90; 2.02
	C/D	1.08	0.72; 1.62

Source: Applicant summary of clinical pharmacology.
(A): Group A- Child-Pugh A; (B): Control A; (C): Group B- Child-Pugh B; (D): Control B
Total and unbound exposures of the metabolites M18/M21, M27, M30/34 (C_{max},md, $AUC_{(0\text{-}24)}$md) were not significantly changed in subjects with mild or moderate hepatic function as shown in Table 154, Table 155, and Table 156.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo., geometric; LS, least squares; md, multiple dose; N, number of subjects; t_{last}, time of the last quantifiable concentration

Table 154. Assessment of Effect of Hepatic Functions on Metabolite M18/21 of Elinzanetant, Total and Unbound Concentration in Plasma, Study 21668

	Parameter	Comparison	Geom. LS Mean	90% CI for the ratio	Geom. CV(%)
BAY3462934 (M18/M21)	$AUC(0\text{-}t_{last})_u$ (µg·h/L)	Group A / Control A	1.3834	[1.0116 ; 1.8917]	38.12
		Group B / Control B	0.9419	[0.6949 ; 1.2768]	
	$AUC(0\text{-}t_{last})$ (µg·h/L)	Group A / Control A	1.0639	[0.7609 ; 1.4874]	41.03
		Group B / Control B	0.7117	[0.5319 ; 0.9857]	
	$AUC(0\text{-}24)_{md,u}$ (µg·h/L)	Group A / Control A	1.4119	[1.0689 ; 1.8650]	33.62
		Group B / Control B	0.9966	[0.7545 ; 1.3163]	
	$AUC(0\text{-}24)_{md}$ (µg·h/L)	Group A / Control A	1.0858	[0.7418 ; 1.5893]	47.13
		Group B / Control B	0.7716	[0.5271 ; 1.1293]	
	$C_{max,u}$ (µg/L)	Group A / Control A	1.2249	[0.9035 ; 1.6606]	37.00
		Group B / Control B	0.8734	[0.6498 ; 1.1740]	
	C_{max} (µg/L)	Group A / Control A	0.9420	[0.6998 ; 1.2679]	36.07
		Group B / Control B	0.6599	[0.4944 ; 0.8808]	
	$C_{max,md,u}$ (µg/L)	Group A / Control A	1.1223	[0.8539 ; 1.4750]	32.98
		Group B / Control B	0.9743	[0.7414 ; 1.2805]	
	$C_{max,md}$ (µg/L)	Group A / Control A	0.8631	[0.6427 ; 1.1589]	35.72
		Group B / Control B	0.7544	[0.5618 ; 1.0130]	

Source: Applicant's response to FDA's information request dated January 7, 2025, table 2-6
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo., geometric; LS, least squares; md, multiple dose; N, number of subjects; t_{last}, time of the last quantifiable concentration

Table 155. Assessment of Effect of Hepatic Functions on Metabolite M27 of Elinzanetant, Total and Unbound Concentration in Plasma, Study 21668

	Parameter	Comparison	Geom. LS Mean	90% CI for the ratio	Geom. CV(%)
BAY3462932 (M27)	$AUC(0\text{-}t_{last})_u$ (µg·h/L)	Group A / Control A	1.2056	[0.9014 ; 1.6124]	35.25
		Group B / Control B	1.0226	[0.7709 ; 1.3566]	
	$AUC(0\text{-}t_{last})$ (µg·h/L)	Group A / Control A	1.0156	[0.7701 ; 1.3395]	33.46
		Group B / Control B	0.8961	[0.6847 ; 1.1726]	
	$AUC(0\text{-}24)_{md,u}$ (µg·h/L)	Group A / Control A	1.2040	[0.8475 ; 1.7105]	43.10
		Group B / Control B	1.1103	[0.7815 ; 1.5773]	
	$AUC(0\text{-}24)_{md}$ (µg·h/L)	Group A / Control A	1.0143	[0.7251 ; 1.4189]	41.05
		Group B / Control B	0.9424	[0.6737 ; 1.3183]	
	$C_{max,u}$ (µg/L)	Group A / Control A	1.0298	[0.7934 ; 1.3366]	31.44
		Group B / Control B	0.9993	[0.7756 ; 1.2875]	
	C_{max} (µg/L)	Group A / Control A	0.8675	[0.6780 ; 1.1101]	29.64
		Group B / Control B	0.8756	[0.6891 ; 1.1126]	
	$C_{max,md,u}$ (µg/L)	Group A / Control A	1.0513	[0.7630 ; 1.4485]	39.06
		Group B / Control B	1.0656	[0.7734 ; 1.4682]	
	$C_{max,md}$ (µg/L)	Group A / Control A	0.8857	[0.6579 ; 1.1923]	36.05
		Group B / Control B	0.9045	[0.6719 ; 1.2176]	

Source: Applicant's response to FDA's information request dated January 7, 2025, table 2-6
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo., geometric; LS, least squares; md, multiple dose; N, number of subjects; t_{last}, time of the last quantifiable concentration

Table 156. Assessment of Effect of Hepatic Functions on Metabolite M30/34 of Elinzanetant, Total and Unbound Concentration in Plasma, Study 21668

	Parameter	Comparison	Geom. LS Mean	90% CI for the ratio	Geom. CV(%)
BAY3462933 (M30/M34)	$AUC(0\text{-}t_{last})_u$ (µg·h/L)	Group A / Control A	1.1756	[0.8872 ; 1.5579]	34.07
		Group B / Control B	1.0597	[0.8061 ; 1.3932]	
	$AUC(0\text{-}t_{last})$ (µg·h/L)	Group A / Control A	1.1042	[0.8558 ; 1.4248]	30.69
		Group B / Control B	1.1832	[0.9236 ; 1.5157]	
	$AUC(0\text{-}24)_{md,u}$ (µg·h/L)	Group A / Control A	1.1799	[0.8934 ; 1.5583]	33.59
		Group B / Control B	1.0416	[0.7887 ; 1.3757]	
	$AUC(0\text{-}24)_{md}$ (µg·h/L)	Group A / Control A	1.1083	[0.8280 ; 1.4834]	35.31
		Group B / Control B	1.1813	[0.8826 ; 1.5812]	
	$C_{max,u}$ (µg/L)	Group A / Control A	0.9147	[0.6947 ; 1.2044]	33.25
		Group B / Control B	0.8431	[0.6453 ; 1.1015]	
	C_{max} (µg/L)	Group A / Control A	0.8592	[0.6570 ; 1.1235]	32.38
		Group B / Control B	0.9413	[0.7253 ; 1.2217]	
	$C_{max,md,u}$ (µg/L)	Group A / Control A	0.9655	[0.7145 ; 1.3048]	36.54
		Group B / Control B	0.9738	[0.7206 ; 1.3160]	
	$C_{max,md}$ (µg/L)	Group A / Control A	0.9069	[0.6698 ; 1.2280]	36.79
		Group B / Control B	1.1044	[0.8156 ; 1.4954]	

Source: Applicant's response to FDA's information request dated January 7, 2025, table 2-6
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; Geo., geometric; LS, least squares; M, metabolite; md, multiple dose; N, number of subjects; t_{last}, time of the last quantifiable concentration

Elinzanetant is highly bound to plasma protein. No effect on unbound fraction was observed in subjects with mild hepatic impairment function (geometric mean fu: 0.18 [90% CI: 0.09; 0.27]) relative to heathy control (geometric mean fu: 0.17, 90% CI: 0.11-0.26). In contrast, an approximately 2-fold lower geometric mean of fu (0.10, 90% CI: 0.04-0.2) was observed in subjects with moderate hepatic impairment function compared to the matched healthy control group (0.235, 90% CI: 0.151-0.326).

14.2.4. Clinical DDI Studies

14.2.4.1. DDI Between Elinzanetant and Itraconazole, Study 21679 (R-13587)

Title

An open-label single-sequence crossover study in healthy female subjects to investigate the effect of an inhibitor of cytochrome P450 3A and p-glycoprotein (itraconazole) on exposure to elinzanetant (NT-814)

Study Design

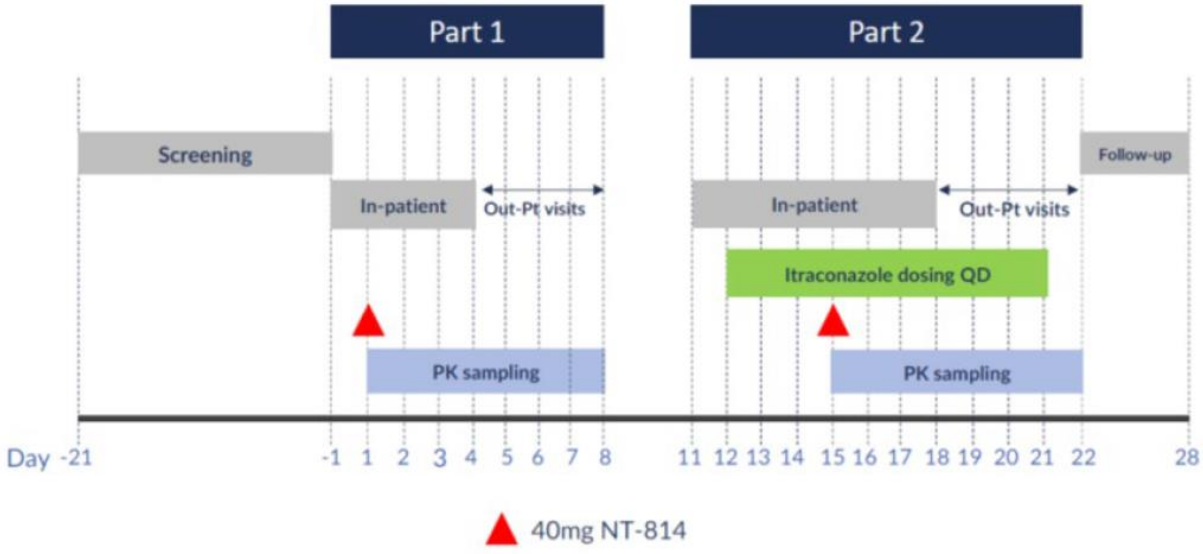
All subjects received a single oral dose of NT-814 40 mg alone (Reference) in Part 1 and then a second single oral dose of NT-814 40 mg in the presence of itraconazole (Test) in Part 2.

In Part 1, NT-814 was administered 90 minutes after the start of a standard breakfast on Study Day 1. Blood samples were collected at intervals up to 168 hours after dosing for assay of plasma concentration of NT-814. After a washout period, subjects entered Part 2 of the study. Subjects received itraconazole 200 mg (2x100 mg capsules) once daily in the morning from Study Days 12 to 21. All doses of itraconazole were taken following an overnight fast of at least 10 hours and 30 minutes after the start of a standard breakfast. On Study Day 15, NT-814 was administered 90 minutes after the start of the standard breakfast, i.e., 60 minutes after the administration of itraconazole. Blood samples were collected at the same intervals relative to the NT-814 as in Part 1 for assay of plasma concentration of NT-814.

Sentinel dosing applied to Part 2, with two subjects receiving the combination treatment (itraconazole and NT-814) at least 24 hours before the main group of subjects. Dosing of the remaining subjects only proceeded after satisfactory review of safety data from the sentinel subjects collected up to 24 hours after dosing.

The overall study design is illustrated in Figure 52.

Figure 52. Study Design, Study 21679



Out-Pt=out-patient; PK=pharmacokinetic; QD=once daily.
Source: Figure 9.1 of CSR

Study Population

In total, including the 2 sentinel subjects, 16 healthy female subjects aged 40 to 65 years inclusive were enrolled and analyzed.

PK Results

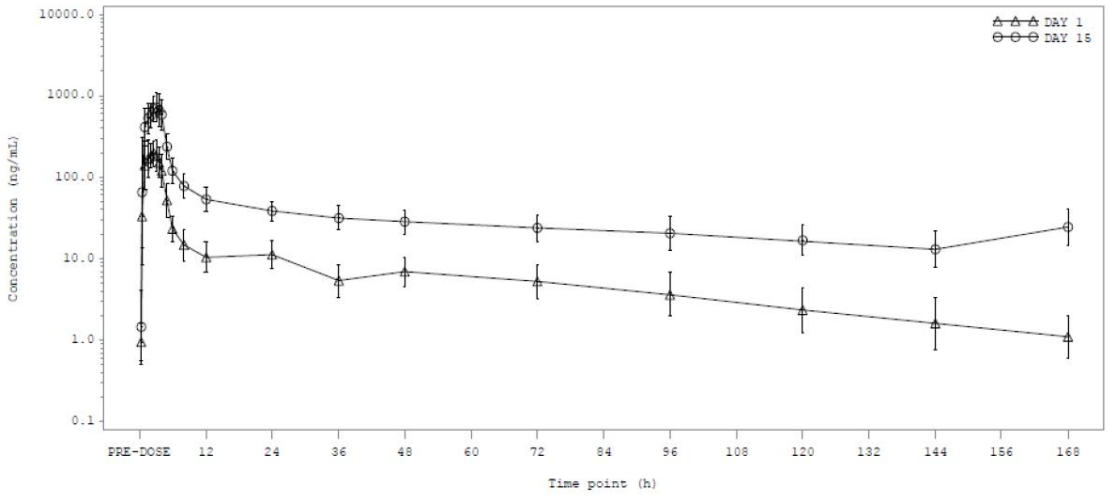
An overall summary is provided in Table 157. Mean profiles for NT-814 concentration-time data are presented in Figure 53.

Table 157. Summary of Pharmacokinetic Parameters of NT-814 by Treatment, PK Set, Study 21679, (FAS)

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{last} (ng·h/mL)	AUC_{inf} (ng·h/mL)	CL/F (mL/min)	V_z/F (L)
40 mg NT-814	n	16	16	16	16	16	16	16
	Geometric mean±gSD	253±1.48	NC	52.429±1.287	1510±1.49	1690±1.45	395±1.45	1790±1.48
	gCV%	40.7	NC	25.6	41.6	38.8	38.8	40.7
	Median	277	2.250	53.154	1590	1690	396	1470
	Range	114 to 469	1.00 to 4.00	32.96 to 82.13	664 to 2950	814 to 3420	195 to 819	1210 to 4040
40 mg NT-814 + 200 mg Itraconazole	n	16	16	16	16	16	16	16
	Geometric mean±gSD	835±1.41	NC	97.224±1.279	6990±1.37	10700±1.54	62.6±1.54	527±1.36
	gCV%	35.5	NC	25.0	32.0	45.0	45.0	31.1
	Median	863	2.750	94.030	6750	10400	64.2	523
	Range	390 to 1510	1.00 to 4.00	65.40 to 153.42	3970 to 14,000	5660 to 27,000	24.7 to 118	328 to 1010

Source: Table 14.2.2.1.1.
AUC=area under the concentration versus time curve; AUC_{inf}=AUC from time of dosing extrapolated to infinity; AUC_{last}=AUC from time of dosing to time after dosing of last quantifiable concentration; CL/F=apparent clearance after extravascular administration; C_{max}=maximum observed concentration; gCV%=geometric coefficient of variation; gSD=geometric standard deviation; h=hour(s); NC=not calculated; PK=pharmacokinetic; $t_{1/2}$=terminal elimination half-life; t_{max}=time after dosing of maximum observed concentration; V_z/F=apparent volume of distribution after extravascular administration.
Note: PK parameters were calculated from all PK concentration data across all time points.

Figure 53. Plasma Concentration-Time Profiles for NT-814, PK Set, Study 21679



Source: Figure 14.2.3.2.
PK=pharmacokinetic; SD=standard deviation.
Note: Data presented are the geometric mean±geometric SD.

The C_{max} was 3.3-fold higher and AUC_{inf} was 6.3-fold higher with NT-814+itraconazole than with NT-814 alone. An overall summary is provided in Table 158.

Table 158. Assessment of the Effect of Itraconazole on Pharmacokinetic Parameters of NT-814, PK Set, Study 21679

Treatment	40 mg NT-814 (n=16)	40 mg NT-814+ 200 mg itraconazole (n=16)	40 mg NT-814+ 200 mg itraconazole/40 mg NT-814
	Adjusted Geometric Mean[a]		Adjusted GMR (90% CI)[a]
C_{max} (ng/mL)[b]	253	835	3.31 (2.74, 4.00)
t_{max} (h)[a]	2.250	2.750	0.25 (0.00, 0.75)[c]
Full Analysis[d]			
AUC_{last} (ng·h/mL)[b]	1510	6990	4.63 (3.88, 5.52)
AUC_{inf} (ng·h/mL)[b]	1690	10700	6.32 (5.36, 7.44)
Sensitivity Analysis[e]			
AUC_{last} (ng·h/mL)[b]	1490	6520	4.37 (3.66, 5.21)
AUC_{inf} (ng·h/mL)[b]	1680	8140	4.84 (4.02, 5.83)

Source: Table 14.2.2.2.1, Table 14.2.2.2.2 and Table 14.2.2.3.1.
AUC=area under the concentration versus time curve; AUC_{inf}=AUC from time of dosing extrapolated to infinity; AUC_{last}=AUC from time of dosing to time after dosing of last quantifiable concentration; CI=confidence interval; C_{max}=maximum observed concentration; GMR=geometric mean ratio; h=hour(s); PK=pharmacokinetic(s); t_{max}=time after dosing of maximum observed concentration.

[a] For t_{max}, values are median and difference in median (90% CI) for the comparison between NT-814 alone and NT-814+itraconazole.
[b] Results obtained from mixed effects model of natural log-transformed PK parameters including terms: treatment as a fixed effect and subject as a random effect.
[c] P-value for null hypothesis that the Hodges-Lehmann estimate is zero using non-parametric Wilcoxon signed-rank test: 0.26. Hodges-Lehmann median difference is not necessarily the same as the difference between medians.
[d] PK parameters were calculated from all PK concentration data across all time points.
[e] PK parameters were calculated from all PK concentration data up to and including 144 hours, i.e. excluding the 168-hour sample.

14.2.4.2. DDI Between Elinzanetant and Carbamazepine, Study 21667 (PH-42357)

Title

Open-label, fixed sequence crossover study to investigate the effects of carbamazepine on the pharmacokinetics of elinzanetant (BAY 3427080) in healthy subjects

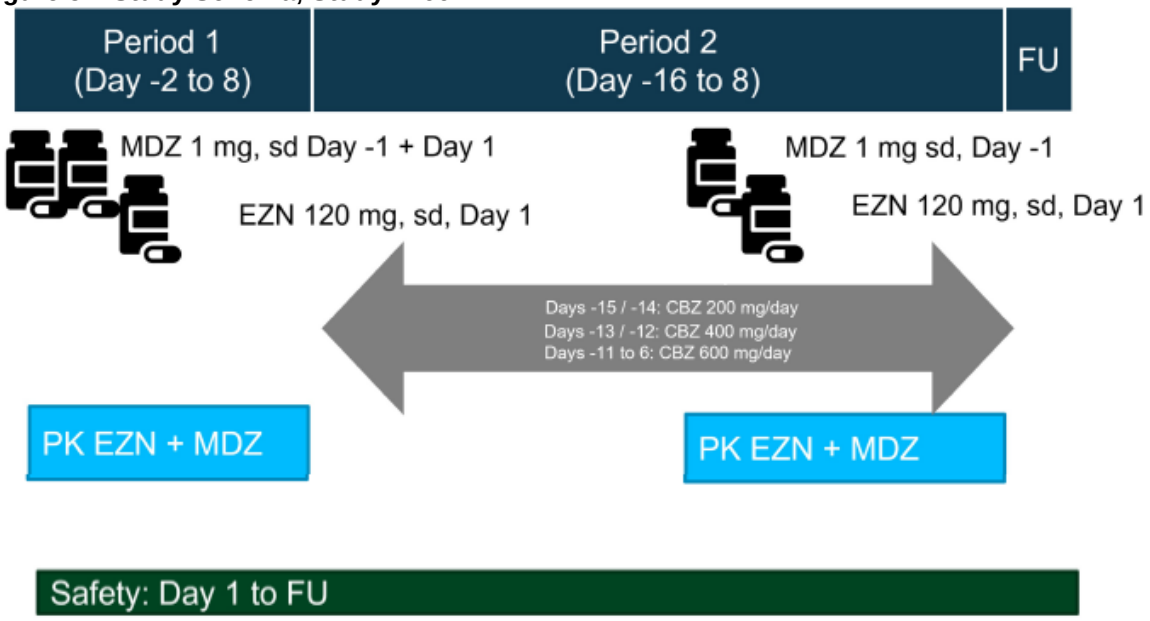
Study Design

The study evaluated the drug-drug-interaction potential of carbamazepine (precipitant, inducer of cytochrome CYP3A4) on the pharmacokinetics of elinzanetant (object).

Midazolam was used as probe substrate (object) for CYP3A4 to confirm CYP3A4 induction by carbamazepine and to investigate the inhibitory potential of elinzanetant (precipitant) on CYP3A4.

Study Schema is shown in Figure 54.

Figure 54. Study Schema, Study 21667



Abbreviations: FU: Follow-up EZN: Elinzanetant; MDZ: midazoplam, CBZ: carbamazepine; PK: pharmacokinetics, sd: single dose

Source: Figure 7-1 of CSR

In Period 1, midazolam was administered alone, and the pharmacokinetics of midazolam was assessed on Day -1, while on Day 1, midazolam and elinzanetant were coadministered and the pharmacokinetics for both drugs were assessed. In Period 2, carbamazepine was given from Day -15 until Day 6. Midazolam was administered on Day -1. Elinzanetant was administered on Day 1, and the pharmacokinetics for elinzanetant was assessed.

Study Population

Sixteen subjects were treated with at least one dose of study medication (120 mg elinzanetant/1 mg midazolam). Two subjects did not complete Period 2 due to TEAEs and thus were excluded from the PK analysis set for elinzanetant but remained in the analysis set for midazolam.

Treatment Administered

Table 159. Treatment Administered, Study 21667

Day	Dose	Amount / Formulation	Route of administration	Frequency of administration	No. of participants planned
Period 1, Day -1	1 mg midazolam	0.5 mL midazolam solution 2 mg/mL	oral	single dose (morning)	16
Period 1, Day 1	120 mg elinzanetant	2 x 60 mg elinzanetant soft gel capsules	oral	single dose (morning)	16
	1 mg midazolam	0.5 mL midazolam solution 2 mg/mL			
Period 2, Day -15 / Day -14	200 mg carbamazepine	200 mg modified release tablet (2 x 100 mg (half tablet))	oral	twice daily (morning and evening)	16
Period 2, Day -13 / Day -12	400 mg carbamazepine	200 mg modified release tablet (2 x 1 tablet)	oral	twice daily (morning and evening)	16
Period 2, Day -11 / Day -2	600 mg carbamazepine	300 mg modified release tablet (2 x 1 tablet)	oral	twice daily (morning and evening)	16
Period 2, Day -1	1 mg midazolam	0.5 mL midazolam solution 2 mg/mL	oral	single dose (morning)	16
	600 mg carbamazepine	300 mg modified release tablet (2 x 1 tablet)	oral	twice daily (morning and evening)	
Period 2, Day 1	120 mg elinzanetant	2 x 60 mg elinzanetant soft gel capsules	oral	single dose (morning)	16
	600 mg carbamazepine	300 mg modified release tablet (2 x 1 tablet)	oral	twice daily (morning and evening)	
Period 2, Day 2 to Day 6	600 mg carbamazepine	300 mg modified release tablet (2 x 1 tablet)	oral	twice daily (morning and evening)	16

Source:

Table 160. Food and Drink Before and After Dosing of Elinzanetant/Midazolam, Study 21667

Time	Food and drink
From 10 h prior to dosing of elinzanetant or midazolam	No food
From 2 h prior to dosing of elinzanetant or midazolam	Nothing to drink
Time point of elinzanetant or midazolam dosing	**240 mL non-carbonated water** at room temperature together with the study intervention (at dosing timepoint for elinzanetant)
Until 2 h after dosing with midazolam	Nothing by mouth
Until 4 h after dosing with elinzanetant	Nothing by mouth

Source:

PK Results

Pharmacokinetics of Elinzanetant With and Without Carbamazepine

Plasma concentrations of elinzanetant (BAY 3427080) (calculated if ≥2/3 of individual values > LLOQ) without and with subsequent intake of carbamazepine up to 168 h following administration were evaluated. Table 161 below summarizes the PK parameters from the noncompartmental analysis.

Table 161. Summary Statistics of Noncompartmental PK Parameters of Elinzanetant

Parameter (Unit)	Elinzanetant without carbamazepine (N=14)	Elinzanetant with carbamazepine (N=14)
AUC (µg·h/L)	7110/57.6 (2340 – 17300)	2550/45.9 (1160 – 5020)
AUC(0-t_{last}) (µg·h/L)	6960/55.8 (2310 – 15400)	2500/46.7 (1130 – 4980)
C_{max} (µg/L)	1470/45.9 (665 – 2900)	820/43.3 (339 – 1380)
$t_{1/2}$ (h)	32.9/35.4 (16.6 – 67.2)	21.5/31.4 (14.6 – 50.7)
t_{max} (h)*	1.00 (0.750 – 3.50)	1.50 (0.750 – 2.50)
CL/F	16.9/57.6 (6.93 – 51.4)	47.0/45.9 (23.9 – 103)
V_z/F	801/30.8 (470 – 1380)	1460/42.3 (716 – 3010)

* median (range)
Displayed values are based on 3 valid digits. Raw individual values were used for the calculation of above descriptive statistics.
Source: Table 9-1 of the CSR
Geometric Mean/CV [Range] in Plasma; PKS1, N=14
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

Geometric mean ratios for AUC and C_{max} of elinzanetant and its metabolites are shown below (Table 162).

Table 162. Assessment of Drug-Drug Interaction With Carbamazepine, Point Estimates and 90% CIs of the Treatment Ratios "Elinzanetant With Carbamazepine/Elinzanetant Without Carbamazepine" of Elinzanetant and its Metabolites

Parameter	Ratio Elinzanetant with carbamazepine/ elinzanetant without carbamazepine for	Geo. LS mean	90% confidence interval	Geo. CV (%)
AUC	Elinzanetant	0.3591	[0.3144 ; 0.4101]	20.05
	M18/M21 (BAY 3462934)	0.4141	[0.3697 ; 0.4639]	17.08
	M27 (BAY 3462932)	0.3511	[0.3028 ; 0.4027]	22.41
	M30/M34 (BAY 3462933)	0.2958	[0.2560 ; 0.3417]	21.83
C_{max}	Elinzanetant	0.5572	[0.5032 ; 0.6171]	15.33
	M18/M21 (BAY 3462934)	0.7771	[0.6832 ; 0.8839]	19.41
	M27 (BAY 3462932)	0.6343	[0.5630 ; 0.7146]	17.96
	M30/M34 (BAY 3462933)	0.6316	[0.5567 ; 0.7166]	19.03

Source: Table 9-7 of the CSR
PKS1, N=14
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geo., geometric; LS, least squares; M, metabolite; N, number of subjects

The analysis indicates a reduction of AUC to elinzanetant by 64% by the concomitant use of 600 mg carbamazepine daily. C_{max} decrease was less pronounced, with a reduction of 44%.

For the metabolites M18/M21, M27, and M30/M34, the analysis indicated similar reductions by 59%, 65%, and 70%, respectively, for AUC, and by 22%, 37%, and 37%, respectively, for C_{max}.

Pharmacokinetics of Midazolam With and Without Elinzanetant

For midazolam, the administration of 1 mg alone was compared to the concomitant administration of midazolam together with 120 mg elinzanetant. Summary statistics from noncompartmental PK analysis are shown in Table 163.

Table 163. Summary Statistics of Noncompartmental PK Parameters of Midazolam in Plasma

Parameter (Unit)	Midazolam alone (N=16)	Midazolam with elinzanetant (N=16)
AUC (µg·h/L)	11.7/47.6	16.9/52.8
	(6.27 – 33.2)	(7.13 – 50.4)
AUC(0-t_{last}) (µg·h/L)	11.3/44.4	16.1/48.4
	(6.21 – 28.8)	(7.00 – 40.3)
C_{max} (µg/L)	4.20/35.5	4.81/37.2
	(2.64 – 8.90)	(2.59 – 9.54)
$t_{1/2}$ (h)	5.56/20.8	5.97/28.0
	(4.48 – 9.41)	(3.93 – 12.1)
t_{max} (h)	0.750	0.750
	(0.500 – 1.00)	(0.500 – 1.50)

* median (range)
Displayed values are based on 3 valid digits. Raw individual values were used for the calculation of above descriptive statistics.
Source: Table 9-6 of the CSR
Geometric Mean/%CV [Range]; PKS2, N=16
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; PK, pharmacokinetic; t1/2, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration

Point estimates and 90% CIs for the ratio 'midazolam with elinzanetant / midazolam without elinzanetant' for both AUC and C_{max} are shown below in Table 164.

Table 164. Assessment of Drug-Drug Interaction With Elinzanetant, Point Estimates and 90% Confidence Intervals of Treatment Ratios for Midazolam

Parameter	Ratio	Geo. LS mean	90% confidence interval	Geo. CV (%)
AUC	Midazolam with elinzanetant / midazolam alone	1.4484	[1.3667 ; 1.5350]	9.38
C_{max}	Midazolam with elinzanetant / midazolam alone	1.1432	[1.0637 ; 1.2286]	11.67

Source: Table 9-9 of the CSR
PKS2, N=16
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geo., geometric; LS, least squares; N, number of subjects

According to the analysis, midazolam C_{max} and AUC were increased by 14% and 45%, respectively.

Pharmacokinetics of Midazolam With and Without Carbamazepine

After a single dose of 1 mg midazolam alone on Day -1 of Period 1, geometric mean AUC was 11.7 µg·h/L and geometric mean C_{max} 4.20 µg/L. When midazolam was administered on top of multiple doses of carbamazepine on Day -1 of Period 2, AUC and C_{max} were significantly decreased, with values of 3.29 µg·h/L and 1.85 µg/L, respectively. Interindividual variability was moderate with geometric mean CVs for AUC and C_{max} ranging from 35.5% to 48.5%.

Concomitant use of 600 mg carbamazepine daily reduced midazolam exposure by 56% (C_{max}) and 72% (AUC), indicating carbamazepine is a moderate CYP3A inducer at the dose tested.

14.2.4.3. DDI Between Elinzanetant and Midazolam, Study 21840 (PH-42574)

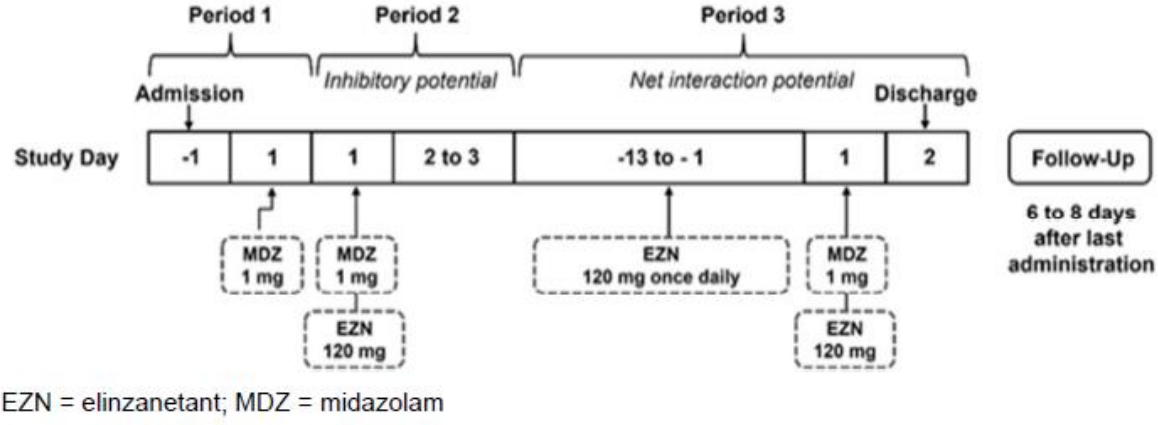
Title

Open-label, fixed sequence crossover study to investigate the effects of elinzanetant (BAY 3427080) on the pharmacokinetics of midazolam in healthy male and female subjects.

Study Design

A schema of the overall study design is presented in Figure 55.

Figure 55. Study Design, Study 21840



EZN = elinzanetant; MDZ = midazolam

Source: CSR, figure 7-1

In Period 1, midazolam was administered alone on Day 1, and pharmacokinetics of midazolam was assessed. In Period 2, both midazolam and elinzanetant were given on Day 1 and pharmacokinetics for midazolam was assessed on Days 1 to 2 and for elinzanetant on Days 1 to 3. In Period 3, elinzanetant was administered on Day -13 to Day -1 and both elinzanetant and midazolam were given on Day 1. Pharmacokinetics for elinzanetant was evaluated on Days -13 to 2 and for midazolam on Days 1 to 2.

Study Population

A total of 15 healthy male and female subjects were assigned to treatment sequence (midazolam → midazolam + elinzanetant [single dose] → midazolam + elinzanetant [multiple doses]). All 15 subjects completed the study.

Treatment Administered

Table 165. Treatment Administered, Study 21840

Arm Title	Period 1	Period 2	Period 3
Arm Type	Experimental	Experimental	Experimental
Arm Description	On Study Day 1 of Period 1, participants received a single dose of 1 mg midazolam.	On Study Day 1 of Period 2, participants received a single dose of 1 mg midazolam and a single dose of 120 mg elinzanetant.	Participants were dosed once daily with 120 mg elinzanetant from Study Day -13 to Study Day 1 (= 14 days) of Period 3. On Study Day 1 of Period 3, also a single dose of 1 mg midazolam was administered.
Associated Intervention Labels	Reference Drug	Test Drug Reference Drug	Test Drug Reference Drug

Source: Applicant's submitted Study 21840 CSR

PK Results

Results for Midazolam

Table 166 summarizes the pharmacokinetic parameters of midazolam.

Table 166. Pharmacokinetic Parameters of Midazolam in Plasma

Parameter	Unit	Midazolam (N=15)	Midazolam + elinzanetant (SD) (N=15)	Midazolam + elinzanetant (MD) (N=15)
AUC	µg*h/L	10.4 / 59.1 (3.64-30.9)	15.6 / 59.7 (4.96-44.4)	18.7 / 46.6 (8.41-34.4)
AUC(0-t_{last})	µg*h/L	10.1 / 57.3 (3.62-28.8)	15.0 / 57.8 (4.91-40.3)	18.0 / 44.2 (8.40-31.2)
C_{max}	µg/L	4.21 / 39.0 (2.65-9.25)	4.85 / 42.5 (2.42-9.65)	6.29 / 32.4 (3.43-9.65)
$t_{1/2}$	h	5.03 / 30.8 (2.74-8.90)	5.53 / 29.6 (3.16-7.62)	5.15 / 32.3 (2.95-8.51)
t_{max}[a]	h	0.50 (0.500-0.767)	0.617 (0.567-1.08)	0.750 (0.500-1.00)
CL/F	L/h	96.3 / 59.1 (32.4- 275)	64.0 / 59.7 (22.5-202)	53.6 / 46.6 (29.1-119)
V_Z/F	L	699 / 49.7 (313-1410)	511 / 55.3 (229-1270)	398 / 31.9 (207-665)

[a] median (range)
Displayed values are based on 3 valid digits. Raw individual values were used for the calculation of above descriptive statistics.
Source: Table 9-1 of the CSR
Geometric Mean/%CV [Range]
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; M, metabolite; MD, multiple dose; N, number of subjects; SD, single dose; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

Results for Elinzanetant and Its Metabolites

Table 167 summarizes the pharmacokinetic parameters of elinzanetant.

Table 167. Pharmacokinetic Parameters of Elinzanetant in Plasma

Parameter	Unit	N	Midazolam + elinzanetant (SD) (N=15)	N	Midazolam + elinzanetant (MD) (N=15)
AUC	µg*h/L	7	4180 / 57.2 (1820-8030)		
AUC(0-t_{last})	µg*h/L	15	5130 / 56.6 (1780-13800)		
AUC(0-24)	µg*h/L	15	4430 / 52.6 (1680-11200)		
AUC(0-24)$_{md}$	µg*h/L			15	6910 / 54.8 (2990-15100)
C_{max}	µg/L	15	1370 / 46.0 (744-3420)	15	
$C_{max,md}$	µg/L				1810 / 49.1 (870-3950)
$t_{1/2}$	h	7	14.1 / 14.3 (12.2-17.1)		
t_{max}[a]	h	15	1.05 (0.750-2.50)		
$t_{max,md}$[a]	h			15	1.00 (0.500-2.50)
R_AAUC(0-24)		15			1.56 / 29.7 (0.888 – 2.86)
$R_A C_{max}$		15			1.33 / 33.3 (0.696 – 2.59)

[a] median (range)
Displayed values are based on 3 valid digits. Raw individual values were used for the calculation of above descriptive statistics.
Source: Table 9-2 of the CSR
Values presented as geometric mean/STD (range); (PKS, n=15)
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; M, metabolite; MD, multiple dose; N, number of subjects; R_A, accumulation ratio; SD, single dose; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration

Results for M27, M18/21 and M30/24

Table 168, Table 169, and Table 170 summarize the pharmacokinetic parameters of M27, M18/21, and M30/34, respectively.

Table 168. Pharmacokinetic Parameters of M27 in Plasma

Parameter	Unit	N	Midazolam + elinzanetant (SD) (N=15)	N	Midazolam + elinzanetant (MD) (N=15)
AUC	µg*h/L	8	1370 / 53.9 (472-2130)		
AUC(0-t_{last})	µg*h/L	15	1460 / 39.8 (458-1940)		
AUC(0-24)	µg*h/L	15	1200 / 36.4 (418-1650)		
$AUC(0\text{-}24)_{md}$	µg*h/L			15	2160 / 39.3 (779-4290)
C_{max}	µg/L	15	217 / 25.9 (128-298)		
$C_{max,md}$	µg/L			15	288 / 24.6 (193-448)
$t_{1/2}$	h	8	12.3 / 19.4 (8.40-16.0)		
t_{max}[a]	h	15	1.50 (1.00-2.50)		
$t_{max,md}$[a]	h			15	1.50 (1.00-2.50)
R_AAUC(0-24)		15			1.80 / 25.3 (1.31-3.08)
R_AC_{max}		15			1.32 / 20.3 (0.962-1.98)

[a] median (range)
Displayed values are based on 3 valid digits. Raw individual values were used for the calculation of above descriptive statistics.
Source: Table 9-3 of the CSR
Values Presented as Geometric Mean/STD (Range); PKS, N=15
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; M, metabolite; MD, multiple dose; N, number of subjects; R_A, accumulation ratio; SD, single dose; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration

Table 169. Pharmacokinetic Parameters of M18/21 in Plasma

Parameter	Unit	N	Midazolam + elinzanetant (SD) (N=15)	N	Midazolam + elinzanetant (MD) (N=15)
AUC	µg*h/L	14	2010 / 39.9 (653-2820)		
AUC(0-t_{last})	µg*h/L	15	1860 / 38.9 (631-2610)		
AUC(0-24)	µg*h/L	15	1610 / 36.4 (631-2380)		
$AUC(0\text{-}24)_{md}$	µg*h/L			15	2380 / 36.8 (1010-4610)
C_{max}	µg/L	15	288 / 31.9 (175-426)		
$C_{max,md}$	µg/L			15	323 / 31.8 (126-453)
$t_{1/2}$	h	14	11.7 / 32.3 (5.16-17.0)		
t_{max}[a]	h	15	2.00 (1.50-4.12)		
$t_{max,md}$[a]	h			15	2.00 (1.50-3.00)
R_AAUC(0-24)		15			1.48 / 22.5 (1.12-2.74)
R_AC_{max}		15			1.12 / 26.5 (0.721-1.81)

[a] median (range)
Displayed values are based on 3 valid digits. Raw individual values were used for the calculation of above descriptive statistics.
Source: Table 9-4 of the CSR
Values Presented as Geometric Mean/STD (Range); PKS, N=15
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; M, metabolite; MD, multiple dose; N, number of subjects; R_A, accumulation ratio; SD, single dose; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration

Table 170. Pharmacokinetic Parameters of M30/M34 in Plasma

Parameter	Unit	N	Midazolam + elinzanetant (SD) (N=15)	N	Midazolam + elinzanetant (MD) (N=15)
AUC	µg*h/L	15	3930 / 36.6 (1540-5960)		
AUC(0-t_{last})	µg*h/L	15	3760 / 34.9 (1530-5470)		
AUC(0-24)	µg*h/L	15	3250 / 30.8 (1470-4320)		
$AUC(0-24)_{md}$	µg*h/L			15	4540 / 32.6 (2580-8620)
C_{max}	µg/L	15	453 / 21.0 (326-610)		
$C_{max,md}$	µg/L			15	544 / 22.8 (344-828)
$t_{1/2}$	h	15	11.1 / 17.7 (7.88-14.1)		
t_{max}[a]	h	15	1.65 (1.50-4.12)		
$t_{max,md}$[a]	h			15	2.00 (1.50-3.00)
R_AAUC(0-24)		15			1.40 / 19.8 (1.08-2.09)
R_AC_{max}		15			1.20 / 16.8 (0.941-1.65)

[a] median (range)
Displayed values are based on 3 valid digits. Raw individual values were used for the calculation of above descriptive statistics.
Source: Table 9-5 of the CSR
Values Presented as Geometric Mean/Standard Deviation (Range); PKS, N=15
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; M, metabolite; MD, multiple dose; N, number of subjects; R_A, accumulation ratio; SD, single dose; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration

FDA Analysis

- Following coadministration of a single dose of 120 mg elinzanetant, total systemic exposure (AUC) and peak exposure (C_{max}) of 1 mg midazolam increased by 50% and 15%, respectively, compared to midazolam alone.
- Following multiple doses of 120 mg elinzanetant, AUC and C_{max} of 1 mg midazolam increase by 80% and 49%, respectively, compared to midazolam alone.
- AUC_{0-24} and C_{max} of elinzanetant increased by ~50% and ~32%, respectively, after multiple oral doses than after a single dose.
- Exposure of all three metabolites was increased with the approximately same magnitude as the parent drug after multiple dosing.

14.2.4.4. DDI Between Elinzanetant and Dabigatran Etexilate, Study 22081 (PH-42660)

Title

Open-label, fixed sequence crossover study to determine the effects of a single dose of elinzanetant (EZN) on the pharmacokinetics of dabigatran etexilate in healthy subjects

Study Design

The study was conducted in a single-center, nonrandomized, open-label, fixed-sequence, crossover design in healthy male and female subjects aged 18 to 65 years.

The study had two periods. In Period 1, dabigatran etexilate was administered alone on Day 1 and pharmacokinetics of dabigatran was assessed. In Period 2, both dabigatran etexilate and elinzanetant were given on Day 1 and pharmacokinetics for dabigatran and elinzanetant were assessed on Days 1 to 4.

Study Population

A total of 20 healthy male and female subjects were enrolled. All 20 subjects completed the study.

Treatment Administered

All study interventions were administered in the morning (after overnight fasting) with approximately 240 mL of noncarbonated water at room temperature.

Table 171. Treatment Administered, Study 22081

Study intervention	Dose / route of administration	Amount / formulation	Frequency of administration	No. of participants treated
Period 1 Day 1	75 mg DBG orally	1 capsule	single dose	20
Period 2 Day 1	120 mg EZN orally + 75 mg DBG orally	2 capsules + 1 capsule	single dose 30 min between EZN and DBG etexilate administration	20

Source: Applicant's submitted Study 22081 CSR
Abbreviations: DBG, dabigatran; EZN, elinzanetant

PK Results

Results of Dabigatran

Summary statistics of PK parameters of unconjugated and total dabigatran in plasma is provided in Table 172.

Table 172. Summary Statistics of Noncompartmental PK Parameters of Unconjugated and Total Dabigatran in Plasma

Parameter (Unit)	Dabigatran etexilate alone	Dabigatran etexilate with elinzanetant	Dabigatran etexilate alone	Dabigatran etexilate with elinzanetant
	unconjugated		total	
AUC (µg*h/L)	314/78.0 (67.3 – 806)	375/118 (66.8 – 1660)	378 /79.6 (75.5 – 1010)	453/114 (86.8 – 1980)
AUC(0-t_{last}) (µg*h/L)	295/84.7 (54.6 – 797)	352/132 (50.7 – 1660)	359/85.5 (61.6 - 1000)	433/122 (69.5 - 1970)
C_{max} (µg/L)	38.6/82.7 (8.42 – 108)	45.2/122 (7.42 – 261)	44.7/ 82.0 (9.70 - 131)	51.4 /114 (9.79 - 297)
$t_{1/2}$ (hours)	7.00/17.9 (4.59 – 9.66)	6.55/19.6 (3.89 – 9.63)	7.01/22.0 (4.54 – 11.2)	7.02 /17.4 (4.65 – 9.61)
CL/F (L/h)	239/78.0 (93.0 – 1110)	200/118 (45.1 – 1120)	198/79.6 (74.5 - 994)	166/114 (37.9 – 864)
MRT (HOURS)	9.96/14.5 (7.24 – 13.0)	9.67/14.6 (6.63 – 13.2)	9.86/16.2 (6.96 – 13.2)	10.1/13.7 (7.93 – 12.9)
V_z/F (L)	2410/70.8 (885 – 7380)	1890/101 (398 – 8520)	2000/68.8 (796 – 6500)	1680/96.8 (359 – 8010)
t_{max} (hours)*	1.75 (1.00 – 2.50)	2.50 (1.50 – 4.00)	2.00 (1.00 – 3.00)	2.27 (1.50 – 4.00)

* median (range)

Source: Table 9-1 of the CSR
Geom. Mean/CV% [range]; PKS, N=20
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geom., geometric; MRT, mean residence time; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

The logarithms of AUC and C_{max} of dabigatran (unconjugated and total) without and with subsequent intake of EZN were analyzed using an analysis of variance (ANOVA) including treatment (dabigatran alone or administered in combination with EZN) and subject effects. The results are shown in Table 173 and Table 174.

Table 173. Assessment of the Effect of Elinzanetant on Unconjugated Dabigatran in Plasma

Parameter (Unit)	Ratio	Geom. LS mean	90% confidence interval	Geom. CV (%)
AUC (µg*h/L)	Dabigatran etexilate with elinzanetant / Dabigatran etexilate alone	1.1968	[0.7823; 1.8308] [0.1132; 12.6522][a]	91.12
C_{max} (µg/L)	Dabigatran etexilate with elinzanetant / Dabigatran etexilate alone	1.1706	[0.7526; 1.8207] [0.1010; 13.5679][a]	95.94

[a] 95% prediction intervals

Source: Table 9-6 of the CSR
PKS, N=20
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geom., geometric; LS, least squares; N, number of subjects

Table 174. Assessment of the Effect of Elinzanetant on Total Dabigatran in Plasma

Parameter (Unit)	Ratio	Geom. LS mean	90% confidence interval	Geom. CV (%)
AUC (µg*h/L)	Dabigatran etexilate with elinzanetant / Dabigatran etexilate alone	1.1973	[0.7924; 1.8093] [0.1213; 11.8223][a]	87.65
C_{max} (µg/L)	Dabigatran etexilate with elinzanetant / Dabigatran etexilate alone	1.1486	[0.7513; 1.7560] [0.1090; 12.0994][a]	90.94

[a] 95% prediction intervals
Source: Table 9-7 of the CSR
PKS, N=20
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geom., geometric; LS, least squares; N, number of subjects

Results of Elinzanetant and its Metabolites

Geometric mean values of AUC and C_{max} for elinzanetant were 5250 µg*h/L and 1170 µg/L, respectively. PK parameters of elinzanetant and its metabolites were comparable to those observed in other studies after single dose administration of 120 mg elinzanetant.

14.2.4.5. DDI Between Elinzanetant and Rosuvastatin, Study 21666 (PH-42048)

Title

Open-label, one-sequence crossover study to determine the effects of multiple doses of elinzanetant on the pharmacokinetics of rosuvastatin in healthy subjects

Rationale

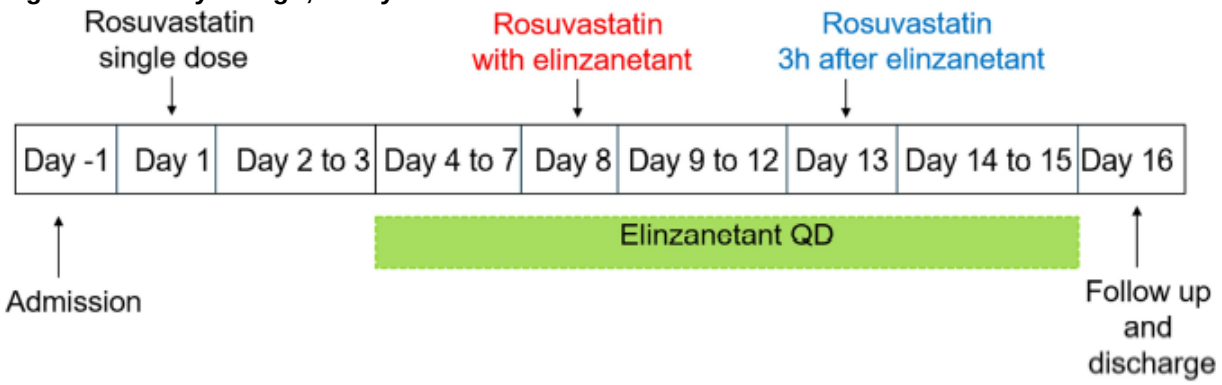
Based on in vitro data, elinzanetant showed a moderate inhibition of human OATP1B1 and BCRP. Therefore, the in vivo interaction potential of elinzanetant as perpetrator on OATP1B1 and BCRP was investigated in the study using rosuvastatin, a sensitive probe substrate for BCRP, OATP1B1/OATP1B3. The potential inhibition of these transporters by elinzanetant 120 mg/day at steady state was evaluated in two different ways:

- To investigate the overall interaction potential including maximum inhibition at the gastrointestinal tract plus systemic inhibition, elinzanetant and rosuvastatin were administered concomitantly at the same time point.
- To investigate overall interaction potential including maximum systemic inhibition and inhibition at the gastrointestinal tract, rosuvastatin was administered staggered, with a time delay of 3 hours after the elinzanetant administration in order to separately assess the potential BCRP-mediated interaction at the gut wall from the potential systemic (hepatic) interactions on OATP1B1 and OATP1B3.

Study Design

This was a single-center, open-label, one-sequence crossover study. Study schema and blood sampling for pharmacokinetics are shown in Figure 56 and Figure 57.

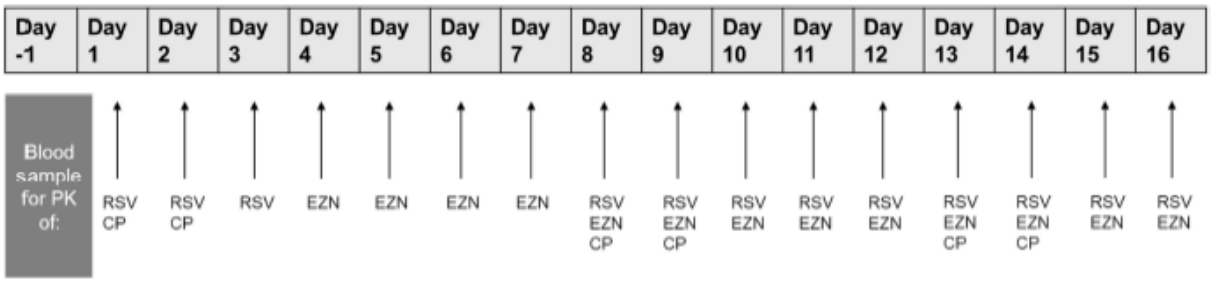
Figure 56. Study Design, Study 21666



Source: CSR, figure 3-1
Abbreviation: QD, once daily

Figure 57. Blood Sampling for Pharmacokinetics, Study 21666

Figure 3–2: Blood sampling for pharmacokinetics



Source: CSR, figure 3-2
Abbreviations: CP, coproporphyrins; CSR, clinical study report; EZN, elinzanetant; PK, pharmacokinetics; RSV, rosuvastatin

Study Population

A total of 16 healthy male subjects were assigned and completed the following treatment in a fixed order.

- Day 1, 5 mg rosuvastatin (Crestor) alone.
- Day 4 to Day 7, 120 mg elinzanetant once daily (morning).
- Day 8, 5 mg rosuvastatin together with 120 mg elinzanetant.
- Day 9 to Day 12, 120 mg elinzanetant once daily (morning).
- Day 13, 5 mg rosuvastatin (Crestor) at 3 h after administration of 120 mg elinzanetant.
- Day 14 to Day 15, 120 mg elinzanetant once daily (morning).

One subject (Subject (b) (6)) was excluded because rosuvastatin PK profile on Day 8 was unplausible low compared to the other profile days which rendered the evaluation of interaction potential impossible.

Treatment Administered

The study interventions and arm assignments are outlined in Table 175.

Table 175. Study Interventions Administered, Study 21666

Study Day	Dose	Amount/ Formulation	Frequency of administration
1	5 mg rosuvastatin	1 x 5 mg tablet	single dose
4 to 7	120 mg elinzanetant	2 x 60 mg capsules / once daily	daily dose
8	120 mg elinzanetant 5 mg rosuvastatin	2 x 60 mg capsules 1 x 5 mg tablet	single dose
9 to 12	120 mg elinzanetant	2 x 60 mg capsules / once daily	daily dose
13	120 mg elinzanetant 5 mg rosuvastatin	2 x 60 mg capsules 1 x 5 mg tablet	single dose
14 to 15	120 mg elinzanetant	2 x 60 mg capsules / once daily	daily dose

Source: Applicant's submitted Study 21666 CSR

PK Results

Results for Rosuvastatin

Summary statistics of noncompartmental PK parameters of rosuvastatin in plasma is provided in Table 176.

Table 176. Summary Statistics of Pharmacokinetic Parameters of Rosuvastatin in Plasma, PK Analysis Set, Study 21666

Parameter (Unit)	Rosuvastatin alone (Day 1) (N=15)	Elinzanetant + Rosuvastatin (Day 8) (N=15)	Elinzanetant + Rosuvastatin (3 h after) (Day 13) (N=15)
AUC (µg·h/L)	22.8/49.6 (10.4-49.4)	27.9/45.4 (14.0-57.7)	19.3/63.0 (7.46-44.3)
AUC(0-t_{last}) (µg·h/L)	21.6/51.9 (9.02-46.3)	27.1/46.3 (13.6-56.7)	18.2/65.4 (6.37-41.1)
C_{max} (µg/L)	2.15/53.4 (0.943-4.60)	2.76/52.3 (1.24-6.17)	1.97/70.8 (0.779-4.48)
$t_{1/2}$ (h)	16.4/39.9 (10.0-35.8)	17.9/26.4 (11.6-32.2)	18.3/20.6 (14.0-26.8)
*t_{max} (h)	5.00 (1.50-5.00)	5.00 (2.00-5.00)	4.00 (2.00-4.00)
AUC Ratio vs rosuvastatin alone	Not applicable	1.23/27.5 (0.833-2.08)	0.848/ 36.9 (0.443-1.46)
C_{max} Ratio vs rosuvastatin alone	Not applicable	1.28/28.3 (0.710-2.02)	0.913/36.0 (0.491-1.69)

Displayed values are based on 3 valid digits.
*t_{max} values are presented by median and range.
Source: Table 5-8 of the CSR
Geometric Mean / Geometric CV% (Range); N=15
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetics; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration

The two-sided 90% confidence intervals for the effect of elinzanetant on rosuvastatin, resulting from an ANOVA model are given in Table 177.

Table 177. Assessment of Effect of Elinzanetant on Rosuvastatin, Noncompartmental, PK Analysis Set, Study 21666

Parameter	Ratio	Geometric LS mean	90% CI	Geometric CV(%)
AUC (µg·h/L)	B/A	1.2257	[1.0729; 1.4003]	21.69
	C/A	0.8481	[0.7423; 0.9689]	
C_{max} (µg /L)	B/A	1.2815	[1.1093; 1.4804]	23.54
	C/A	0.9135	[0.7907; 1.0552]	

(A): Rosuvastatin alone; (B): Elinzanetant + rosuvastatin; (C): Elinzanetant + rosuvastatin (3 h after)
Source: Table 5-14 of the CSR
N=15
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; LS, least squares; N, number of subjects

Elinzanetant increased the AUC and C_{max} of rosuvastatin by 23% and 28%, respectively, when administered together with rosuvastatin. The AUC and C_{max} of rosuvastatin were reduced by 15% and 9%, respectively, when rosuvastatin was administered 3 hours after elinzanetant. These changes in the exposure of rosuvastatin are not considered clinically meaningful.

Results for Elinzanetant

Summary statistics of noncompartmental PK parameters of elinzanetant in plasma is provided in Table 178.

Table 178. Summary Statistics of Pharmacokinetic Parameters of Elinzanetant in Plasma, PK Analysis Set, Study 21666

Parameter (Unit)	Elinzanetant + Rosuvastatin (Day 8) (N=15)	Elinzanetant + Rosuvastatin (3 h after) (Day 13) (N=15)
$AUC(0\text{-}24)_{md}$ (µg·h/L)	8070/46.6 (4140-18800)	8470/43.0 (4320-18400)
$C_{max,md}$ (µg/L)	1410/56.5 (349-3070)	1610/41.0 (779-3260)
* $t_{max,md}$ (h)	1.50 (1.00-4.00)	1.00 (0.95-1.50)

Displayed values are based on 3 valid digits.
* $t_{max,md}$ values for Day 8 and Day 13 are presented by median and range.
Source: Table 5-9 of the CSR
Geometric Mean / Geometric CV% (Range); N=15
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; md, multiple dose; N, number of subjects; PK, pharmacokinetics; t_{max}, time to maximum concentration

14.2.4.6. DDI Between Elinzanetant and Tamoxifen, Study 22004 (PH-42712)

Title

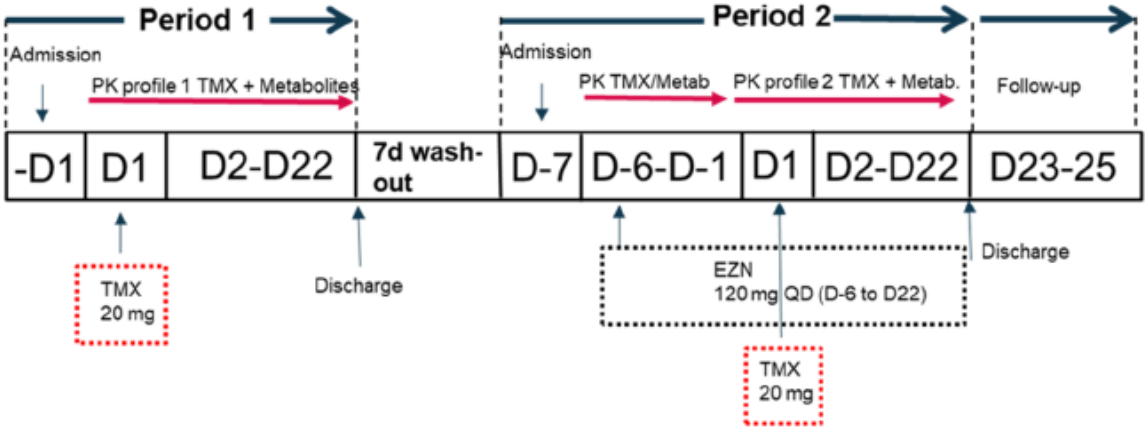
A Phase 1 study with a fixed-sequence, crossover, open-label design to investigate the effects of elinzanetant (BAY 3427080) soft gel capsules on the pharmacokinetics of tamoxifen immediate release tablets in healthy female and male subjects

Study Design

This study was conducted in a single-center with nonrandomized, open-label, fixed-sequence design. The study had two periods separated by a washout period of 7 days. Subjects were administered with a single dose of 20 mg tamoxifen (immediate release tablet), a recommended clinical standard dose, on Day 1 of Period 1. In Period 2, subjects received 28 QD doses of 120 mg elinzanetant (administered as 2 x 60 mg soft capsules) (Day -7 to Day 22) and a single dose of 20 mg tamoxifen (Day 1).

A schema of the overall study design is presented in Figure 58.

Figure 58. Study Design, Study 22004



Source: Applicant's submitted Study 22004 CSR
Additional PK samples for tamoxifen and its main metabolites were collected from D -6 to D -1 of Period 2 to determine the potential carry-over.
Abbreviations: D, study day; EZN, elinzanetant; Metab, metabolites; PK, pharmacokinetics; TMX, tamoxifen

Scientific Rationale for the Study

A fixed treatment sequence was applied, starting with tamoxifen in Period 1 followed by a PK monitoring phase of 21 days (baseline PK profiles). In Period 2, elinzanetant was administered over 6 days (Days -6 to -1) prior to the combined administration with a single dose of tamoxifen on Day 1, to achieve steady-state concentrations and thus maximum inhibition of metabolic enzymes and/or drug transporters. Treatment with elinzanetant alone continued until 21 days after combined administration of elinzanetant with tamoxifen to maintain maximum CYP3A4 and/or drug transporter inhibition during disposition of elinzanetant.

PK samples for tamoxifen and its principal metabolites 4-hydroxytamoxifen, *N*-desmethyltamoxifen, and endoxifen were collected until 21 days (504 hours) after tamoxifen administration in both periods and from Day -6 to Day -1 of Period 2, due to the long half-lives of tamoxifen (~7 days) and endoxifen (approximately 207 hours). Corrected PK parameters were calculated for analytes that had concentrations in Period 2 prior to second tamoxifen dosing greater than 5% of C_{max} in Period 1.

PK samples for elinzanetant and its principal metabolites M18/M21, M27, and M30/M34 were collected until 24 hours after tamoxifen administration in Period 2.

Healthy male subjects aged 18 to 65 years and female subjects aged 30 to 65 years were included in the study. PK properties of tamoxifen and elinzanetant show no relevant gender-related differences. Results obtained in this population were therefore deemed as translatable to breast cancer patients who are receiving tamoxifen for therapeutic reasons.

Study Population

A total of 20 subjects were assigned to treatment sequence (tamoxifen – tamoxifen +Elinzanetant). PKS1 dataset included 17 subjects (2 subjects dropped out and 1 subject was excluded as she was identified as a CYP2D6 poor metabolizer. PKS2 dataset included 18 subjects (all but 2 dropouts).

PK Results

Results for Tamoxifen and its Metabolites

As valid AUC could not be reliably determined for all subjects, $AUC_{(0\text{-}tlast)}$ was used to evaluate total exposure of tamoxifen and its principal metabolites *N*-desmethyltamoxifen, 4-hydroxytamoxifen, and endoxifen. In this study, $AUC_{(0\text{-}tlast)}$ of tamoxifen and its metabolites equals $AUC_{(0\text{-}504\ h)}$ (504 hours=21 days).

Tamoxifen

Summary statistics of noncompartmental PK parameters of tamoxifen in plasma is provided in Table 179.

Table 179. Summary Statistics of Pharmacokinetic Parameters of Tamoxifen in Plasma (PKS1), Study 22004

Parameter	Unit	Tamoxifen alone (PKS1, N=17)	Tamoxifen with elinzanetant (PKS1, N=17)
AUC	µg*h/L	2760 / 36.0 (1420-6330)	4260 / 40.6 (2040-10400)
AUC(0-t_{last})[a]	µg*h/L	2280 / 25.6 (1340-3940)	3460 / 26.8 (1940-5610)
%AUC(t_{last} - ∞)[a]	%	13.6 / 87.5 (3.25-37.7)	14.4 / 87.2 (3.12-46.1)
C_{max}	µg/L	34.0 / 22.8 (22.5-49.9)	41.6 / 22.8 (29.3-65.1)
$t_{1/2}$	h	201 / 42.5 (98.3-402)	206 / 43.4 (107-513)
t_{max}[b]	h	5.00 (3.00-8.02)	5.02 (2.02-8.05)
CL/F	L/h	43.5 / 18.0 (30.2-57.7)	32.4 / 16.7 (21.7-41.5)
V_z/F	L	12600 / 47.9 (5040-22900)	9630 / 41.4 (4450-18800)

[a] t_{last} = 504 h (21 d); [b] median (range)
Source: Table 9-1 of the CSR
Geometric Mean/CV[Range]; N=17
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; N, number of subjects; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

Tamoxifen Metabolite N-desmethyltamoxifen

Summary statistics of noncompartmental PK parameters of tamoxifen metabolite N-desmethyltamoxifen in plasma is provided in Table 180.

Table 180. Summary Statistics of Pharmacokinetic Parameters of Tamoxifen Metabolite N-Desmethyltamoxifen in Plasma (PKS1), Study 22004

Parameter	Unit	Tamoxifen alone (PKS1, N=17)	Tamoxifen with elinzanetant (PKS1, N=17)
AUC	µg*h/L	5610 / 41.3 (3380-12300)	8970 / 89.6 (3810-108000)
AUC(0-t_{last})[a]	µg*h/L	3450 / 19.0 (2570-4660)	3650 / 19.3 (2600-4790)
AUC(0-t_{last})[a] carry-over corrected	µg*h/L		3010 / 21.4 (2010-4220)
%AUC(t_{last} - ∞)[a]	%	32.8 / 50.7 (13.5-68.8)	49.5 / 40.4 (24.8-96.0)
C_{max}	µg/L	10.1 / 25.6 (5.83-14.9)	6.85 / 17.2 (4.81-9.94)
C_{max} carry-over corrected	µg/L		4.94 / 28.5 (3.23-7.67)
$t_{1/2}$	h	322 / 54.0 (146-897)	554 / 106 (202-8230)
t_{max}[b]	h	8.00 (5.00-24.00)	12.00 (4.03-24.0)
CL/F	L/h	112 / 29.1 (75.6-201)	153 / 18.5 (101-219)
V_z/F	L	51900 / 69.2 (16000-200000)	122000 / 103 (38900-1470000)

[a] t_{last} = 504 h (21 d); [b] median (range)
Source: Table 9-2 of the CSR
Geometric Mean/CV[Range]; N=17
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; N, number of subjects; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

Tamoxifen Metabolite 4-hydroxytamoxifen

Summary statistics of noncompartmental PK parameters of tamoxifen metabolite 4-hydroxytamoxifen in plasma is provided in Table 181.

Table 181. Summary Statistics of Pharmacokinetic Parameters of Tamoxifen Metabolite 4-Hydroxytamoxifen in Plasma (PKS1), Study 22004

Parameter	Unit	Tamoxifen alone (PKS1, N=17)	Tamoxifen with elinzanetant (PKS1, N=17)
AUC	µg*h/L	55.9 / 34.8 (28.8-118)	81.2 / 40.0 (43.4-189)
AUC(0-t_{last})[a]	µg*h/L	46.5 / 36.5 (22.5-97.8)	67.2 / 36.1 (35.7-147)
%AUC(t_{last} - ∞)[a]	%	14.6 / 53.4 (6.25-35.4)	15.0 / 56.6 (5.38-32.1)
C_{max}	µg/L	0.352 / 30.5 (0.210-0.639)	0.380 / 27.7 (0.226-0.622)
$t_{1/2}$	h	181 / 45.3 (77.9-498)	189 / 31.9 (115-312)
t_{max}[b]	h	6.00 (4.00-12.00)	7.00 (4.03-24.0)
CL/F	L/h	3440 / 31.5 (1760-5870)	2980 / 29.0 (1600-5340)
Vz/F	L	899000 / 66.0 (385000-2790000)	812000 / 47.4 (362000-1570000)

[a] t_{last} = 504 h (21 d); [b] median (range)
Source: Table 9-3 of the CSR
Geometric Mean/CV [Range]; N=17
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; N, number of subjects; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

Tamoxifen Metabolite Endoxifen

Summary statistics of noncompartmental PK parameters of tamoxifen metabolite endoxifen in plasma is provided in Table 182.

Table 182. Summary Statistics of Pharmacokinetic Parameters of Tamoxifen Metabolite Endoxifen in Plasma (PKS1), Study 22004

Parameter	Unit	Tamoxifen alone (PKS1, N=17)	Tamoxifen with elinzanetant (PKS1, N=17)
AUC	µg*h/L	363 / 64.2 (91.2-1060)	469 / 79.9 (154-1930)
AUC(0-t_{last})[a]	µg*h/L	188 / 56.6 (56.0-541)	177 / 51.4 (70.1-551)
AUC(0-t_{last})[a] carry-over corrected	µg*h/L		136 / 60.6 43.3-436
%AUC(t_{last} - ∞)[a]	%	42.6 / 40.6 (22.6-73.6)	55.1 / 34.5 (25.6-89.4)
C_{max}	µg/L	0.266 / 56.5 (0.0830-0.678)	0.223 / 51.3 (0.113-0.714)
C_{max} carry-over corrected	µg/L		0.113 / 62.7 0.0517-0.382
$t_{1/2}$	h	400 / 58.0 (173-1000)	608 / 83.3 (196-3040)
t_{max}[b]	h	24.00 (8.00-24.0)	12.00 (4.03-24.0)
CL/F	L/h	4750 / 56.3 (1830-13500)	4390 / 50.9 (1390-9980)
V_Z/F	L	2740000 / 104 (775000-9280000)	3850000 / 88.8 (939000-1260000)

[a] t_{last} = 504 h (21 d); [b] median (range)
Source: CSR, table 9-4
Geometric Mean/CV [range]; N=17
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; $t_{1/2}$, elimination half-life; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration; V_Z/F, apparent volume of distribution during terminal phase

Results for Elinzanetant and Its Metabolites

Summary statistics of noncompartmental PK parameters of elinzanetant and its principal metabolites (M18/M21, M27, and M30/M34) in plasma after treatment with tamoxifen and multiple doses of elinzanetant is provided in Table 183.

Table 183. Summary Statistics of Pharmacokinetic Parameters of Elinzanetant and its Principal Metabolites M18/M21, M27, and M30/M34 in Plasma After Treatment With Tamoxifen and Multiple Doses of Elinzanetant

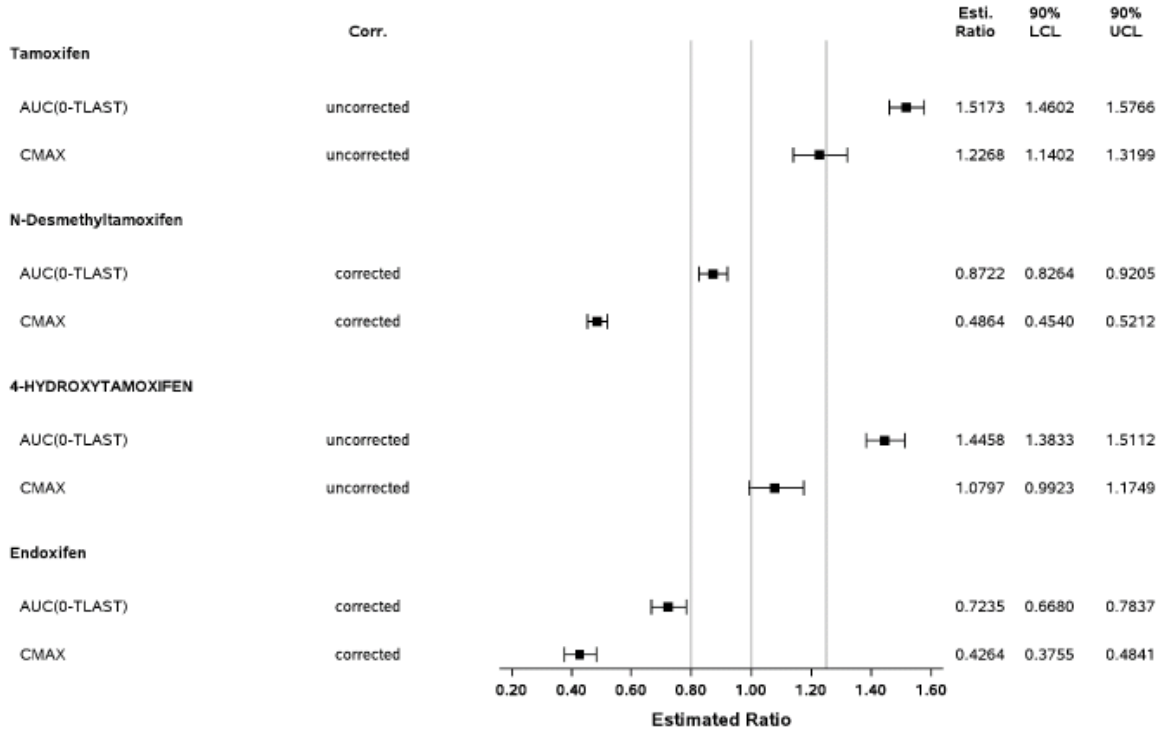
Parameter	Unit	Elinzanetant (n=17)	M18/M21 (n=17)	M27 (n=17)	M30/M34 (n=17)
AUC(0-24)$_{md}$	µg*h/L	8660 / 40.4 (4660-18900)	2630 / 37.3 (1280-5510)	2500 / 38.6 (1170-4170)	5180 / 35.1 (2730-9610)
$C_{max,md}$	µg/L	1850 / 36.9 (990-3000)	319 / 20.3 (215-443)	305 / 20.9 (206-394)	557 / 22.6 (387-832)
$t_{last,md}$	h	24.0 / 0.0627 (24.0-24.0)	24.0 / 0.0627 (24.0-24.0)	24.0 / 0.0627 (24.0-24.0)	24.0 / 0.0627 (24.0-24.0)
$t_{max,md}$[a]	h	1.02 (1.00-2.02)	2.00 (1.50-3.00)	1.52 (1.00-2.02)	2.00 (1.00-4.00)
CL/F$_{md}$	L/h	13.9 / 40.4 (6.33-25.8)	47.9 / 37.3 (22.8-98.2)	49.2 / 38.6 (29.5-105)	23.7 / 35.1 (12.8-45.0)

[a] median (range)
Source: Table 9-5 of the CSR
Geometric Mean/CV [Range]
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; LS, least squares; M, metabolite; md, multiple dose; n, number of subjects; t_{last}, time of the last quantifiable concentration; t_{max}, time to maximum concentration

Effect of Elinzanetant on Pharmacokinetics of Tamoxifen and its Metabolites in Plasma

Geometric mean ratios (90% confidence intervals) of C_{max} and AUC for tamoxifen and its metabolites ("tamoxifen with elinzanetant / tamoxifen alone") were calculated. For N-desmethyltamoxifen and endoxifen, carry-over corrected values were used. The results are shown in Figure 59.

Figure 59. Assessment of the Effect of Elinzanetant on Tamoxifen and its Metabolites (Carry-Over Corrected Values for N-Desmethyltamoxifen and Endoxifen) (PKS1), Study 22004



Ratio: point estimates for ratios "tamoxifen with elinzanetant / tamoxifen alone"
Source: Figure 9-25 of the CSR
N=17
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geom., geometric; LCL, lower control limit; LS, least squares; N, number of subjects; UCL, upper control limit

FDA Analysis

Concomitant administration of 120 mg elinzanetant increased the AUC of tamoxifen and 4-hydroxytamoxifen by 52% and 45%, respectively, and decreased the AUC of N-desmethyltamoxifen and endoxifen by 13% and 28%, respectively. The overall changes in the exposure of tamoxifen and its metabolites are not considered clinically meaningful.

14.2.4.7. DDI Between Elinzanetant and Esomeprazole, Study 21772 (PH-42383)

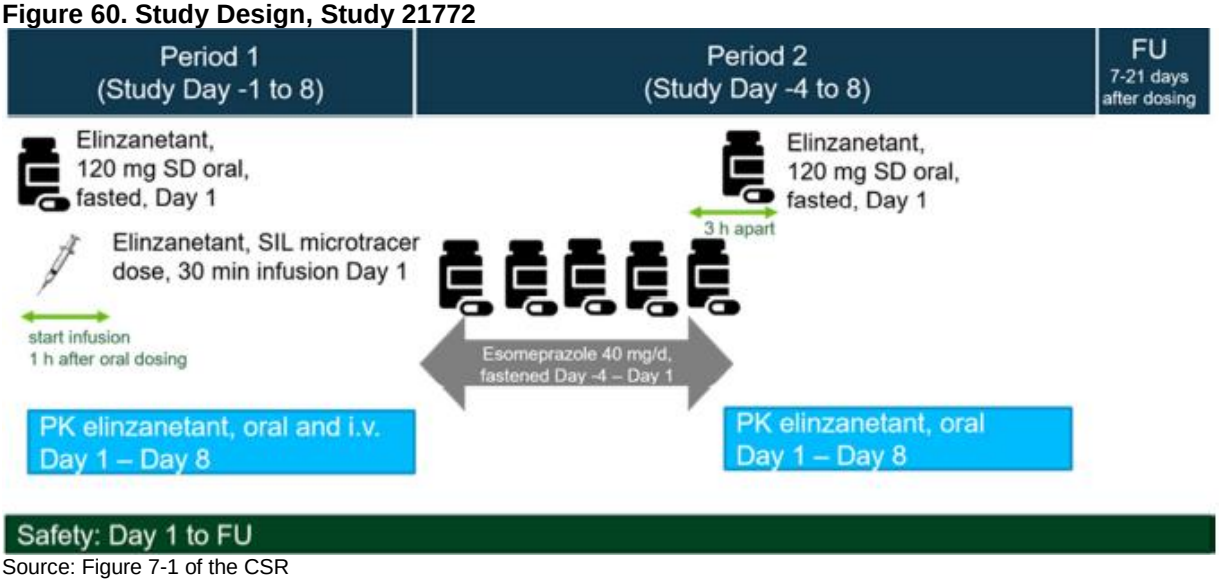
Title

An open-label, nonrandomized, fixed-sequence crossover study to investigate the effects of the proton pump inhibitor esomeprazole on the pharmacokinetics of elinzanetant (BAY 3427080) as well as assessment of the absolute bioavailability of elinzanetant using a single intravenous microtracer dose of [$^{13}C_5$] BAY 3427080 in male and female healthy subjects

Study Design

A schema of the study design is presented in Figure 60.

Figure 60. Study Design, Study 21772



Source: Figure 7-1 of the CSR
Abbreviations: CSR, clinical study report; D, day; FU, follow-up; i.v., intravenous; PK, pharmacokinetics; SD, single dose; SIL, stable isotope labeled

Justification for Dose

- 120 mg elinzanetant was selected because it is the proposed therapeutic dose.
- 100 µg [$^{13}C_5$] BAY 3427080 is the highest appropriate dose in the microdosing approach per ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010). This dose is predicted to allow proper quantification of the tracer over the course of 168 hours.
- Administration of 40 mg esomeprazole once daily is the highest recommended dosage for its approved indications (e.g., for the treatment of gastric ulcers). Administration for 5 days ensured a maximum increase of gastric pH for investigation of the interaction with elinzanetant (as recommended by the FDA guidance for industry *Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications* (March 2023).

Study Population

A total of 14 male and female healthy subjects were assigned to treatment sequence (elinzanetant + [$^{13}C_5$] BAY 3427080 → elinzanetant + esomeprazole). All 14 subjects received assigned treatments. One subject did not complete the study (subject decision) and dropped out during the second treatment phase (Period 2).

Treatment Administered

Each subject was administrated one single dose of elinzanetant together with 240 mL noncarbonated water at room temperature on Day 1 of each period. Following study drug administration, subjects remained in an upright sitting position for 1 hour.

The study interventions administered in this study are described below.

Table 184. Treatment Administered, Study 21772

Period	Treatment	Amount/ Formulation	Route of administration	Frequency of administration	No. of participants planned
1	120 mg elinzanetant	2x 60 mg elinzanetant soft gel capsules	oral	single dose (Day 1)	14
1	100 µg [$^{13}C_5$]BAY 3427080	10 mL solution administered over 30 min	IV	single dose (Day 1)	14
2	40 mg esomeprazole	40 mg gastro-resistant tablet	oral	once daily over 5 days (Day -4 to Day 1)	14
2	120 mg elinzanetant	2x 60 mg elinzanetant soft gel capsules	oral	single dose (Day 1)	14

Source: Study 21772 CSR.
Abbreviation: IV, intravenous

PK Results

Summary statistics of noncompartmental PK parameters of elinzanetant in plasma is provided in Table 185. Similar C_{max} and AUC of elinzanetant were observed when coadministered without or with esomeprazole.

Table 185. Pharmacokinetic Parameters of Elinzanetant in Plasma (PKS1), Study 21772

Parameter	Unit	n	Elinzanetant + [$^{13}C_5$]BAY 3427080	n	Elinzanetant + Esomeprazole
AUC	ug*h/L	14	6210 / 69.8 (2790 - 25100)	14	7020 / 58.5 (3580 - 27700)
AUC(0-t_{last})	ug*h/L	14	6080 / 68.8 (2730 - 24200)	14	6880 / 57.9 (3540 - 27100)
AUC/D	h/L	14	0.0517 / 69.8 (0.0233 - 0.209)	14	0.0585 / 58.5 (0.0298 - 0.231)
CL/F	L/h	14	19.3 / 69.8 (4.79 - 43.0)	14	17.1 / 58.5 (4.34 - 33.5)
C_{max}	ug/L	14	1810 / 55.1 (841 - 5910)	14	1830 / 46.6 (1030 - 6620)
$t_{1/2}$	h	14	31.9 / 27.2 (19.0 - 43.5)	14	34.5 / 30.7 (20.0 - 57.7)
t_{max}[(a)]	h	14	0.983 (0.750 - 1.47)	14	1.25 (0.750 - 2.00)
V_z/F	L	14	890 / 61.7 (284 - 2040)	14	850 / 62.9 (207 - 2370)

a) Median (range)

Source: Table 9-3 of the CSR
Geometric Mean/%CV (Range); N=14
Abbreviations: AUC, area under the concentration-time curve; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geom., geometric; LS, least squares; M, metabolite; N, number of subjects; $t_{1/2}$, elimination half-life; t_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase

Geometric mean ratios and 90% CIs of AUC and C_{max} for elinzanetant and its metabolites ('elinzanetant + esomeprazole / elinzanetant alone') are shown below Table 186.

Table 186. Point Estimators (LS Means), Two-Sided 90% Confidence Intervals and 95% Prediction Intervals for the Ratios Of "Elinzanetant + Esomeprazole"/ "Elinzanetant Alone" for Elinzanetant and its Metabolite in Plasma (PKS1), Study 21772

Analyte	Parameter	n	Estimated ratio	90% CI for the ratio	95% prediction interval for the ratio	Geom. CV(%)
Elinzanetant	AUC (ug*h/L)	14	1.1305	[1.0383; 1.2308]	[0.7565; 1.6892]	12.75
	C_{max} (ug/L)	14	1.0106	[0.8681; 1.1764]	[0.4929; 2.0718]	23.00
M18/M21	AUC (ug*h/L)	14	1.0807	[1.0238; 1.1408]	[0.8369; 1.3956]	8.10
	C_{max}(ug/L)	14	1.0004	[0.8861; 1.1294]	[0.5639; 1.7746]	18.27
M27	AUC (ug*h/L)	14	1.1685	[1.0957; 1.2461]	[0.8622; 1.5835]	9.63
	C_{max} (ug/L)	14	1.0661	[0.9706; 1.1712]	[0.6840; 1.6618]	14.10
M30/M34	AUC (ug*h/L)	14	1.0612	[1.0111; 1.1138]	[0.8443; 1.3338]	7.24
	C_{max} (ug/L)	14	1.0353	[0.9311; 1.1513]	[0.6270; 1.7095]	15.96

Source: Table 9-9 of the CSR
N=14
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CSR, clinical study report; CV, coefficient of variation; Geom., geometric; LS, least squares; M, metabolite; N, number of subjects

No clinically significant drug-drug interaction on the pharmacokinetics of elinzanetant and its metabolites was observed when coadministered with the proton pump inhibitor esomeprazole.

Summary statistics of noncompartmental PK parameters of [$^{13}C_5$] BAY 3427080 in plasma after IV infusion of 100 µg over 30 minutes is provided in Table 187.

Table 187. Pharmacokinetic Parameters of [$^{13}C_5$] BAY 3427080 in Plasma (PKS1), Study 21772

Parameter	Unit	n	Elinzanetant + [$^{13}C_5$]BAY 3427080
AUC	ug*h/L	10	11.4 / 59.2 (6.02 - 30.4)
AUC(0-t_{last})	ug*h/L	14	8.36 / 60.0 (3.70 - 27.7)
AUC/D	h/L	10	0.114 / 59.2 (0.0602 - 0.304)
CL	L/h	10	8.77 / 59.2 (3.29 - 16.6)
C_{max}	ug/L	14	4.18 / 45.3 (2.32 - 8.81)
MRT_{IV}	h	10	15.7 / 72.9 (8.55 - 40.2)
$t_{1/2}$	h	10	19.0 / 61.2 (10.0 - 40.6)
t_{max}[a]	h	14	0.583 (0.583 - 0.667)
Vss	L	10	137 / 29.5 (78.5 - 207)
Vz	L	10	241 / 30.2 (157 - 365)

a) Median (range)

Source: CSR, table 9-8
Geometric Mean/%CV (range); N=14
Abbreviations: AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; IV, intravenous; MRT, mean residence time; $t_{1/2}$, elimination half-life; t_{max}, time to maximum concentration; Vss, volume of distribution at steady state; Vz, volume of distribution during the terminal phase

To assess the absolute bioavailability of elinzanetant given as 2 x 60 mg soft gel capsules, ANOVA was conducted to calculate the point estimate (LS-mean) and the corresponding 2-sided 90% CI for the ratio "elinzanetant capsules/[$^{13}C_5$] BAY 3427080 infusion" of AUC/D. The absolute bioavailability of elinzanetant given as oral 2 x 60 mg soft gel capsules and 100 µg [$^{13}C_5$] BAY 3427080 administered intravenously as a 10 mL solution over 30 min is 52% (Point estimate 0.5192 [90% CI: 0.4632 to 0.5819]).

14.2.4.8. DDI Between Elinzanetant and Midazolam, Study 21674

This study was divided into two distinct parts. Part A employed a parallel group, randomized, placebo-controlled design to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of GSK1144814 (elinzanetant). This segment consisted of three cohorts. Cohorts 1 and 2 focused on the pharmacokinetics of elinzanetant following single and repeated oral doses of 30 mg, 90 mg, and 200 mg. Cohort 3 examined the safety, tolerability, and pharmacokinetics of a 200 mg once-daily dose of GSK1144814 administered for 28 days, and its

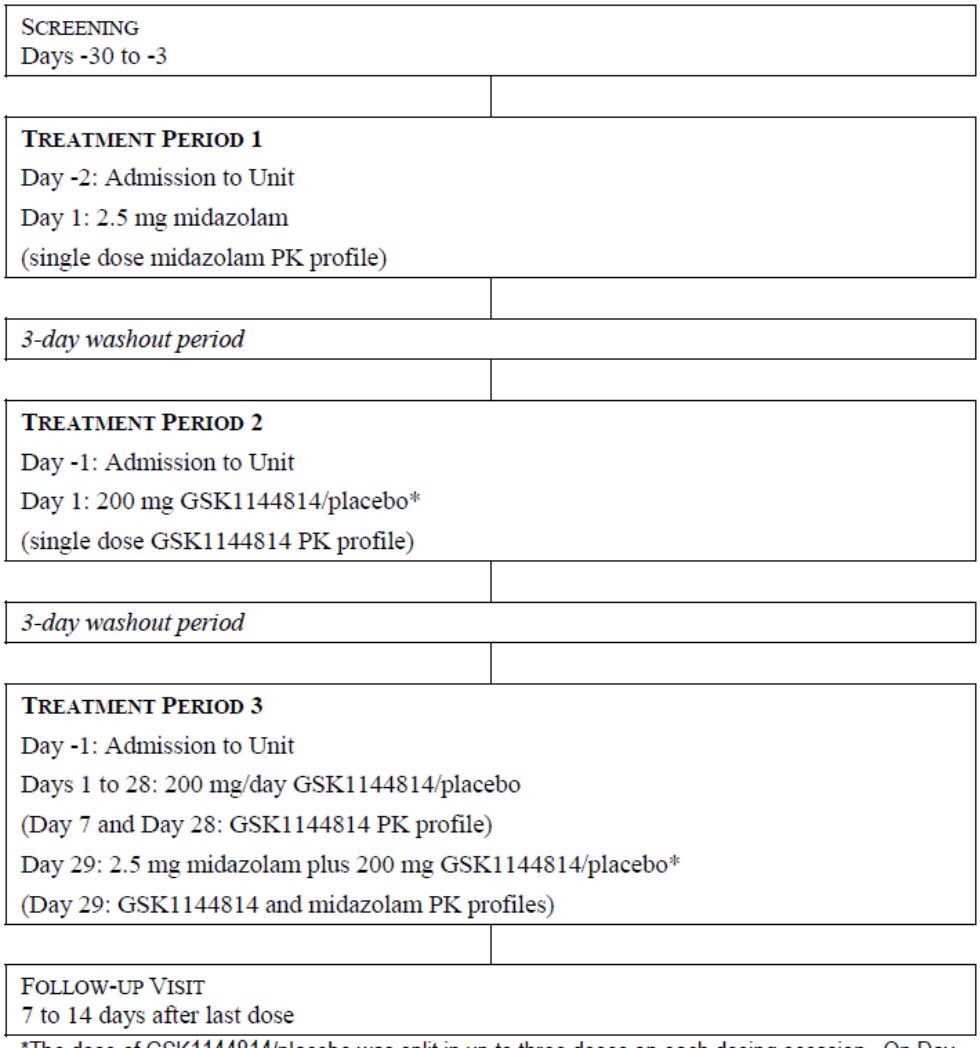
impact on the pharmacokinetics of a single oral 2.5 mg dose of midazolam, a CYP3A4-sensitive substrate.

Part B involved four healthy male subjects and aimed to evaluate NK1 receptor occupancy of elinzanetant after repeated oral dosing. This was accomplished through PET scanning using the NK1 radiotracer ligand [^{11}C]GR205171.

This review will focus on the effect of elinzanetant on the pharmacokinetics of midazolam, specifically addressing Cohort 3 of Part A. The study design for cohort 3 of part A is given in Figure 61.

Study Design (Part A: Cohort 3)

Figure 61. Study Design, Study 21674 (Part A: Cohort 3)



*The dose of GSK1144814/placebo was split in up to three doses on each dosing occasion. On Day 29, midazolam was administered with the first split dose of GSK1144814/placebo

Source: CSR, figure 2

Interaction With Midazolam

The effect of multiple once daily doses of 200 mg elinzanetant on the pharmacokinetics of midazolam are presented in Table 188**.**

Table 188. Geometric Mean Ratio (90% Confidence) of Midazolam + Elinzanetant/Midazolam Alone) in Plasma, Study 21674

Parameter	Comparison	LS Geom. Mean, test	LS Geom. Mean, ref	Ratio	90%CI
AUC	MDZ + Elinzanetant / MDZ alone	79.0	41.6	1.90	[1.62; 2.23]
C_{max}	MDZ + Elinzanetant / MDZ alone	23.9	14.0	1.71	[1.40; 2.10]

Source: Applicant's clinical pharmacology summary, table 2-10
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; Geom., geometric; LS, least squares; MDZ, midazolam

FDA Analysis

A mean increase of 90% and 71% increase in the AUC and C_{max} of midazolam was observed, respectively, when midazolam was administered after treatment with elinzanetant 200 mg once daily compared to when midazolam was administered alone. These results indicate that elinzanetant is a weak inhibitor of CYP3A4 at the dose of 200 mg administered once daily.

14.3. Bioanalytical Method Validation and Performance

Validated analytical methods were used for quantification of elinzanetant and its metabolites in plasma and urine samples as shown in Table 189 in clinical pharmacology studies. These analytical methods utilized protein precipitation followed by LC-MS/MS. Quantification was achieved by weighted linear or quadratic regression using isotope-labeled internal standards.

Table 189. Summary of Bioanalytical Method Details for the Determination of Elinzanetant and its Metabolites in Human Plasma and Urine

Method ID	Assay Type (Matrix)	Method Title	Method Report ID	Validation Report ID	Effective Date	Method used in Studies
GSK1144814 HUPL VALA	LC-MS/MS (plasma)	The Validation of a Method for the Determination of GSK 1144814 in Human Plasma (range 1.5 to 1500 ng/mL) using HPLC-MS/MS	VD2008/00568/00	B002017 (Module 4.2.2.1, B002017)	16 Dec 2008	21673[A], 21674 21675[A], 21676
GSK1144814 HUPL VALB	LC-MS/MS (plasma)	The Validation of a Method for the Determination of GSK 1144814 in Human Plasma (range 0.15 to 150 ng/mL) using HPLC-MS/MS	VD2009/00320/00	B002024 (Module 4.2.2.1, B002024)	05 Aug 2009	21674
VPT4371 V05	LC-MS/MS (plasma)	NT-814: The Validation of a Method for the Determination of NT-814 in Human Plasma (Range 1.5 to 1000 ng/mL) using LC-MS/MS	VPT4371/2016	R-13599 (Module 4.2.2.1, R-13599)	07 Mar 2018	21677, 21678 21679, 21680 21681, 21686
NT81HPP V01	LC-MS/MS (plasma)	Validation of a Method for the Determination of NT-814 and M27 in Human Plasma by HPLC with MS/MS Detection	8441-721	R-13913 (Module 4.2.2.1, R-13913)	16 Jun 2020	21703
KM18HPP V01	LC-MS/MS (plasma)	Validation of a Method for the Determination of M18/21 and M30/34 in Human Plasma by HPLC with MS/MS Detection	8441-724	R-13909 (Module 4.2.2.1, R-13909)	19 Oct 2020	21703
NT81HUP V01	LC-MS/MS (urine)	Validation of a Method for the Determination of NT-814 and M27 in Human Urine by HPLC with MS/MS Detection	8441-723	R-13914 (Module 4.2.2.1, R-13914)	30 Jun 2020	21703
KM18HUP V02	LC-MS/MS (urine)	Validation of a Method for the Determination of M18/21 and M30/34 in Human Urine by HPLC with MS/MS Detection	8441-730	R-13910 (Module 4.2.2.1, R-13910)	07 Jan 2021	21703
(b) (4)-20320	LC-MS/MS (plasma)	Validation of a method for the determination of BAY 3427080, BAY 3462934, BAY 3462935, BAY 3462932 and BAY 3462933 in human plasma samples by LC-MS/MS	(b) (4)-20320	B002278 (Module 4.2.2.1, B002278)	30 Apr 2022	21664[B], 21665 21666, 21667 21668, 21669 21756, 21772 21774, 21840
(b) (4)-22103	LC-MS/MS (plasma)	Partial validation of a method for the determination of BAY 3427080, BAY 3462932, BAY 3462933 and BAY 3462934 in human plasma samples by LC-MS/MS	(b) (4)-22103	B002467 (Module 4.2.2.1, B002467)	05 Aug 2022	21651, 21652 21670, 21810 22004, 22050 22081
(b) (4)-21036	LC-MS/MS (urine)	Validation of a method for the determination of BAY 3427080, BAY 3462932, BAY 3462933 in human urine samples by LC-MS/MS	(b) (4)-21036	R-14352 (Module 4.2.2.1, R-14352)	04 Aug 2022	21668
-21186	LC-MS/MS (plasma)	Partial validation of a method for the quantitative determination of [$^{13}C_6$]BAY 3427080 in human plasma samples by LC-MS/MS	-21186	R-14370 (Module 4.2.2.1, R-14370)	08 Aug 2022	21668
21285	LC-MS/MS (plasma and buffer for protein binding)	Qualification of a method for the determination of BAY 3427080 in various matrices for plasma protein binding samples by LC-MS/MS	21285	R-14310 (Module 4.2.2.1, R-14310)	14 Dec 2021	21668 21669
21067	LC-MS/MS (plasma)	Qualification of a method for the determination of BAY 3462932, BAY 3462933 and BAY 3462934 in various matrices for plasma protein binding samples by LC-MS/MS	21067	R-13903 (Module 4.2.2.1, R-13903)	04 May 2021	21668 21669

A: 21673 and 21675 no dedicated performance information on the bioanalytical assay is reported in the bioanalytical report. Performance of the bioanalytical assay is reported in the corresponding validation reports (Module 4.2.2.1, B002017)
B: M22 was analyzed with a validated method in study 21664 only

Source: Applicant's summary of biopharmaceutics, table 1-7

For the determination of elinzanetant and its metabolites in plasma, methods for a concentration range from 1.00 to 1000 µg/L for elinzanetant, and its metabolites were validated in plasma ((b) (4)20320 and (b) (4)22103, utilizing stable isotope-labeled internal standards for each analyte). Method (b) (4)22103 was employed to analyze plasma samples in the Phase 3 studies (OASIS 1, OASIS 3, and OASIS 3). Furthermore, other Phase 1 studies that supported product labeling used methods VPT4371 V05, NT81HPP V01, (b) (4)21186, (b) (4)21285, and (b) (4) 21067. Therefore, in this review, we focus on the results of validation and performance for methods (b) (4)20320, (b) (4)22103, (b) (4)21186, VPT4371 V05, NT81HPP V01, (b) (4)21285, and (b) (4)21067.

Bioanalytical Method Validation

Table 190. Plasma Validation, (b) (4) 20320

Method description	Validation of a method for the determination of elinzanetant, M18/21, M22, M27 and M30/34 in human plasma samples by LC-MS/MS
Materials used for standard calibration curve and concentration	Human plasma, elinzanetant, M27, M30/34, M18/21 and M22 reference standards. Calibrator concentrations: 1.00, 2.00, 10.0, 50.0, 100, 500, 750, 1000 µg/L
Validated assay range	1.00 to 1000 µg/L for all analytes
Materials used for quality controls (QCs) and concentration	Control human plasma and elinzanetant, M27, M30/34, M18/21 and M22 reference standards. QC concentrations: 1.00, 3.00, 100 and 750 µg/L
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	Control human potassium EDTA plasma from (b) (4) (b) (4) Elinzanetant reference standard from (b) (4) M27, M30/34 and M18/21 reference standard from (b) (4) and M22 reference standard from (b) (4) $[^{13}C_2\ ^2H_6]$Elinzanetant ISTD from GlaxoSmithKline, Stevenage UK, and Netupitant ISTD from (b) (4) (b) (4)
Regression model and weighting	Linear, 1/x2 weighting for elinzanetant Quadratic, 1/x weighting for M27, M30/34, M18/21 and M22

Validation parameters	**Method Validation Summary**	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8 (two sets)
	Cumulative accuracy (%bias) at LLOQ:	
	Elinzanetant	-1.0%
	M27	-0.4%
	M30/34	-3.8%
	M18/21	-2.6%
	M22	-1.6%
	Cumulative precision (%CV) at LLOQ:	
	NT-814	4.3%
	M27	9.7%
	M30/34	9.2%
	M18/21	7.6%
	M22	7.1%

Validation parameters	**Method Validation Summary**	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs (6 for each batch)**	
	Elinzanetant	-0.5 to 7.0%
	M27	1.3 to 11.0%
	M30/34	-1.6 to 4.0%
	M18/21	-0.1 to 5.0%
	M22	-0.8 to 5.0%
	Inter-batch %CV	
	Elinzanetant	2.1 to 10.7%
	M27	4.0 to 13.4%
	M30/34	5.4 to 15.5%
	M18/21	3.9 to 13.4%
	M22	5.8 to 15.7%

Selectivity & matrix effect	Selectivity was assessed by comparing blank peak heights (n=6) to the mean peak height of a sample prepared at the LLOQ. No significant interference with the analyte (≤ 20%) or internal standard (≤ 5%) was observed. ≤3.3% (Elinzanetant) ≤2.4% (M27) ≤1.8% (M30/34) ≤3.7% (M18/21) ≤2.9% (M22) ≤0.1% [$^{13}C_2{}^2H_6$]Elinzanetant ISTD ≤0.1% Netupitant ISTD The matrix factor was calculated as the ratio of the peak response in the presence of matrix ions to the mean peak response in the absence of matrix ions. The ISTD normalized matrix factor was calculated by dividing the matrix factor of the analyte by the matrix factor of the internal standard. The precision of the matrix factor evaluation met the acceptance criteria (≤15.0% CV) and the matrix factor was not considered to impact assay performance. Elinzanetant 0.583 to 0.716 (3.00; 100 and 750 µg/L) M27 0.824 to 0.838 (3.00; 100 and 750 µg/L) M30/34 0.860 to 1.072 (3.00; 100 and 750 µg/L) M18/21 0.709 to 0.770 (3.00; 100 and 750 µg/L) M22 0.738 to 0.915 (3.00; 100 and 750 µg/L)

Validation parameters	**Method Validation Summary**
Interference & specificity	The potential contribution of the analytes to the internal standards was assessed by comparing the mean analytical response for the internal standards in blank samples spiked with the analytes at the ULOQ to the mean analytical response obtained for samples processed with the internal standards at the working concentration. The response of any interfering peak in the ULOQ samples at the retention time of the internal standards did not exceed 5 % of the internal standard signal in blank samples.
Hemolysis effect	The working solution at the low (3.00 µg/L) and high (750 µg/L) concentration level was spiked into matrix containing 5% hemolytic blood (2% for M18/21) (n=3): Elinzanetant ≤±5.6% (%bias) and ≤5.2 (%CV) M27 ≤±11.3% (%bias) and ≤5.8 (%CV) M30/34 ≤±4.0% (%bias) and ≤3.6 (%CV) M18/21 ≤±14.1% (%bias) and ≤5.8 (%CV) M22 ≤±9.6% (%bias) and ≤3.7 (%CV) The results indicate that there was no influence of very high-grade hemolysis (corresponding to 5% hemolytic blood) on the analysis of elinzanetant, M22, M27 and M30/34. Quantification of M18/21 was impacted by very high levels of hemolysis (corresponding to 5% hemolytic blood) but not high to moderate levels of hemolysis (corresponding to 0.5% to 2% hemolytic blood).
Lipemic effect	The working solution at the low (3.00 µg/L) and high (750 µg/L) concentration level was spiked with triglycerides content of at least 300mg/dL (n=3): Elinzanetant ≤±5.0% (%bias) and ≤2.7 (%CV) M27 ≤±3.7% (%bias) and ≤9.4 (%CV) M30/34 ≤±10.3% (%bias) and ≤5.7 (%CV) M18/21 ≤±1.3% (%bias) and ≤11.2 (%CV) M22 ≤±7.0% (%bias) and ≤12.8 (%CV)

Validation parameters	Method Validation Summary
Dilution linearity	5 replicate QC samples (4000 µg/L) with concentrations higher than the ULOQ of 1000 µg/L were diluted by a factor of 10 with blank human plasma prior to analysis. The calculated concentrations were compared to the nominal concentrations of the samples: Elinzanetant ≤±3.0% (%bias) and ≤1.7 (%CV) M27 ≤±4.3% (%bias) and ≤5.3 (%CV) M30/34 ≤±2.5% (%bias) and ≤5.1 (%CV) M18/21 ≤±6.8% (%bias) and ≤4.5 (%CV) M22 ≤±2.0% (%bias) and ≤2.7 (%CV)
Bench-top/process stability	5 hours bench-top stability at 3.00 and 750 µg/L was established (n=3). ISTD normalized difference (%) between 5 h against nominal concentration was as follows: Elinzanetant -3.7% (3.00 µg/L), -6.3% (750 µg/L) M27 0.0% (3.00 µg/L), -8.5% (750 µg/L) M30/34 1.3% (3.00 µg/L), -6.4% (750 µg/L) M18/21 -4.3% (3.00 µg/L), -8.0% (750 µg/L) M22 -7.0% (3.00 µg/L), -10.3% (750 µg/L)
Whole blood stability	24 hours whole blood stability at room temperature for blood spiked with 100 µg/L was established by comparing the mean analyte to internal standard peak area ratio of samples extracted after storage for 24 hours against those of the samples extracted immediately upon spiking (n=3). The difference (%) against nominal concentration was as follows: Elinzanetant -8.7% (100 µg/L) M27 -10.0% (100 µg/L) M30/34 -5.5% (100 µg/L) M18/21 -7.6% (100 µg/L) M22 -9.4% (100 µg/L)

Validation parameters	Method Validation Summary
Freeze-Thaw stability	3.00 and 750 µg/L QC samples were prepared, stored at ≤-20°C and at ≤-80°C and subjected to three freeze-thaw cycles. Mean difference between nominal and observed (%bias) and precision in each batch (%CV, n=3) at the respective QC level were below the following values: Elinzanetant 3.00 and 750 µg/L at ≤-20°C -5.7%; -6.3% (bias) and 2.2%; 2.4% (%CV) 3.00 and 750 µg/L at ≤-80°C -2.0%; -5.1% (bias) and 2.6%; 1.2% (%CV) M27 3.00 and 750 µg/L at ≤-20°C -11.0%; -6.3% (bias) and 4.2%; 1.9% (%CV) 3.00 and 750 µg/L at ≤-80°C -0.3%; -8.0% (bias) and 2.0%; 4.9% (%CV) M30/34 3.00 and 750 µg/L at ≤-20°C 1.3%; -3.9% (bias) and 4.7%; 1.0% (%CV) 3.00 and 750 µg/L at ≤-80°C -2.7%; -8.8% (bias) and 4.5%; 4.8% (%CV) M18/21 3.00 and 750 µg/L at ≤-20°C -4.0%; -2.1% (bias) and 4.6%; 2.4% (%CV) 3.00 and 750 µg/L at ≤-80°C 1.3%; -4.9% (bias) and 2.9%; 5.5% (%CV) M22 3.00 and 750 µg/L at ≤-20°C -8.3%; -11.1% (bias) and 1.4%; 1.9% (%CV) 3.00 and 750 µg/L at ≤-80°C -9.7%; -9.2% (bias) and 2.0%; 2.6% (%CV)

Validation parameters	Method Validation Summary
Long-term storage	Low, and high QC samples (n=3) were prepared and stored at ≤-20°C and at ≤-80°C. Respective plasma stability for 364 days were as follows: Elinzanetant ≤-20°C 0.0% (3.00 µg/L); -0.7% (750 µg/L) ≤-80°C -2.7% (3.00 µg/L); -2.9% (750 µg/L) M27 ≤-20°C -2.3% (3.00 µg/L); -5.3% (750 µg/L) ≤-80°C -9.3% (3.00 µg/L); -2.3% (750 µg/L) M30/34 ≤-20°C 0.0% (3.00 µg/L); -0.3% (750 µg/L) ≤-80°C -0.3% (3.00 µg/L); -0.4% (750 µg/L) M18/21 ≤-20°C -3.7% (3.00 µg/L); -5.5% (750 µg/L) ≤-80°C -7.0% (3.00 µg/L); -2.0% (750 µg/L) M22 ≤-20°C -0.7% (3.00 µg/L); 3.9% (750 µg/L) ≤-80°C -2.3% (3.00 µg/L); 2.1% (750 µg/L)
Parallelism	Not applicable
Carry-over	The carry-over was calculated from a chromatographic run, where blank samples were injected after a ULOQ sample. The acceptance criteria for the analyte were ≤20% and the ISTD were ≤5% of the LLOQ signal and fulfilled after the second blank sample.

Source: Applicant's summary of biopharmaceutics, table 5-10

Table 191. Plasma Validation, (b) (4) 22103

Method description	Partial validation of a method for the determination of elinzanetant, M27, M30/34 and M18/21 in human plasma samples by LC-MS/MS
Materials used for standard calibration curve and concentration	Human plasma, elinzanetant, M27, M30/34 and M18/21 reference standards. Calibrator concentrations: 1.00, 2.00, 10.0, 50.0, 100, 500, 750, 1000 µg/L
Validated assay range	1.00 to 1000 µg/L for all analytes
Materials used for quality controls (QCs) and concentration	Control human plasma and elinzanetant, M27, M30/34 and M18/21 reference standards. QC concentrations: 1.00, 3.00, 100 and 750 µg/L
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	Control human potassium EDTA plasma from (b) (4) Elinzanetant reference standard from Bayer AG, Germany, M27, M30/34 and M18/21 reference standard from (b) (4) (b) (4) [$^{13}C_2$ $^{2}H_6$]Elinzanetant ISTD from GlaxoSmithKline, Stevenage UK., [$^{13}C^{2}H_3$]M27, [$^{13}C^{2}H_3$]M30/34 and [^{13}C $^{2}H_3$]M18/21 ISTDs from Bayer AG, Germany.
Regression model and weighting	Linear, 1/x2 weighting for all analytes

Validation parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8 (two sets)
	Cumulative accuracy (%bias) at LLOQ:	
	Elinzanetant	-0.7%
	M27	-0.6%
	M30/34	0.0%
	M18/21	-0.7%
	Cumulative precision (%CV) at LLOQ:	
	Elinzanetant	4.0%
	M27	6.5%
	M30/34	6.2%
	M18/21	8.0%
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QCs (6 for each batch)**	
	Elinzanetant	-3.7 to -0.8%
	M27	-3.5 to 3.0%
	M30/34	-2.8 to 1.0%
	M18/21	-5.4 to 1.3%
	Inter-batch %CV	
	Elinzanetant	3.8 to 6.9%
	M27	3.9 to 10.4%
	M30/34	4.3 to 7.8%
	M18/21	4.2 to 9.8%

Validation parameters	Method Validation Summary
Selectivity & matrix effect	Selectivity was assessed by comparing blank peak heights (n=6) to the mean peak height of a sample prepared at the LLOQ. No significant interference with the analyte (≤ 20%) or internal standard (≤ 5%) was observed. ≤7.0% (Elinzanetant) ≤4.9% (M27) ≤7.6% (M30/34) ≤5.5% (M18/21) ≤0.1% [$^{13}C_2$ $^{2}H_6$]Elinzanetant ISTD ≤0.1% [$^{13}C^{2}H_3$]M27 ISTD ≤0.1% [^{13}C $^{2}H_3$]M30/34 ISTD ≤0.1% [^{13}C $^{2}H_3$]M18/21 ISTD The matrix factor was calculated as the ratio of the peak response in the presence of matrix ions to the mean peak response in the absence of matrix ions. The ISTD normalized matrix factor was calculated by dividing the matrix factor of the analyte by the matrix factor of the internal standard. The precision of the matrix factor evaluation met the acceptance criteria (≤15.0% CV) and the matrix factor was not considered to impact assay performance. Elinzanetant 0.947 to 1.061 (3.00; 100 and 750 µg/L) M27 0.987 to 1.103 (3.00; 100 and 750 µg/L) M30/34 0.879 to 0.996 (3.00; 100 and 750 µg/L) M18/21 0.977 to 1.020 (3.00; 100 and 750 µg/L)
Interference & specificity	The potential contribution of the analytes to the internal standards was assessed by comparing the mean analytical response for the internal standards in blank samples spiked with the analytes at the ULOQ to the mean analytical response obtained for samples processed with the internal standards at the working concentration. The response of any interfering peak in the ULOQ samples at the retention time of the internal standards did not exceed 5% of the internal standard signal in blank samples.
Hemolysis effect	The working solution at the low (3.00 µg/L) and high (750 µg/L) concentration level was spiked into matrix containing 5% hemolytic blood (n=3): Elinzanetant ≤±5.5% (%bias) and ≤4.1 (%CV) M27 ≤±2.7% (%bias) and ≤2.6 (%CV) M30/34 ≤±2.9% (%bias) and ≤5.9 (%CV) M18/21 ≤±9.3% (%bias) and ≤7.9 (%CV) The results indicate that there was no influence of hemolysis (corresponding to 5% hemolytic blood) on the analysis.

Validation parameters	Method Validation Summary
Lipemic effect	The working solution at the low (3.00 µg/L) and high (750 µg/L) concentration level was spiked with triglycerides content of at least 300 mg/dL (n=3): Elinzanetant ≤±11.2% (%bias) and ≤5.8 (%CV) M27 ≤±5.2% (%bias) and ≤7.0 (%CV) M30/34 ≤±6.0% (%bias) and ≤5.7 (%CV) M18/21 ≤±2.4% (%bias) and ≤12.2 (%CV)
Dilution linearity	5 replicate QC samples (4000 µg/L) with concentrations higher than the ULOQ of 1000 µg/L were diluted by a factor of 10 with blank human plasma prior to analysis. The calculated concentrations were compared to the nominal concentrations of the samples: Elinzanetant ≤±8.8% (%bias) and ≤2.7 (%CV) M27 ≤±7.5% (%bias) and ≤2.3 (%CV) M30/34 ≤±6.3% (%bias) and ≤2.4 (%CV) M18/21 ≤±5.0% (%bias) and ≤1.7 (%CV)
Bench-top/process stability	Bench-top stability at 3.00 and 750 µg/L was established (n=3). ISTD normalized difference (%) between 24 h (M27 and M18/21) and 72 h (Elinzanetant and M30/34) against nominal concentration was as follows: Elinzanetant (72 h) -6.3% (3.00 µg/L), -6.3% (750 µg/L) M27 (24 h) -13.7% (3.00 µg/L), -9.3% (750 µg/L) M30/34 (72 h) -11.7% (3.00 µg/L), -14.3% (750 µg/L) M18/21 (24 h) -12.3% (3.00 µg/L), -14.9% (750 µg/L)
Long term stability	All analytes were stable after storage at -85±10°C for 1158 days and at -25±5°C for 513 days. Elinzanetant and M27, but not M30/34 and M18/21, were stable at -20±5°C for 1158 days.

Source: Applicant's summary of biopharmaceutics, table 5-12

Table 192. Plasma Validation, (b) (4) 21186

Method description	Partial validation of a method for the quantitative determination of [$^{13}C_5$]Elinzanetant in human plasma samples by LC-MS/MS
Materials used for standard calibration curve and concentration	Human plasma and [$^{13}C_5$]Elinzanetant reference standards. Calibrator concentrations: 0.05, 0.10, 0.50, 2.50, 5.00, 25.0, 37.5 and 50.0 µg/L
Validated assay range	0.05 to 50.0 µg/L
Materials used for quality controls (QCs) and concentration	Control human plasma and [$^{13}C_5$]Elinzanetant reference standards. QC concentrations: 0.05, 0.15, 5.00 and 37.5 µg/L
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	Control human potassium EDTA plasma from (b) (4) and [$^{13}C_5$]Elinzanetant reference standard from Bayer AG, Germany. [$^{13}C_2$ $^2H_6$]Elinzanetant ISTD from Bayer AG, Germany.
Regression model and weighting	Linear, 1/x2 weighting

Validation parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8 (two sets)
	Cumulative accuracy (%bias) at LLOQ: [$^{13}C_5$]Elinzanetant	1.2%
	Cumulative precision (%CV) at LLOQ: [$^{13}C_5$]Elinzanetant	4.2%
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QCs (one batch)** [$^{13}C_5$]Elinzanetant	-13.0 to 0.6%
	Inter-batch %CV [$^{13}C_5$]Elinzanetant	0.4 to 6.4%

Validation parameters	Method Validation Summary
Selectivity & matrix effect	Selectivity was assessed by comparing blank peak heights (n=6) to the mean peak height of a sample prepared at the LLOQ. No significant interference with the analyte (≤ 20%) or internal standard (≤ 5%) was observed. <0.1% [$^{13}C_5$]Elinzanetant ≤0.1% [$^{13}C_2$ $^2H_6$]Elinzanetant ISTD The matrix factor was calculated as the ratio of the peak response in the presence of matrix ions to the mean peak response in the absence of matrix ions. The ISTD normalized matrix factor was calculated by dividing the matrix factor of the analyte by the matrix factor of the internal standard. The precision of the matrix factor evaluation met the acceptance criteria (≤15.0% CV) and the matrix factor was not considered to impact assay performance. [$^{13}C_5$]Elinzanetant (%CV) 3.4 to 6.9 (0.15 and 37.5 µg/L)

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Interference & specificity	The impact of elinzanetant concentrations up to 1000 µg/L on [$^{13}C_5$]Elinzanetant was evaluated. Three double blanks and three QC 0.05 µg/L samples were fortified with elinzanetant at a concentration of 100 and 1000 µg/L. The indicated elinzanetant concentration displayed a contribution of up to 92.9% of the LLOQ response in double blank samples and QC 0.05 µg/L samples fortified with 1000 µg/L elinzanetant were measured with 161.6% accuracy. The results indicated a significant interference of elinzanetant a concentration of 1000 µg/L in quantification of [$^{13}C_5$]Elinzanetant LLOQ concentration. No impact of the indicated elinzanetant concentrations on [$^{13}C_5$]Elinzanetant was found in samples fortified with 100 µg/L elinzanetant (LLOQ (0.05 µg/L): 105.2% and QC 5.00µg/L: 101.2%). This demonstrates that [$^{13}C_5$]Elinzanetant can be accurately measured in study samples that contain elinzanetant a concentration up to 2000- fold higher than the concentration of [$^{13}C_5$]Elinzanetant. Furthermore, the presence of elinzanetant up to 100 µg/L in BLQ study samples (< 0.0500 µg/L) does not result in a significant interference in the measurement of [$^{13}C_5$]Elinzanetant.

Validation parameters	**Method Validation Summary**
Bench-top/process stability	5 hours bench-top stability at 0.15 and 37.5 µg/L was established (n=3). ISTD normalized difference (%) between 5 h against nominal concentration was as follows: [$^{13}C_5$]Elinzanetant -2.0% (0.15 µg/L), -6.1% (37.5 µg/L)
Whole blood stability	Not assessed
Freeze-Thaw stability	0.15 and 37.5 µg /L QC samples were prepared, stored at ≤-20°C and at ≤-80°C and subjected to four freeze-thaw cycles. Mean difference between nominal and observed (%bias) and precision in each batch (%CV, n=3) at the respective QC level were below the following values: [$^{13}C_5$]Elinzanetant 0.15 and 37.5 µg/L at ≤-20°C -1.3%; -3.7% (bias) and 1.4%; 0.7% (%CV) 0.15 and 37.5 µg/L at ≤-80°C -4.7%; -2.7% (bias) and 2.5%; 1.4% (%CV)
Long-term storage	Low, and high QC samples (n=3) were prepared and stored at ≤-20°C and at ≤-80°C. Respective plasma stability for 61 days were as follows: [$^{13}C_5$]Elinzanetant ≤-20°C 3.3% (0.15 µg/L); 6.9% (37.5 µg/L) ≤-80°C 6.7% (0.15 µg/L); 2.1% (37.5 µg/L)
Parallelism	Not applicable
Carry over	The carry-over was calculated from a chromatographic run, where blank samples were injected after a ULOQ sample. The acceptance criteria for the analyte were ≤20% and the ISTD were ≤5% of the LLOQ signal and fulfilled after the second blank sample.

Source: Applicant's summary of biopharmaceutics, table 5-11

Table 193. Plasma Validation, VPT4371 APPEARS THIS WAY ON ORIGINAL

Method description	Method for the Determination of elinzanetant in Human Plasma (range 1.50 to 1000 µg/L) using LC-MS/MS
Materials used for standard calibration curve and concentration	Control human plasma and elinzanetant reference standards. Calibrator concentrations: 1.50, 3.00, 7.50, 30.0, 75.0, 300, 750, 1000 µg/L
Validated assay range	1.50 to 1000 µg/L
Materials used for quality controls (QCs) and concentration	Control human plasma and elinzanetant reference standards. QC concentrations: 4.50, 75.0 and 750 µg/L
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	Control human potassium EDTA plasma from (b) (4) Elinzanetant reference standard from (b) (4) (b) (4) [$^{2}H_6$,$^{13}C_2$]elinzanetant ISTD from NeRRe Therapeutics Ltd., UK
Regression model and weighting	Linear, 1/x2 weighting

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Validation parameters	**Method Validation Summary**	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ Cumulative accuracy (%bias) at LLOQ: Cumulative precision (%CV) at LLOQ:	8 (two sets) -0.2% 3.9%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs (6 for each batch) Inter-batch %CV	-1.3 to 3.3% 1.0 to 4.9%
Selectivity & matrix effect	Selectivity was assessed by comparing blank peak heights (n=6) to the mean peak height of a sample prepared at the LLOQ. No significant interference with the analyte (≤ 20%) or internal standard (≤ 5%) was observed. Mean internal standard normalized matrix factors for samples (n=6) prepared to contain elinzanetant were: 1.002 (4.50 µg/L) and 0.994 (750 µg/L)	

Validation parameters	Method Validation Summary
Interference & specificity	The interfering effect of the presence of itraconazole and hydroxy itraconazole (spiked at 350 and 500 µg/L, respectively) on the method for the quantification of elinzanetant was established by the analysis of validation samples and blank samples. No interferences were observed in blank samples (greater than 20% of the response at the LLOQ for elinzanetant and less than and 5% of the mean internal standard response for the internal standard).
Hemolysis effect	The working solution at the low (4.50 µg/L) and high (750 µg/L) concentration level was spiked into matrix containing hemolytic plasma (n=1). No significant influence of hemolytic plasma on the analysis of drug was observed.
Lipemic effect	The working solution at the low (4.50 µg/L) and high (750 µg/L) concentration level was spiked into matrix containing 5% hyperlipidemic plasma (n=1). No significant influence of hyperlipidemic plasma on the analysis of drug was observed.
Dilution linearity	6 replicate QC samples (15000 µg/L) with concentrations higher than the ULOQ of 1000 µg/L were diluted by a factor of 20 with blank human plasma prior to analysis. The calculated concentrations were compared to the nominal concentrations of the samples: 0.2% (%bias) and 0.7% (%CV)
Bench-top/process stability	24 hours bench-top stability at 4.50 and 750 µg/L was established. ISTD normalized difference (%) between 24 h against nominal concentration was as follows: Elinzanetant: -1.8% (4.50 µg/L), 0.6% (750 µg/L)
Whole blood stability	2 hours whole blood stability at 37°C for blood spiked with 4.50 and 750 µg/L was established by comparing the mean analyte to internal standard peak area ratio of samples extracted (25 µL aliquot with 150 µL of acetonitrile containing internal standard) after storage for 2 hours against those of the samples extracted immediately upon spiking. The difference (%) against nominal concentration was as follows: Elinzanetant: -2.4% (4.50 µg/L), -1.6% (750 µg/L)

Validation parameters	Method Validation Summary
Freeze-Thaw stability	4.50 and 750 µg/L QC samples were prepared, stored at ≤-20°C and at ≤-80°C and subjected to three freeze-thaw cycles Mean difference between nominal and observed (%bias) and precision in each batch (%CV, n=6) at the respective QC level were below the following values: Elinzanetant at 4.50 and 750 µg/L: -4.8 and 1.0 (%bias) and 1.1 and 0.5 (%CV)
Long-term storage	Low, and high QC samples (n=6) were prepared and stored at ≤-20°C and at ≤-80°C. Respective plasma stability periods were as follows: Elinzanetant at 4.50 and 750 µg/L: 579 days
Parallelism	Not applicable
Carry over	The carryover was calculated from a chromatographic run, where blank samples were injected after a ULOQ sample. The acceptance criteria for the analyte were ≤20% and the ISTD were ≤5% of the LLOQ signal and fulfilled after the second blank sample.

Source: Applicant's summary of biopharmaceutics, table 5-8

Table 194. Plasma Validation, NT81HPPV01

Method description	Determination of elinzanetant and M27 in Human Plasma using Liquid Chromatography with Tandem Mass Spectrometric Detection
Materials used for standard calibration curve and concentration	Human plasma, elinzanetant M27 reference standards. Calibrator concentrations: 1.00, 2.00, 10.0, 50.0, 300, 600, 900, 1000 µg/L
Validated assay range	1.00 to 1000 µg/L elinzanetant and M27)
Materials used for quality controls (QCs) and concentration	Control human plasma and elinzanetant and M27 reference standards. QC concentrations: 1.00, 3.00, 40.0, 400, 800 and 8000 µg/L
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	Control human potassium EDTA plasma, Elinzanetant reference standard from (b) (4) M27 reference standard from (b) (4) [$^{2}H_{6}$,$^{13}C_{2}$]Elinzanetant ISTD from (b) (4)
Regression model and weighting	Linear, 1/x2 weighting

Validation parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8 (two sets)
	Cumulative accuracy (%bias) at LLOQ:	
	Elinzanetant	-0.6%
	M27	0.0%
	Cumulative precision (%CV) at LLOQ:	
	Elinzanetant	3.2%
	M27	4.5%
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs (6 for each batch)**	
	Elinzanetant	-1.5 to 4.8%
	M27	-0.6 to 6.3%
	Inter-batch %CV	
	Elinzanetant	2.3 to 4.7%
	M27	4.0 to 8.8%

Validation parameters	Method Validation Summary
Selectivity & matrix effect	Selectivity was assessed by comparing blank peak heights (n=6) to the mean peak height of a sample prepared at the LLOQ. No significant interference with the analyte (≤ 20%) or internal standard (≤ 5%) for 5 out of 6 samples was observed. ≤7.0% (Elinzanetant) ≤10.0% (M27) The matrix factor was calculated as the ratio of the peak response in the presence of matrix ions to the mean peak response in the absence of matrix ions. The ISTD normalized matrix factor was calculated by dividing the matrix factor of the analyte by the matrix factor of the internal standard. The precision of the matrix factor evaluation met the acceptance criteria (≤15.0% CV) and the matrix factor was not considered to impact assay performance. Elinzanetant 1.01 (3.00 µg/L) and 1.02 (800 µg/L) M27 0.970 (3.00 µg/L) and 0.973 (800 µg/L)
Interference & specificity	The interfering effect of the presence of the not analyzed metabolites M18/21, M22 and M30/34 was investigated. LQC samples of elinzanetant or of M27 were spiked with 200 and 400 µg/L of M22, 1000 µg/L of M18/22 and 1000 µg/L of M30/34. Interfering effect of elinzanetant with other metabolites of elinzanetant was observed. It was observed that M18/21 interferes with M27 and M22 interferes with elinzanetant.
Hemolysis effect	The working solution at the low (3.00 µg/L) and high (800 µg/L) concentration level was spiked into matrix containing hemolytic plasma (n=6): Elinzanetant ≤±9.3% (%bias) and ≤2.3 (%CV) M27 ≤±9.7% (%bias) and ≤3.9 (%CV)
Lipemic effect	The working solution at the low (3.00 µg/L) and high (800 µg/L) concentration level was spiked into matrix containing 5% hyperlipidemic plasma (n=6): Elinzanetant ≤±6.0% (%bias) and ≤4.3 (%CV) M27 ≤±6.8% (%bias) and ≤5.4 (%CV)

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Validation parameters	Method Validation Summary
Dilution linearity	6 replicate QC samples (8000 µg/L) with concentrations higher than the ULOQ of 1000 µg/L were diluted by a factor of 10 with blank human plasma prior to analysis. The calculated concentrations were compared to the nominal concentrations of the samples: Elinzanetant ≤±4.1% (%bias) and ≤1.9 (%CV) M27 ≤±7.6% (%bias) and ≤1.9 (%CV)
Bench-top/process stability	24 hours bench-top stability at 3.00 and 800 µg/L was established (n=3). ISTD normalized difference (%) between 24 h against nominal concentration was as follows: Elinzanetant -0.7% (3.00 µg/L), -3.1% (800 µg/L) M27 -2.3% (3.00 µg/L), 0.4% (800 µg/L)
Whole blood stability	2 hours whole blood stability at room temperature for blood spiked with 40.0 µg/L was established by comparing the mean analyte to internal standard peak area ratio of samples extracted after storage for 2 hours against those of the samples extracted immediately upon spiking (n=3). The difference (%) against nominal concentration was as follows: Elinzanetant -2.4% (40.0 µg/L) M27 -2.3% (40.0 µg/L)
Freeze-Thaw stability	3.00 and 800 µg/L QC samples were prepared, stored at ≤-20°C and at ≤-80°C and subjected to four freeze-thaw cycles. Mean difference between nominal and observed (%bias) and precision in each batch (%CV, n=3) at the respective QC level were below the following values: Elinzanetant 3.00 and 800 µg/L at ≤-20°C -0.3%; -1.4% (bias) and 1.6%; 1.1% (%CV) 3.00 and 800 µg/L at ≤-80°C 0.0%; 0.9% (bias) and 1.4%; 0.9% (%CV) M27 3.00 and 800 µg/L at ≤-20°C 0.3%; 2.9% (bias) and 2.4%; 1.8% (%CV) 3.00 and 800 µg/L at ≤-80°C 0.3%; 5.1% (bias) and 4.0%; 1.6% (%CV)

Validation parameters	Method Validation Summary
Long-term storage	Low, and high QC samples (n=3) were prepared and stored at ≤-20°C and at ≤-80°C. Respective plasma stability for 77 days were as follows: Elinzanetant ≤-20° C -3.0% (3.00 µg/L); -1.6% (800 µg/L) ≤-80° C 2.0% (3.00 µg/L); 1.1% (800 µg/L) M27 ≤-20° C -6.3% (3.00 µg/L); -0.1% (800 µg/L) ≤-80° C 1.3% (3.00 µg/L); 3.4% (800 µg/L)
Parallelism	Not applicable
Carry over	The carry-over was calculated from a chromatographic run, where blank samples were injected after a ULOQ sample. The acceptance criteria for the analyte were ≤20% and the ISTD were ≤5% of the LLOQ signal and fulfilled after the second blank sample.

Source: Applicant's summary of biopharmaceutics, table 5-8.

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In-Study Performance of Elinzanetant and its Metabolites M27, M30/34, M18/21

Table 195. In-Study Performance of Method, VPT4371

Clinical Study ID	Analyte Code(s)	Run acceptance rate [%] (n)	Std. curve performance		QC performance		ISR passing rate
			%bias	%CV	%bias	%CV	%
814-1-01 (21677)	Elinzanetant	100 (20 of 20)	-1.5 to 1.8	≤ 4.2	-0.4 to 1.2	≤ 3.8	100
814-1-02 (21678)	Elinzanetant	100 (23 of 23)	-1.3 to 0.9	≤ 3.2	n.a.	n.a.	97.6
814-1-03 (21679)	Elinzanetant	100 (10 of 10)	-3.7 – 4.4	≤ 5.4	n.a.	n.a.	100
814-1-05 (21680)	Elinzanetant	100 (3 of 3)	-1.9 to 3.8	≤ 6.2	-2.0 to 1.4	≤ 5.1	100
RELENT-1 (21681)	Elinzanetant	97.4 (37 of 38)	-1.1 to 1.3	≤ 4.0	-0.8 to 4.3	≤ 11.2	98.4
Switch-1 (21686)	Elinzanetant	100 (9 of 9)	3.4 to 1.7	≤ 6.5	-1.7 to 0.4	≤ 5.4	100

Source: Applicant's summary of biopharmaceutics, table 5-20.

Table 196. In-Study Performance of Method NT81HPP V01 (Plasma, Parent and M27)

Clinical Study ID	Analyte Code(s)	Run acceptance rate	Std. curve performance		QC performance		ISR passing rate
		[%] (n)	%bias	%CV	%bias	%CV	%
814-1-07 (21703)	Elinzanetant	100 (11 of 11)	-1.3 to 1.2	≤ 6.1	-0.5 to 5.0	≤ 4.4	100
	M27	100 (9 of 9)	-2.0 to 3.0	≤ 5.4	-3.8 to 2.1	≤ 4.6	85.4

Source: Applicant's summary of biopharmaceutics, table 5-21.

Table 197. In-Study Performance of Plasma Method, (b) (4) 20320

Clinical Study ID	Analyte Code(s)	Run acceptance rate	Std. curve performance		QC performance		ISR passing rate
		[%] (n)	%bias	%CV	%bias	%CV	%
814-1-06 (21664)	Elinzanetant	100 (4 of 4)	-2.9 to 2.4	≤ 7.0	-1.9 to -0.4	≤ 3.0	100
	M27	100 (4 of 4)	-5.0 to 5.0	≤ 9.8	-9.0 to -0.8	≤ 9.2	95.2
	M30/34	100 (4 of 4)	-4.5 to 4.0	≤ 9.8	-9.3 to 0.0	≤ 6.6	95.2
	M18/21	100 (4 of 4)	-2.4 to 5.2	≤ 8.8	-5.7 to -1.0	≤ 6.2	95.2
	M22	100 (4 of 4)	-4.0 to 8.0	≤ 9.9	-2.0 to -1.3	≤ 10.9	n.a.[A]
21665	Elinzanetant	100 (16 of 16)	-3.2 to 3.0	≤ 7.0	2.4 to 5.0	≤ 7.1	91.6
	M27	100 (16 of 16)	-1.2 to 2.0	≤ 10.2	3.0 to 4.0	≤ 5.4	90.4
	M30/34	100 (16 of 16)	-2.2 to 1.1	≤ 7.4	0.3 to 3.3	≤ 6.8	89.2
	M18/21	100 (16 of 16)	-1.0 to 2.0	≤ 10.8	2.0 to 4.0	≤ 9.7	92.8
21666	Elinzanetant	100 (12 of 12)	-1.6 to 2.0	≤ 4.7	0.5 to 6.7	≤ 7.3	100
	M27	83.3 (15 of 18)	-2.2 to 1.0	≤ 10.4	0.8 to 6.3	≤ 7.1	100
	M30/34	93.8 (15 of 16)	-1.2 to 1.0	≤ 8.7	0.9 to 8.0	≤ 6.7	95.8
	M18/21	93.8(15 of 16)	-4.4 to 2.0	≤ 8.5	2.7 to 5.0	≤ 7.1	94.4
21667	Elinzanetant	94.7 (18 of 19)	-2.0 to 1.0	≤ 4.6	-2.1 to 4.7	≤ 3.3	100
	M27	94.7 (18 of 19)	-2.4 to 2.0	≤ 7.5	0.5 to 5.0	≤ 5.9	98.6
	M30/34	94.7 (18 of 19)	-3.4 to 2.0	≤ 7.0	-0.9 to 3.3	≤ 5.6	98.6
	M18/21	94.7 (18 of 19)	-3.6 to 4.0	≤ 10.1	-0.9 to 3.7	≤ 7.1	100
21668	Elinzanetant	96.3 (26 of 27)	-1.0 to 1.1	≤ 4.9	-0.8 to 5.3	≤ 7.6	99.1
	M27	88.9 (24 of 27)	-0.8 to 1.0	≤9.1	1.0 to 4.7	≤ 8.2	94.3
	M30/34	92.6 (25 of 27)	-2.0 to 2.0	≤7.5	-1.0 to 6.0	≤ 8.7	89.6
	M18/21	88.9 (24 of 27)	-1.0 to 0.7	≤9.7	1.0 to 3.7	≤ 7.3	92.5
21669	Elinzanetant	100 (10 of 10)	-0.9 to 1.2	≤ 5.0	-1.5 to 1.7	≤ 5.6	98.6
	M27	90.0 (9 of 10)	-3.0 to 1.7	≤9.1	-0.9 to 1.3	≤ 6.2	97.3
	M30/34	90.0 (9 of 10)	-1.0 to 1.0	≤5.6	-3.5 to 0.0	≤ 3.4	98.6
	M18/21	90.0 (9 of 10)	-4.0 to 2.0	≤6.7	-1.9 to 7.0	≤ 8.0	95.9
21670	Elinzanetant	100 (15 of 15)	-3.8 to 1.6	≤ 4.8	-0.8 to 2.3	≤ 4.3	100
	M27	100 (15 of 15)	-3.6 to 1.9	≤6.4	-1.1 to 0.7	≤ 5.8	100
	M30/34	100 (15 of 15)	-3.4 to 1.2	≤5.4	-1.2 to 1.0	≤ 5.0	100
	M18/21	100 (15 of 15)	-3.4 to 2.0	≤6.8	-0.5 to 2.7	≤ 7.9	100
21756	Elinzanetant	100 (10 of 10)	-0.6 to 1.0	≤ 5.1	-1.2 to 2.7	≤ 4.7	100
	M27	100 (8 of 8)	-1.5 to 1.0	≤8.6	-2.3 to 5.7	≤ 4.6	100
	M30/34	100 (8 of 8)	-0.2 to 0.2	≤3.8	-1.7 to 4.0	≤ 4.3	100
	M18/21	80.0 (8 of 10)	-1.0 to 0.5	≤6.8	-1.6 to 2.0	≤ 5.2	100
21772	Elinzanetant	100 (13 of 13)	-5.0 to 5.0	≤ 5.0	1.0 to 5.0	≤ 3.4	98.5
	M27	100 (13 of 13)	-2.5 to 3.0	≤8.4	2.7 to 7.0	≤ 6.7	86.6
	M30/34	100 (13 of 13)	-4.8 to 5.0	≤7.0	0.3 to 4.7	≤ 7.7	95.5
	M18/21	86.7 (13 of 15)	-6.9 to 4.4	≤8.4	4.1 to 9.3	≤ 14.2	89.6
21774	Elinzanetant	100 (32 of 32)	-0.8 to 0.5	≤ 4.8	-1.9 to 4.7	≤ 4.1	97.1
	M27	93.8 (30 of 32)	-2.5 to 2.2	≤8.5	0.0 to 4.7	≤ 6.7	93.3
	M30/34	93.8(30 of 32)	-2.1 to 3.0	≤7.5	-1.2 to 4.0	≤ 7.9	94.2
	M18/21	87.5 (28 of 32)	-2.5 to 2.4	≤9.6	-1.5 to 4.7	≤ 6.8	97.1
21840	Elinzanetant	100 (10 of 10)	-1.6 to 1.9	≤ 4.6	-2.4 to -0.3	≤ 4.8	100
	M27	100 (10 of 10)	-1.2 to 1.9	≤7.5	-4.1 to -1.3	≤ 7.2	100
	M30/34	100 (10 of 10)	-1.0 to 1.0	≤3.5	-3.3 to 0.0	≤ 4.6	100
	M18/21	100 (10 of 10)	-1.7 to 2.2	≤6.3	-5.5 to 1.3	≤ 6.6	100

A: All values were below LLOQ, therefore no ISR performed

Source: Applicant's summary of biopharmaceutics, table 5-25.

Table 198. In-Study Performance of Plasma Method, (b) (4) 22103

Clinical Study ID	Analyte Code(s)	Run acceptance rate	Std. curve performance		QC performance		ISR passing rate
		[%] (n)	%bias	%CV	%bias	%CV	%
21651	Elinzanetant	100 (25 of 25)	-1.2 to 1.0	≤ 6.8	-1.6 to 2.7	≤ 8.0	94.4
	M27	100 (25 of 25)	-2.0 to 1.0	≤6.7	-1.6 to 1.3	≤ 7.3	96.8
	M30/34	100 (25 of 25)	-1.2 to 1.0	≤5.8	-2.0 to 2.0	≤ 6.4	96.0
	M18/21	100 (25 of 25)	-2.0 to 1.0	≤8.3	-2.1 to 2.3	≤ 6.8	96.8
21652	Elinzanetant	100 (25 of 25)	-1.6 to 1.0	≤ 4.9	-1.2 to 3.0	≤ 4.4	97.7
	M27	100 (25 of 25)	-2.0 to 1.3	≤6.6	-1.1 to 1.3	≤ 5.8	96.8
	M30/34	100 (25 of 25)	-2.4 to 2.0	≤5.9	-1.6 to 2.0	≤ 4.4	96.8
	M18/21	100 (25 of 25)	-2.4 to 2.0	≤6.4	-1.5 to 3.0	≤ 5.7	96.8
21670	Elinzanetant	100 (15 of 15)	-3.8 to 1.6	≤ 4.8	-0.8 to 2.3	≤ 4.3	100
	M27	100 (15 of 15)	-3.6 to 1.9	≤6.4	-1.1 to 0.7	≤ 5.8	100
	M30/34	100 (15 of 15)	-3.4 to 1.2	≤5.4	-1.2 to 1.0	≤ 5.0	100
	M18/21	100 (15 of 15)	-3.4 to 2.0	≤6.8	-0.5 to 2.7	≤ 7.9	100
21810	Elinzanetant	100 (27 of 27)	-1.6 to 2.0	≤ 5.1	-1.5 to 2.3	≤ 6.1	97.6
	M27	100 (27 of 27)	-1.5 to 1.0	≤6.6	-1.3 to 2.0	≤ 6.4	96.7
	M30/34	100 (27 of 27)	-2.0 to 1.0	≤5.3	-2.1 to 0.7	≤ 5.6	98.5
	M18/21	100 (27 of 27)	-1.8 to 2.0	≤6.5	-1.5 to 2.0	≤ 7.0	98.5
22004	Elinzanetant	100 (4 of 4)	-1.4 to 1.4	≤ 5.8	-0.9 to 1.0	≤ 8.6	100
	M27	100 (4 of 4)	-2.0 to 2.2	≤9.1	1.3 to 2.3	≤ 5.3	100
	M30/34	100 (4 of 4)	-1.5 to 2.5	≤5.5	-1.5 to 1.0	≤ 8.4	100
	M18/21	100 (4 of 4)	-1.8 to 1.6	≤5.9	-3.7 to 3.3	≤ 10.2	100
22050	Elinzanetant	100 (16 of 16)	-1.2 to 0.5	≤5.8	-2.9 to 3.7	≤10.8	100
	M27	100 (16 of 16)	-2.5 to 2.5	≤7.2	-3.3 to 2.3	≤12.2	100
	M30/34	100 (16 of 16)	-2.1 to 0.8	≤5.0	-3.6 to 4.7	≤12.3	100
	M18/21	100 (16 of 16)	-2.3 to 2.0	≤6.8	-5.3 to 0.7	≤13.1	100
22081	Elinzanetant	100 (6 of 6)	-0.5 to 0.5	≤7.2	-0.3 to 3.0	≤4.1	100
	M27	100 (5 of 5)	-5.0 to 3.0	≤4.9	0.1 to 3.0	≤5.9	100
	M30/34	100 (5 of 5)	-1.5 to 1.0	≤4.2	-1.3 to 3.7	≤3.5	100
	M18/21	100 (5 of 5)	-3.0 to 2.0	≤4.7	0.0 to 4.3	≤4.0	100
22653	Elinzanetant	100 (6 of 6)	-1.0 to 1.0	≤2.8	0.9 to 3.0	≤2.0	100
	M27	100 (6 of 6)	-1.3 to 1.0	≤4.9	0.3 to 2.3	≤6.3	100
	M30/34	100 (6 of 6)	-0.6 to 1.0	≤3.5	-0.4 to 2.0	≤3.5	100
	M18/21	100 (6 of 6)	-1.0 to 2.0	≤5.5	1.9 to 4.7	≤4.3	100

Source: Applicant's summary of biopharmaceutics, table 5-26.

Table 199. In-Study Performance of Plasma Method, (b) (4) 21186

Clinical Study ID	Analyte Code(s)	Run acceptance rate	Std. curve performance		QC performance		ISR passing rate
		[%] (n)	%bias	%CV	%bias	%CV	%
21668	[$^{13}C_5$]Elinzanetant	100 (8 of 8)	-5.5 to 2.4	≤5.2	-1.1 to 6.7	≤4.6	86.5

Source: Applicant's summary of biopharmaceutics, table 5-28.

Protein Binding Quantification

Table 200. Protein Binding Qualification Data for Elinzanetant, (b) (4) 21285

Bioanalytical method validation report name, amendments, and hyperlinks	Bioanalytical Method and Qualification Data for Clinical Studies Bayer AG Report ID: Module 4.2.2.1, R-14310
Method description	Qualification of a method for the determination of elinzanetant in various matrices for plasma protein binding samples by LC-MS/MS
Materials used for standard calibration curve and concentration **Validated assay range**	Human plasma, PBS and elinzanetant reference standards. Calibrator concentrations: 1.00, 2.00, 10.0, 50.0, 100, 500, 750, 1000 µg/L 1.00 to 1000 µg/L
Materials used for quality controls (QCs) and concentration	Control human potassium EDTA plasma, PBS and elinzanetant reference standards. QC concentrations: 1.00, 3.00, 100 and 750 µg/L
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	Control human potassium EDTA plasma from (b) (4) and PBS (b) (4) Elinzanetant reference standard from Bayer AG, Germany. [$^{13}C_2$ $^{2}H_6$]Elinzanetant ISTD from Bayer AG, Germany.
Regression model and weighting	Linear, 1/x2 weighting

Validation parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8 (two sets)
	Cumulative accuracy (%bias) at LLOQ:	
	Elinzanetant in PBS/Plasma (9/1, v/v)	0.0%
	Elinzanetant in PBS with 0.2% Triton X-100	-0.5%
	Cumulative precision (%CV) at LLOQ:	
	Elinzanetant in PBS/Plasma (9/1, v/v)	1.4%
	Elinzanetant in PBS with 0.2% Triton X-100	0.9%

Validation parameters	Method Validation Summary	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QCs (6 for each batch)**	
	Elinzanetant in PBS/Plasma (9/1, v/v)	-4.5 to 4.7%
	Elinzanetant in PBS with 0.2% Triton X-100	-3.1 to 4.7%
	Inter-batch %CV	
	Elinzanetant in PBS/Plasma (9/1, v/v)	0.5 to 4.5%
	Elinzanetant in PBS with 0.2% Triton X-100	0.7 to 4.4%
Selectivity & matrix effect	Not assessed	
Interference & specificity	Not assessed	
Hemolysis effect	Not assessed	
Lipemic effect	Not assessed	
Dilution linearity	5 replicate QC samples (20000 µg/L) with concentrations higher than the ULOQ of 1000 µg/L were diluted by a factor of 50 with blank human plasma prior to analysis. The calculated concentrations were compared to the nominal concentrations of the samples: Elinzanetant in PBS/Plasma (9/1, v/v) ≤±4.5% (%bias) and ≤2.6% (%CV) Elinzanetant in PBS with 0.2% Triton X-100 ≤±13.0% (%bias) and ≤4.4% (%CV)	
Bench-top/process stability	Bench-top stability at 3.00 and 750 µg/L was established (n=3). ISTD normalized difference (%) between 4 hours against nominal concentration was as followed (n=3): Elinzanetant in PBS/Plasma (9/1, v/v) ≤±6.0% (%bias) and ≤1.5% (%CV) Elinzanetant in PBS with 0.2% Triton X-100 ≤±3.6% (%bias) and ≤2.3% (%CV)	
Whole blood stability	Not assessed	

Validation parameters	Method Validation Summary
Freeze-Thaw stability	3.00 and 750 µg/L QC samples were prepared, stored at ≤-20°C and at ≤-85°C subjected to three freeze-thaw cycles. Mean difference between nominal and observed (%bias) and precision in each batch (%CV, n=3) at the respective QC level were below the following values: Elinzanetant in PBS/Plasma (9/1, v/v) ≤-20°C ≤±12.0% (%bias) and ≤4.9% (%CV) ≤-85°C ≤±11.5% (%bias) and ≤3.2% (%CV) Elinzanetant in PBS with 0.2% Triton X-100 ≤-20°C ≤±5.6% (%bias) and ≤1.1% (%CV) ≤-85°C ≤±6.5% (%bias) and ≤1.0% (%CV)
Long-term storage	Not assessed
Parallelism	Not applicable
Carry-over	The carry-over was calculated from a chromatographic run, where blank samples were injected after a ULOQ sample. The carry-over was 0.1 % of the ULOQ signal or below in both matrices for elinzanetant. The carry-over was below 20 % of the mean area observed at LLOQ in the second blank sample following injection of the ULOQ in both matrices. In both matrices, no significant carry-over was observed for the internal standard which would have an impact on the analysis of study samples

Source: Applicant's summary of biopharmaceutics, table 5-16

Table 201. Protein Binding Qualification Data for Plasma Validation Data for M27, M30/34 and M18/21, (b) (4) 21067

Bioanalytical method validation report name, amendments, and hyperlinks	Bioanalytical Method and Qualification Data for Clinical Studies Bayer AG Report ID: Module 4.2.2.1, R-13903
Method description	Qualification of a method for the determination of M27, M30/34 and M18/21 in various matrices for plasma protein binding samples by LC-MS/MS
Materials used for standard calibration curve and concentration	Human plasma, M27, M30/34 and M18/21 reference standards. Calibrator concentrations: 1.00, 2.00, 10.0, 50.0, 100, 500, 750, 1000 µg/L
Validated assay range	1.00 to 1000 µg/L for all analytes
Materials used for quality controls (QCs) and concentration	Control human plasma, PBS and M27, M30/34 and M18/21 reference standards. QC concentrations: 1.00, 3.00, 100 and 750 µg/L
Minimum required dilutions (MRDs)	Not applicable
Source and lot of reagents	Control human potassium EDTA plasma from (b) (4) and PBS (b) (4) M27, M30/34 and M18/21 reference standard from (b) (4) Netupitant from (b) (4)
Regression model and weighting	quadratic, 1/x weighting for all analytes

Validation parameters	**Method Validation Summary**	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8 (two sets)
	Cumulative accuracy (%bias) at LLOQ (PBS/Plasma (9/1, v/v):	
	M27	-4.5%
	M30/34	2.0%
	M18/21	-2.0%
	Cumulative accuracy (%bias) at LLOQ (PBS containing Triton X-100):	
	M27	-10.8%
	M30/34	2.0%
	M18/21	-7.1%
	Cumulative precision (%CV) at LLOQ (PBS/Plasma (9/1, v/v):	
	M27	5.3%
	M30/34	5.0%
	M18/21	6.9%
	Cumulative precision (%CV) at LLOQ (PBS containing Triton X-100):	
	M27	2.8%
	M30/34	5.9%
	M18/21	3.2%

Validation parameters	**Method Validation Summary**	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QCs (6 for each batch)**	
	PBS/Plasma (9/1, v/v):	
	M27	-4.3 to 6.0%
	M30/34	-2.0 to 6.0%
	M18/21	-4.7 to 1.0%
	PBS containing Triton X-100:	
	M27	-16.1 to 3.7%
	M30/34	-3.5 to 3.0%
	M18/21	-7.4 to 3.0%
	Inter-batch %CV	
	PBS/Plasma (9/1, v/v):	
	M27	1.5 to 7.7%
	M30/34	0.9 to 4.8%
	M18/21	0.8 to 6.3%
	PBS containing Triton X-100:	
	M27	0.5 to 5.6%
	M30/34	0.8 to 4.4%
	M18/21	0.7 to 10.4%
Selectivity & matrix effect	Not assessed	
Interference & specificity	Not assessed	
Hemolysis effect	Not assessed	
Lipemic effect	Not assessed	

Validation parameters	Method Validation Summary
Dilution linearity	5 replicate QC samples (3000 µg/L) with concentrations higher than the ULOQ of 1000 µg/L were diluted by a factor of 30 with blank human plasma prior to analysis. The calculated concentrations were compared to the nominal concentrations of the samples: PBS/Plasma (9/1, v/v) M27 ≤±6.0% (%bias) and ≤1.8 (%CV) M30/34 ≤±0.3% (%bias) and ≤1.3 (%CV) M18/21 ≤±5.3% (%bias) and ≤2.1 (%CV) PBS with 0.2% Triton X-100 M27 ≤±6.7% (%bias) and ≤1.0 (%CV) M30/34 ≤±0.7% (%bias) and ≤0.7% (%CV) M18/21 ≤±6.0% (%bias) and ≤1.5% (%CV)
Bench-top/process stability	Bench-top stability at 3.00 and 750 µg/L was established (n=3). ISTD normalized difference (%) between 4.25 hours against nominal concentration was as followed (n=3): PBS/Plasma (9/1, v/v) M27 ≤±4.0% (%bias) and ≤3.3% (%CV) M30/34 ≤±0.7% (%bias) and ≤2.1% (%CV) M18/21 ≤±2.5% (%bias) and ≤1.4% (%CV) PBS with 0.2% Triton X-100 M27 ≤±3.7% (%bias) and ≤1.3% (%CV) M30/34 ≤±1.3% (%bias) and ≤1.4% (%CV) M18/21 ≤±1.3% (%bias) and ≤6.9% (%CV)
Whole blood stability	Not assessed

Validation parameters	Method Validation Summary
Freeze-Thaw stability	3.00 and 750 µg/L QC samples were prepared, stored at ≤-20°C and at ≤-85°C subjected to three freeze-thaw cycles. Mean difference between nominal and observed (%bias) and precision in each batch (%CV, n=3) at the respective QC level were below the following values: PBS/Plasma (9/1, v/v) M27 ⩽-20° C ≤±7.0% (%bias) and ≤4.1% (%CV) ⩽-85° C ≤±12.4% (%bias) and ≤6.2% (%CV) M30/34 ≤-20°C ≤±4.4% (%bias) and ≤3.4% (%CV) ≤-85°C ≤±12.3% (%bias) and ≤3.1% (%CV) M18/21 ≤-20°C ≤±12.7% (%bias) and ≤2.8% (%CV) ≤-85°C ≤±14.8% (%bias) and ≤9.4% (%CV) PBS with 0.2% Triton X-100 M27 ≤-20°C ≤±7.6% (%bias) and ≤8.8% (%CV) ≤-85°C ≤±10.1% (%bias) and ≤6.9% (%CV) M30/34 ≤-20°C ≤±9.0% (%bias) and ≤2.6% (%CV) ≤-85°C ≤±8.7% (%bias) and ≤3.5% (%CV) M18/21 ≤-20°C ≤±7.7% (%bias) and ≤8.0% (%CV) ≤-85°C ≤±9.3% (%bias) and ≤4.8% (%CV)
Long-term storage	Not assessed
Parallelism	Not applicable

Validation parameters	Method Validation Summary
Carry-over	The carry-over was calculated from a chromatographic run, where blank samples were injected after a ULOQ sample. The carry-over was below 0.1 % for M27, M30/34 and M18/21 after the highest calibration sample in both matrices. The carry-over was below 20 % of the mean area observed at LLOQ for all analytes in the first blank sample following injection of the ULOQ in both matrices. In both matrices, no significant carry-over was observed for the internal standard which would have an impact on the analysis of study samples

Source: Applicant's summary of biopharmaceutics, table 5-27.

FDA Analysis

The acceptance criteria and performance of the bioanalytical methods are in compliance with the Agency's Bioanalytical Method Validation Guidance (May 2018). Study samples were analyzed within the stability period. Therefore, the performance of the bioanalytical methods in clinical studies are acceptable.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Population PK Analysis

14.5.1.1. Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of describing the pharmacokinetics of elinzanetant and its metabolite M30/34 and providing exposure metrics for E-R analyses. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 202.

Table 202. Specific Comments on Applicant's Final Population PK model

Utility of the Final Model			FDA Analysis
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	No clinically relevant differences in the effects of race on the pharmacokinetics of LYNKUET were observed.	The statement is acceptable. Race is not a significant covariate in the final model. The effect of race on $AUC_{(0-24),ss}$ is not clinically relevant (Figure 68)
		Population pharmacokinetic analysis of the clinical trial data indicate similar exposure of elinzanetant in patients with mild and moderate renal impairment compared to patients with normal renal function.	The statement is acceptable. The $AUC_{(0-24),ss}$ of elinzanetant was similar in patients with mild and moderate renal impairment and patients with normal renal function (Figure 70).
Derive exposure metrics for Exposure-response analyses	$C_{trough,ss}$, $C_{max,ss}$		The exposure metrics were calculated based on individual PK parameters and individual dose records. Given the low to moderate level of shrinkage for these parameters in the final model, the Applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses (Table 205).

Source: Module 5.3.3.5, Population Pharmacokinetic Analysis Report
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{trough}, trough concentration; PK, pharmacokinetic; ss, steady state

14.5.1.2. Introduction

The primary objectives of the Applicant's analysis were:

(1) To develop a population pharmacokinetic model for elinzanetant, based on the existing model, to robustly describe the observed pharmacokinetics in OASIS 1, OASIS 2, and OASIS 3 studies.

(2) To assess the variability in pharmacokinetics of elinzanetant in healthy subjects and patients with vasomotor symptoms.

(3) To evaluate the contributions of intrinsic and extrinsic covariates to the variability of elinzanetant pharmacokinetics in healthy subjects and patients with VMS.

(4) To derive individual pharmacokinetic exposure variables for each patient of OASIS 1, OASIS 2, and OASIS 3 studies to be used in future E-R analyses.

(5) To implement an exploratory PK/PD assessment which will simulate occupancy at the NK1 and NK3 receptors for patients in the OASIS 1, OASIS 2 and OASIS 3 studies.

14.5.1.3. Model Development

14.5.1.3.1. Data

The PK analyses for elinzanetant were based on PK data from 11 Phase 1 studies in female healthy subjects, 1 Phase 2 study in women with VMS, and 3 Phase 3 studies in women with VMS. Brief descriptions of the studies included are presented in Table 203.

The overall percent of BLQ samples for elinzanetant, M30/34, M27, and M18/21 was 4.60%, 6.86%, 7.79%, and 8.93%, respectively. These observations were excluded from PK model development but included in model qualification. It seems to be reasonable to exclude BLQ samples. The final NONMEM data file for elinzanetant model development contained 8,703 elinzanetant observations from 1,318 subjects and 5,932 M30/34, 5,873 M27, and 5,800 M18/21 observations from 1,079 subjects. Table 204 provides summary statistics of the baseline demographic covariates in the PK analysis dataset.

Table 203. Summary of Studies With PK Sampling Included in Population PK Analysis

Clinical Study No.	Description	Treatment	Number of Subjects With PK Data	Planned PK Observations
21665	Phase I, randomized, cross-over study to assess relative bioavailability. Single dosing.	Soft gel capsule • Group 1: dosing 1h after standard meal • Group 2: dosing 3h after standard meal • Treatment A: 3 x 40 mg • Treatment B: 2 x 60 mg • Period 1: Treatment A or B • Period 2: Treatment A or B (whichever they did not receive in Period 1)	20 healthy females (10 in each treatment group)	Elinzanetant, M27, M30/34, M18/21 • 0h (predose), 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 20h, 24h, 36h. • Additional samples during Period 1: 60h, 84h, 108h, 132h, 156h, 180h, 204h, 228h, 252h, 276h, 300h, 324h. • Additional samples during Period 2: 60h, 84h, 108h, 132h.
21677	Phase I, partly randomized, three-way cross-over study to explore influence of formulation and feeding on pharmacokinetics. Single dosing.	• Period 1: 100 mg hard gel capsule or 25 mg soft gel capsule administered after overnight fast. • Period 2: 100 mg hard gel capsule or 25 mg soft gel capsule administered after overnight fast (whichever they did not receive in Period 1). • Period 3: 25 mg soft gel capsule administered after a high fat breakfast.	36 healthy females (18 in each treatment arm)	Elinzanetant • Periods 1 and 2: 0h (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 72h. • Period 3c: 0h (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 72h.

Clinical Study No.	Description	Treatment	Number of Subjects With PK Data	Planned PK Observations
21678	Phase I, within-subject cross-over food interaction study. Single and multiple dosing.	40 mg, 80 mg, 120 mg and 160 mg, soft gel capsule administered on Day 1 after a high fat breakfast, on Day 11 after 10 hour fast and on Days 12-17 3 hours after a normal breakfast.	49 healthy females	Elinzanetant • Study Day 1: 0h (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 72h. • Study Day 11: 0 (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, 12h, 24h. • Study Day 17: 0 (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, 12h, 24h, 36h, 48h, 72h.
21703	Phase I, metabolite PK study. Multiple dosing.	Once daily dose of 120 mg, soft gel capsule, for 14 days. First dose after 10 hour fast, all other doses 3 hours after normal breakfast.	12 healthy females	Elinzanetant, M27, M30/34, M18/21 • Study Day 1: 0h (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h, 24h. • Study Days 5 and 8: 0 (predose). • Study Day 14: 0 (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h, 24h, 36h, 48h, 72h, 96h, 120h, 168h.
21772	Phase I, fixed-sequence cross-over, esomeprazole interaction and absolute bioavailability study. Single dosing.	• Period 1: single oral 120 mg, soft gel capsule elinzanetant and 100 µg [$^{13}C_5$]-elinzanetant via IV administered 1 hour after oral dose following overnight fast. • Period 2: Daily dose of 40 mg esomeprazole for 5 days, of 5th day a single 120 mg soft gel capsule of elinzanetant three hours after esomeprazole administration following overnight fast.	14 healthy males and females	Elinzanetant, M27, M30/34, M18/21 • Periods 1: 0h (predose), 0.25h, 0.5h, 0.75h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 7.5h, 10.5h, 13.5h, 17.5h, 24h, 48h, 72h, 96h, 120h, 144h, 168h. • Period 2: 0h (predose), 0.25h, 0.5h, 0.75h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 7.5h, 10.5h, 13.5h, 17.5h, 24h, 48h, 72h, 96h, 120h, 144h, 168h.

Clinical Study No.	Description	Treatment	Number of Subjects With PK Data	Planned PK Observations
21679	Phase I, single-sequence cross-over, itraconazole interaction study. Single dosing.	Single dose 40 mg soft gel capsule 90 minutes after standard breakfast on study Days 1 and 15. Once daily 200 mg oral itraconazole on Days 12 to 21.	16 healthy females	Elinzanetant • Study Day 1: 0h (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 168h. • Study Day 15: 0h (predose), 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, 168h.
21686 (SWITCH-1)	Phase IIb, randomized, placebo controlled, adaptive design study of safety and efficacy study in VMS patients. Multiple dosing.	Five dosing cohorts: once daily dose of 40 mg, 80 mg, 120 mg, 160 mg or placebo. Soft gel capsule for 12 weeks. All doses are to be taken at approximately the same time each evening.	139 female VMS patients	Elinzanetant • One sample at Weeks 2, 4, 8 and 12.
21668	Phase I, nonrandomized, hepatic impairment study. Single and multiple dosing.	120 mg once daily soft gel capsule on Day 1 and from Days 3 to 8.	16 healthy male and female control subjects	Elinzanetant, M27, M30/34, M18/21 • Study Day 1: 0h (predose), 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 24h, 36h, 48h. • Study Days 4 to 7g: 0 (predose) • Study Day 8: 0h (predose), 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 24h, 48h, 72h, 120h, 168h.
21669	Phase I, nonrandomized, renal impairment study. Single dose.	Single 120 mg soft gel capsule	12 healthy male and female control subjects	Elinzanetant, M27, M30/34, M18/21 • Study Day 1: 0h (predose), 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 24h, 31h, 36h, 48h, 55h, 60h, 72h, 79h, 84h, 96h, 103h, 108h, 120h.

Clinical Study No.	Description	Treatment	Number of Subjects With PK Data	Planned PK Observations
21840	Phase I, fixed-sequence cross-over, midazolam interaction study. Multiple dosing.	Period 1: single 1 mg midazolam. Period 2: single 1 mg midazolam and 120 mg soft gel capsule. Period 3: Once daily dose of 120 soft gel capsule on Days -13 to -1. Single 1 mg midazolam and 120 mg soft gel capsule on Day 1.	15 healthy males and females	Elinzanetant, M27, M30/34, M18/21 • Period 2, Study Day 1: 0h (predose), 0.5h, 0.75h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h, 16h, 24h, 48h. • Period 3, Study Days -13, -11, -9, -7,-5, -3, -2 & -1: 0h (predose). • Period 3, Study Day 1: 0h (predose), 0.5h, 0.75h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h, 16h, 24h.
22004	Phase I, fixed-sequence cross-over, tamoxifen interaction study. Multiple dosing.	Period 1: single 20 mg tamoxifen. Period 2: once daily 120 mg soft gel capsule on Days -6 to -1. Once daily 120 mg soft gel capsule on Days 1 to 22. Single 20 mg tamoxifen on Day 1.	18 healthy males and females	Elinzanetant, M27, M30/34, M18/21 • Period 2, Study Days -4 to -1: 0h (predose) • Period 2, Study Day 1: 0h (predose), 0.5h, 1h, 1.5h, 2h, 3h, 4h, 5h, 6h, 8h, 12h, 16h, 24h
22050	Phase I, randomized 2-fold crossover, new versus old batch study. Single and multiple dosing.	Soft gel capsule • Treatment A: 3 x 40 mg • Treatment B: 2 x 60 mg • Period 1: Treatment A or B as single dose on Day 1, and once daily on Days 4 to 12. • Period 2: Treatment A or B (whichever they did not receive in Period 1) single dose on Day 1, and once daily on Days 4 to 12	18 healthy males and females	Elinzanetant, M27, M30/34, M18/21 • Periods 1 and 2, Study Day 1: 0h (predose), 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 20h, 24h, 36h, 48h, 60h, 72h. • Periods 1 and 2, Study Days 4 to 11: 0h (predose). • Periods 1 and 2, Study Day 12: 0h (predose), 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 22h, 24h, 36h.

Clinical Study No.	Description	Treatment	Number of Subjects With PK Data	Planned PK Observations
21651 (OASIS 1)	Phase III, randomized, placebo controlled, safety and efficacy study in VMS patients. Multiple dosing.	Once daily 120 mg soft gel capsule	332 female VMS patients planned (166 on elinzanetant throughout the study, 166 begin study on placebo then switch to elinzanetant)	Elinzanetant, M27, M30/34, M18/21 • Week 1, postdose at 0.5-3h. • Week 16, 0h (predose), and two samples between 0.5-4h, at least 1h apart. • Week 26, one sample any time during visit to clinic.
21652 (OASIS 2)	Phase III, randomized, placebo controlled, safety and efficacy study in VMS patients. Multiple dosing.	Once daily 120 mg soft gel capsule	332 female VMS patients planned (166 on elinzanetant throughout the study, 166 begin study on placebo then switch to elinzanetant)	Elinzanetant, M27, M30/34, M18/21 • Week 1, postdose at 0.5-3h. • Week 16, 0h (predose), and two samples between 0.5-4h, at least 1h apart. • Week 26, one sample any time during visit to clinic.
21810 (OASIS 3)	Phase III, randomized, placebo controlled, safety and efficacy study in VMS patients. Multiple dosing.	Once daily 120 mg soft gel capsule	300 female VMS patients planned for treatment arm (placebo arm does not switch to elinzanetant)	Elinzanetant, M27, M30/34, M18/21 • Week 1, postdose at 0.5-3h. • Week 18, 0h (predose), and two samples between 0.5-4h, at least 1h apart. • Week 24, one sample any time during visit to clinic. • Week 52, one sample any time during visit to clinic.

Source: Applicant's Population PK report, Tables 9-3 and 9-4
Abbreviations: IV, intravenous; M, metabolite; PK, pharmacokinetic; VMS, vasomotor syndrome

Table 204. Summary of Baseline Continuous and Categorical Covariates for PK Analysis

A: Continuous covariates

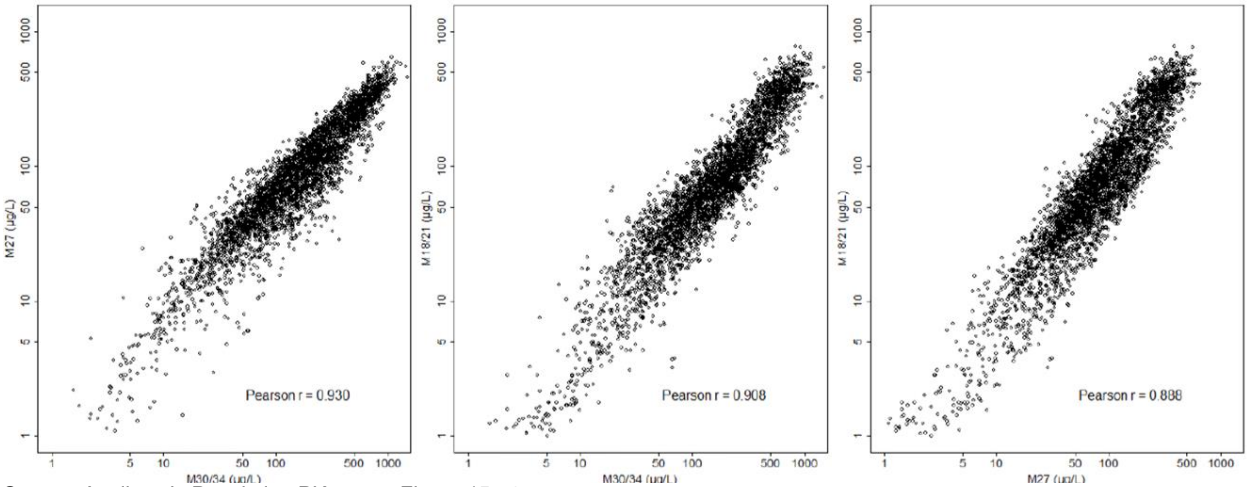
Covariate[a] (unit)	N	Min.	Max.	Median	Arith. Mean	Arith. s.d.	Arith. CV (%)	Geometric mean	Geometric s.d.	Geometric CV (%)
AGE (y)	1318	22	75	54.0	54.4	5.55	10.2	54.06	1.12	11.1
WGHT (kg)	1318	45.1	129.2	72.4	74.0	13.5	18.2	72.85	1.20	18.0
HGHT (cm)	1318	142.8	189	164.0	163.9	6.70	4.08	163.8	1.04	4.08
BMI (kg/m^2)	1318	17.8	41.4	27.1	27.5	4.52	16.4	27.15	1.18	16.5
LBM (kg)	1318	33.9	68.0	48.0	48.3	4.78	9.91	48.03	1.10	9.94
AST (U/L)	1318	7.0	106	23.0	23.7	7.63	32.2	22.74	1.32	28.3
ALT (U/L)	1318	5.0	104	21.0	23.4	11.2	47.8	21.44	1.50	42.6
ALP (U/L)	1318	32.0	368	83.0	86.6	24.4	28.2	83.57	1.30	27.0
BILI (mg/dL)	1318	0.050	1.8	0.380	0.409	0.219	53.5	0.359	1.70	56.7
ALB (g/dL)	1318	3.2	5.53	4.60	4.59	0.321	6.99	4.57	1.07	7.14
EGFR (mL/min)	1318	41.6	156.6	93.4	93.2	16.4	17.6	91.72	1.20	18.1

B: Categorical covariates

Covariate	Category	Number of subjects	% of subjects
RACE	White [RACE=1]	1056	80.1
	Black [RACE=2]	213	16.2
	Asian [RACE=3]	7	0.5
	American Indian [RACE=4]	6	0.5
	Other [RACE=5]	9	0.7
	Not reported [RACE=99]	27	2.0
VMS	Healthy volunteer [VMS=0]	168	12.7
	VMS patient [VMS=1]	1150	87.3
RENFUNC	Normal function [RENFUNC=1]	766	58.1
	Mild impairment [RENFUNC=2]	526	39.9
	Moderate impairment [RENFUNC=3]	26	2.0
	Severe impairment [RENFUNC=4]	0	0.0
NCI	Normal function [NCI=1]	1243	94.3
	Mild impairment [NCI=2]	74	5.6
	Moderate impairment [NCI=3]	1	0.1
	Severe impairment [NCI=4]	0	0

Source: Applicant's Population PK Report, Tables 15-9 and 15-27
Abbreviations: WGHT, body weight; HGHT, body height; BMI, body mass index, LBM, lean body mass; ALB, albumin; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine aminotransferase; BILI, bilirubin; eGFR, baseline estimated glomerular filtration rate; NCI, hepatic function; RENFUNC, renal function

Figure 62. Scatter Plots of Correlations Between Metabolite Concentrations in FAS Data From OASIS Studies



Source: Applicant's Population PK report, Figure 15-18
Abbreviations: FAS, full analysis set; M, metabolite; PK, pharmacokinetic

14.5.1.3.2. Base Model

The population PK model was developed using a nonlinear mixed-effects modeling approach with the first-order conditional estimation with interaction method in NONMEM (Version 7.4.3). A population PK model for elinzanetant and its three metabolites was previously developed using data from 10 Phase 1 and 2 studies. A circadian influence on the clearance of elinzanetant and the clearance and V_{max} parameters of the three metabolites was included in the previous model. The structure of base popPK model was developed by re-estimating and reassessing the previous base popPK model and based on final analysis datafile.

Interindividual variability was modelled assuming a log-normal distribution for patient level random effects. Residual variability was described using additive error model on log-transformed data. The quality of the model fit was assessed by diagnostic plots.

14.5.1.3.3. Covariate Analysis

The preliminary popPK covariate model was reinferred using the final analysis datafile, a new set of post hoc individual random effects (ETA) estimates was derived, and the univariate covariate exploration was repeated using the new ETA estimates. A stepwise forward inclusion ($p<0.01$) and backward deletion ($p<0.001$) covariate search procedure was implemented. In this process, if any new covariates were found to have $p<0.01$ in the updated univariate covariate exploration, they would enter a second forward inclusion ($p<0.01$) and backward deletion ($p<0.001$) covariate search with the reinferred preliminary popPK covariate model as the starting point.

In the covariate searches, the influence of body weight and lean body weight on clearance and volume parameters was tested using an allometric relationship. Other continuous covariates were evaluated using an exponential function and categorical covariates were parameterized as a fractional change.

Primary covariates evaluated in the development of PK model was included in Table 204.

14.5.1.4. Final Model

A 2-compartment model with first-order absorption and elimination for elinzanetant coupled with a 2-compartment model with linear plus nonlinear elimination for M30/34 adequately described the PK data of elinzanetant and M30/34 (Figure 63, Figure 64, and Figure 66). Statistically significant covariate effects on PK model parameters were the following: study population and BMI on clearance of elinzanetant, and age and BMI on clearance of M30/34. Race, mild hepatic impairment and mild/moderate renal impairment are not significant covariates. The parameter estimates for the final covariate model are listed in Table 205. The RSE for all parameters was <30%. Moderate eta-shrinkage (<30%) was observed for all parameters.

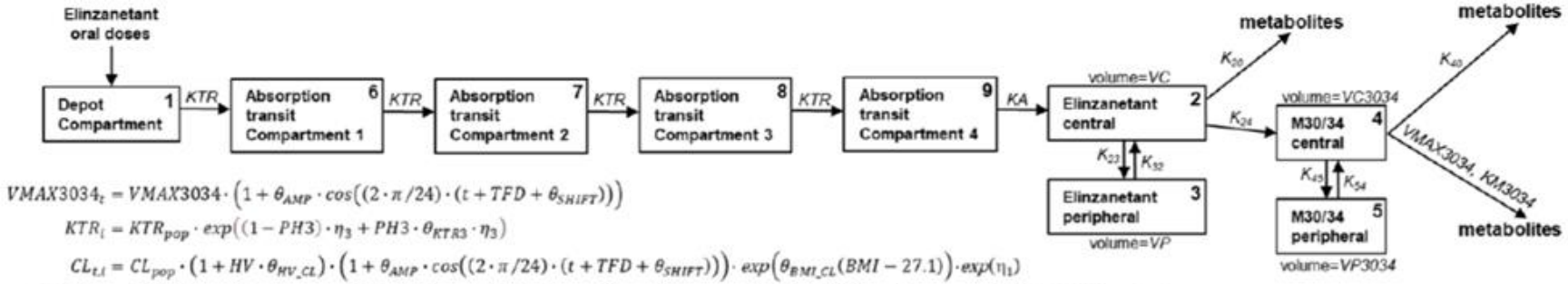
In addition, given the strong correlations between the concentrations of metabolites in the observed data (Figure 62), the concentrations of metabolite M27 and M18/21 for subjects in Phase 3 studies was adequately described by a separate direct linear mixed effects models and based on the concentrations of M30/34 in these subjects (Figure 65, Figure 67). The parameter estimates for the metabolite correlation model are listed in Table 206.

The effects of race, age, body weight, height, BMI, and bilirubin on the $AUC_{(0-24),ss}$ of elinzanetant and M30/34 are explored in Figure 68. The effects of evaluated intrinsic factors (race, age, body weight, height, BMI, and bilirubin) are generally small, and unlikely to be clinically meaningful. Subjects who had lower body weights had lower $AUC_{(0-24),ss}$, and vice versa, due to the negative association between BMI and elinzanetant CL identified in the covariate analysis (Table 205). According to the Applicant, potential explanation for the negative association between BMI and elinzanetant CL included reduction in free fraction of elinzanetant in subjects with higher BMI due to higher fatty acid concentrations in these subjects and decreased levels of hepatic CYP3A4 expression in subjects with higher BMI. Of note, fatty acid concentrations in the plasma of study subjects were not available and there was no evidence to support the first explanation. There was similar $AUC_{(0-24),ss}$ of elinzanetant in subjects with mild hepatic impairment compared to subjects with normal hepatic function (Figure 70). This result is consistent with that from the dedicated hepatic impairment study for the effect of mild hepatic impairment. The effect of moderate hepatic impairment on PK parameters was not evaluated in the popPK analysis due to the limited number of subjects with moderate hepatic impairment (n=1) in the popPK dataset. There were similar exposure of elinzanetant in subjects with mild (n=23) and moderate (n=402) renal impairment compared to subjects with normal renal function (n=586) (Figure 70). In the final PK model, healthy subjects were estimated to have 59.6% higher clearance compared to subjects with VMS in the final model.

The geometric mean terminal half-lives of elinzanetant based on individual post hoc PK estimates for subjects in the three Phase 3 studies from the final model was 45.3 hours (Table 207). The model-predicted geometric mean $AUC_{tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$ of elinzanetant are 8572.0 µg*h/L, 1422.7 µg/L, and 142.8 µg/L, respectively, in subjects treated with 120 mg daily dose of elinzanetant (Table 207).

The influence of weak CYP3A4 inhibitor on the exposure of elinzanetant and its metabolite M30/34 was explored. The geometric mean ratios of $AUC_{(0-24),ss}$ for both elinzanetant and M30/34 (1.125 for elinzanetant and 1.130 for M30/34) increased by about 13% upon coadministration of weak CYP3A4 inhibitors (Figure 69). The increase in the geometric mean $C_{max,ss}$ for both elinzanetant and M30/34 (1.092 for elinzanetant and 1.064 for M30/34) was <10% upon coadministration of weak CYP3A4 inhibitors (Figure 69).

Figure 63. Structure of Final PopPK Model



$$VMAX3034_t = VMAX3034 \cdot \left(1 + \theta_{AMP} \cdot cos\left((2 \cdot \pi/24) \cdot (t + TFD + \theta_{SHIFT})\right)\right)$$

$$KTR_i = KTR_{pop} \cdot exp\left((1 - PH3) \cdot \eta_3 + PH3 \cdot \theta_{KTR3} \cdot \eta_3\right)$$

$$CL_{t,i} = CL_{pop} \cdot \left(1 + HV \cdot \theta_{HV_CL}\right) \cdot \left(1 + \theta_{AMP} \cdot cos\left((2 \cdot \pi/24) \cdot (t + TFD + \theta_{SHIFT})\right)\right) \cdot exp\left(\theta_{BMI_CL}(BMI - 27.1)\right) \cdot exp(\eta_1)$$

$$CL3034_{t,i} = CL3034_{pop} \cdot \left(1 + \theta_{AMP} \cdot cos\left((2 \cdot \pi/24) \cdot (t + TFD + \theta_{SHIFT})\right)\right) \cdot exp\left(\theta_{AGE_CL3034}(AGE - 54)\right) \cdot exp\left(\theta_{BMI_CL3034}(BMI - 27.1)\right) \cdot exp(\eta_2)$$

$K_{20} = (1\text{-}FMET3034) \cdot CL_i/VC$
$K_{24} = FMET3034 \cdot CL_i/VC$
$K_{40} = CL3034_i/VC3034$
$K_{23} = Q/VC$
$K_{32} = Q/VP$
$K_{45} = Q3034/VC3034$
$K_{54} = Q3034/VP3034$
$FMET3034 = 0.60$

$$\Omega = \begin{bmatrix} \omega^2_{CL} & & \\ \omega_{CL,CL3034} & \omega^2_{CL3034} & \\ 0 & 0 & \omega^2_{KTR} \end{bmatrix} \quad \Sigma = \begin{bmatrix} \sigma^2_{e,P1/2} & & & \\ 0 & \sigma^2_{e,P3} & & \\ 0 & 0 & \sigma^2_{M3034,P1/2} & \\ 0 & 0 & 0 & \sigma^2_{M3034,P3} \end{bmatrix}$$

HV, flag variable taking the value 0 for VMS patients and 1 for healthy volunteers; *t*, elapsed time since first dose of elinzanetant; *TFD*, clock time of the first elinzanetant dose as a decimal between 0 and 24; $CL_{t,i}$, time-varying clearance of elinzanetant in an individual subject; CL_{pop}, clearance of elinzanetant in a typical VMS patient at the mid-point between peaks and troughs in circadian variation; θ_{HV_CL}, parameter which describes the influence of healthy volunteer on elinzanetant clearance; θ_{BMI_CL}, parameter which describes the influence of BMI on elinzanetant clearance; θ_{AMP}, amplitude parameter which controls the magnitude of changes in clearance and Vmax parameters with time; θ_{SHIFT}, parameter which controls the position of peaks and troughs in time-varying clearance and Vmax parameters relative to clock time; $CL3034_{t,i}$, time-varying clearance of M30/34 in an individual subject; $CL3034_{pop}$, clearance of M30/34 in a typical VMS patient at the mid-point between peaks and troughs in circadian variation; θ_{AGE_CL3034}, parameter which describes the influence of AGE on M30/34 clearance; θ_{BMI_CL3034}, parameter which describes the influence of BMI on M30/34 clearance; $VMAX3034_t$, time-varying Vmax of M30/34; *VMAX3034*, Vmax of M30/34 at the mid-point between peaks and troughs in circadian variation, KM of M30/34; *VC*, volume of distribution of elinzanetant in central compartment in an individual subject; VC_{pop}, volume of distribution of elinzanetant in central compartment in a typical subject; *VP*, volume of distribution of elinzanetant in peripheral compartment; *Q*, inter-compartmental clearance of elinzanetant; *KA*, absorption rate constant of elinzanetant in an individual subject; *KA*, absorption rate constant of elinzanetant; KTR_i, absorption transit compartment rate constant in an individual subject; KTR_{pop}, absorption transit compartment rate constant for a typical subject; *PH3*, flag variable taking the value 0 for subjects in phase I or phase II studies and 1 for subjects in phase III studies; θ_{KTR3}, parameter which scales the variance of IIV on *KTR* for subjects in phase III studies; Ω, variance-covariance matrix for IIV in *CL*, *CL3034* and *KTR* parameters, where diagonal ω^2 elements are the variances of exponential IIV and the off-diagonal elements are the covariances; η_i, normally distributed variable with variance defined by variance-covariance matix Ω that quantifies the difference between the individual PK parameter and the typical value in the population; Σ, variance-covariance matrix for residual error models, where the diagonal σ^2 elements are the variances of additive residual error for log-transformed concentrations of elinzanetant in phase 1 and phase 2 studies ($\sigma^2_{e,P1/2}$), elinzanetant in phase 3 studies ($\sigma^2_{e,P3}$), M30/34 in phase 1 and phase 2 studies ($\sigma^2_{M3034,P1/2}$), M30/34 in phase 3 studies ($\sigma^2_{M3034,P3}$); *FMET3034*, constant that describes the fraction of elinzanetant that is initially metabolized to M3034; K_{20}, K_{24}, K_{40}, K_{23}, K_{32}, K_{45}, K_{54} first-order rate constants for transfer between specified compartment numbers.

Source: Applicant's Population PK report, Figure 11-1.

Table 205. Parameter Estimates From Selected PopPK Covariate Model

Parameter[a]	Unit	Estimate	RSE[b] [%]	LLCI[c]	ULCI[d]	Description
CL_{pop}	L/h	12.8	0.798	12.6	13.0	Elinzanetant clearance in typical subject with BMI of 27.1 kg/m^2 at mid-point of circadian variation
VC	L	6.20	0.745	6.11	6.29	Elinzanetant volume of central compartment
VP	L	449	0.402	445	452	Elinzanetant volume of peripheral compartment
Q	L/h	15.5	0.561	15.3	15.6	Elinzanetant inter-compartmental clearance
KA	h^{-1}	0.569	0.543	0.563	0.575	Elinzanetant absorption rate constant
KTR_{pop}	h^{-1}	5.71	0.616	5.64	5.78	Elinzanetant absorption transit compartment absorption rate constant in typical subject
$CL3034_{pop}$	L/h	13.5	0.432	13.4	13.6	M30/34 clearance in typical subject with BMI of 27.1 kg/m^2 and AGE of 54 y at mid-point of circadian variation
VC3034	L	5.38	1.72	5.20	5.56	M30/34 volume of central compartment
VP3034	L	53.5	1.24	52.2	54.8	M30/34 volume of peripheral compartment
Q3034	L/h	14.6	0.590	14.4	14.8	M30/34 inter-compartmental clearance
VMAX3034	µg/L/h	72.0	2.64	68.3	75.8	Vmax for M30/34 at mid-point of circadian variation
KM3034	µg/L	18.0	3.20	16.9	19.2	Michaelis-Menten constant for M30/34
θ_{KTR3}	-	1.56	1.80	1.51	1.62	Parameter that scales the variance of IIV on *KTR* for subjects from phase III clinical studies
θ_{AMP}	-	0.330	FIXED	NA	NA	Amplitude of circadian variation for elinzanetant and M30/34 clearance and Vmax parameters
θ_{SHIFT}	h	2.95	FIXED	NA	NA	Parameter which controls position of peaks and troughs in circadian variation of clearance and Vmax parameters relative to clock time
θ_{HV_CL}		0.596	4.14	0.548	0.644	Proportional increase in *CL* for healthy volunteer
$10^2 \cdot \theta_{AGE_CL3034}$	y^{-1}	-0.695	14.0	-0.886	-0.505	Influence of AGE on *CL3034*
$10^2 \cdot \theta_{BMI_CL}$	m^2/kg	-1.90	5.81	-2.12	-1.69	Influence of BMI on *CL*
$10^2 \cdot \theta_{BMI_CL3034}$	m^2/kg	-1.72	7.72	-1.98	-1.46	Influence of BMI on *CL3034*

Parameter	Unit	Estimate	RSE[a] [%]	LLCI[b]	ULCI[c]	Description
Inter-individual variability (OMEGA)						
ETA(1,1) ω^2	-	0.215	4.09	0.198	0.232	Variance of exponential IIV on elinzanetant *CL*
CV[d]	%	49.0		46.8	51.2	
Shrinkage	%	9.9				
ETA(2,2) ω^2	-	0.219	4.99	0.197	0.240	Variance of exponential IIV on *CL3034*
CV[d]	%	49.4		46.7	52.1	
Shrinkage	%	10.0				
ETA(3,3)[e] ω^2	-	0.258	5.52	0.230	0.286	Variance of exponential IIV on *KTR* for subjects in phase 1 clinical studies
CV[d]	%	54.3		50.9	57.6	
Shrinkage	%	13.7				
ETA(2,1) ω	-	0.205	3.60	0.190	0.219	Covariance of IIV between elinzanetant *CL* and *CL3034*
Residual error (SIGMA)						
EPS(1,1) σ^2	-	0.287	0.972	0.281	0.292	Variance of additive residual error for log-transformed elinzanetant observations in phase 1 and phase 2 clinical studies
CV[f]	%	57.6		57.0	58.2	
EPS(2,2) σ^2	-	0.123	1.77	0.119	0.127	Variance of additive residual error for log-transformed M30/34 observations in phase 1 and phase 2 clinical studies
CV[f]	%	36.2		35.5	36.9	
EPS(3,3) σ^2	-	0.474	1.10	0.464	0.484	Variance of additive residual error for log-transformed elinzanetant observations in phase 3 clinical studies
CV[f]	%	77.9		76.8	78.9	
EPS(4,4) σ^2	-	0.321	1.06	0.314	0.328	Variance of additive residual error for log-transformed M30/34 observations in phase 3 clinical studies
CV[f]	%	61.5		60.8	62.3	

Source: Applicant's Population PK report, Tables 11-10 and 11-11
[a] Model parameters are apparent due to the noninclusion of intravenous data (i.e., F is fixed to 1).
[b] RSE = relative standard error (100·SE/estimate)
[c] LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)
[d] ULCI = upper limit of 95% confidence interval (estimate +1.96·SE)
[e] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2
[f] Variance of exponential IIV on KTR for subjects in Phase 3 clinical studies is given by $\theta KTR3\ 2\cdot\omega^2 = 1.562\cdot 0.258 = 0.628$
[g] Both the observations and the model predictions were log-transformed and an additive residual error model was used. This is equivalent to an exponential residual error model on untransformed data and the coefficient of variation (CV) calculated as 100·SQRT(EXP(σ^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of σ^2
Abbreviations: BMI, body mass index; CL, clearance; IIV interindividual variability; M, metabolite; KTR, transit rate constant; PK, pharmacokinetic; SE, standard error; Vmax, maximal rate of metabolism

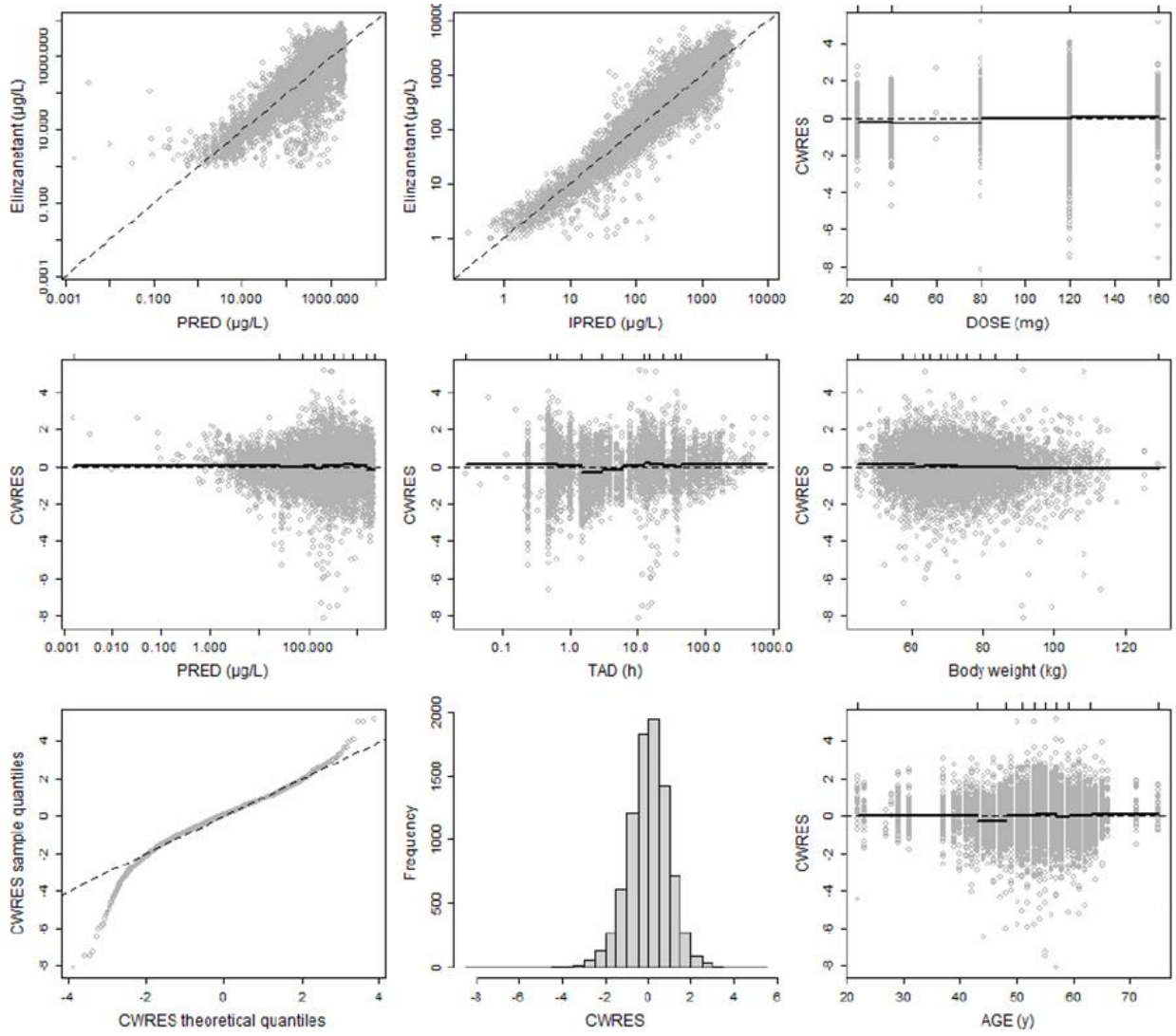
Table 206. Parameter Estimates for Metabolite Correlation Models

Parameter	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Description
Fixed effects (THETA)						
$A_{M27,pop}$	µg/L	1.05	3.47	0.980	1.12	Scale parameter for typical patient linking M27 concentration to predicted M30/34 concentration from RunF005
$A_{M18/21,pop}$	µg/L	0.361	3.89	0.333	0.388	Scale parameter for typical patient linking M18/21 concentration to predicted M30/34 concentration from RunF005
B_{M27}	-	0.889	0.714	0.877	0.902	Exponent parameter linking M27 concentration to predicted M30/34 concentration from RunF005
$B_{M18/21}$	-	1.08	0.614	1.06	1.09	Exponent parameter linking M18/21 concentration to predicted M30/34 concentration from RunF005
Random effects: Inter-individual variability (OMEGA)						
ETA(1,1) ω^2	-	0.0590	6.72	0.0513	0.0668	Variance of exponential IIV on $A_{M27,pop}$
CV[d]	%	24.7		22.9	26.3	
Shrinkage	%	22.2				
ETA(2,2) ω^2	-	0.127	6.66	0.110	0.144	Variance of exponential IIV on $A_{M18/21,pop}$
CV[d]	%	36.8		34.2	39.3	
Shrinkage	%	13.8				
Residual error (SIGMA)						
EPS(1,1) σ^2	-	0.199	3.92	0.184	0.215	Variance of proportional residual error for
CV[e]	%	44.7		42.9	46.3	M27 observations
EPS(2,2) σ^2	-	0.225	4.25	0.207	0.244	Variance of proportional residual error for
CV[e]	%	47.5		45.4	49.4	M18/21 observations

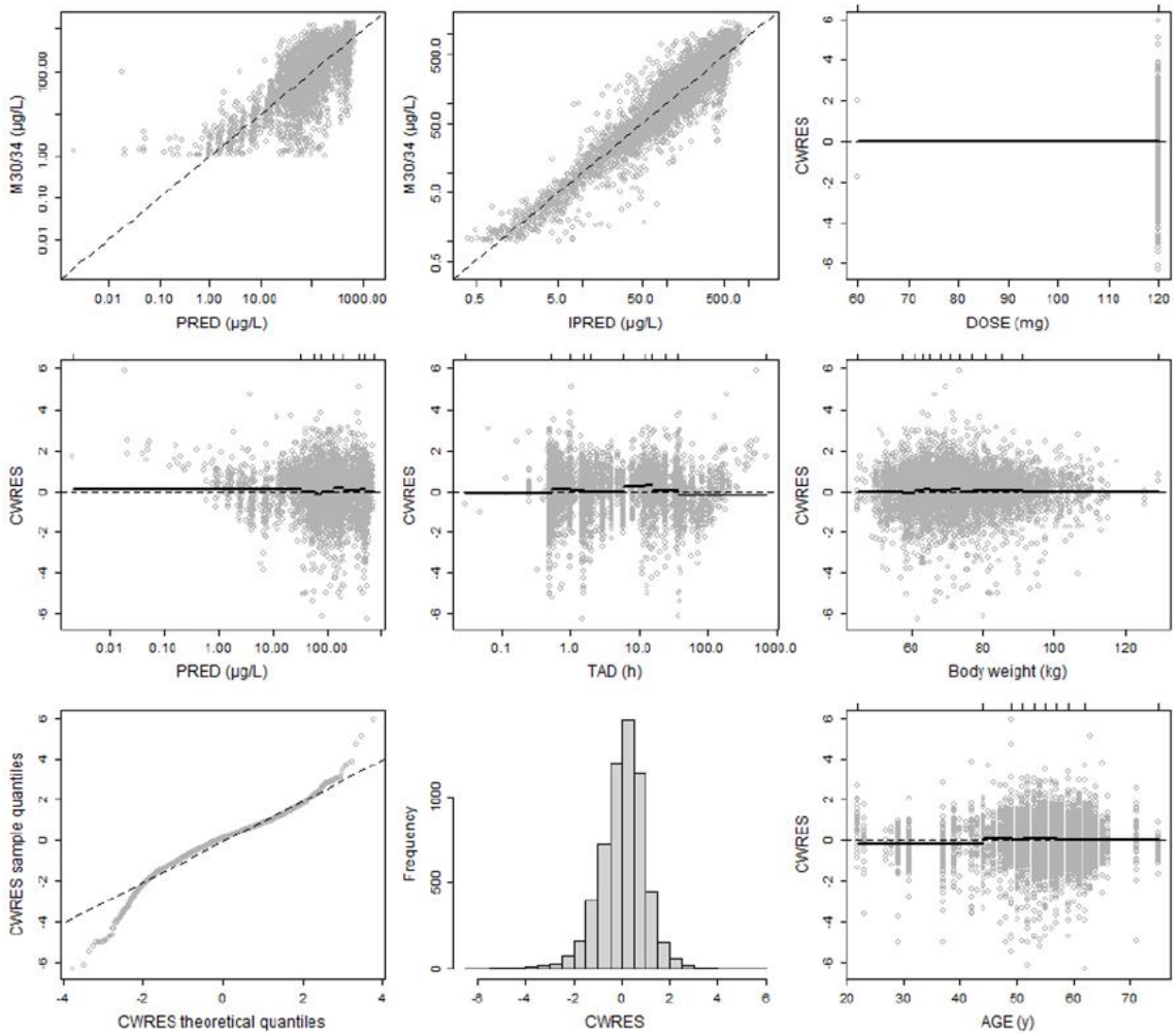
Source: Applicant's Population PK report, Table 11-12
[a] RSE = relative standard error (100·SE/estimate)
[b] LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)
[c] ULCI = upper limit of 95% confidence interval (estimate +1.96·SE)
[d] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.
[e] Coefficient of variation (CV) calculated as 100·SQRT(σ^2). The confidence intervals of CV are derived through transformation of confidence intervals of σ^2.
Abbreviations: IIV interindividual variability; PK, pharmacokinetic; SE, standard error

Figure 64. Goodness-of-Fit Plots for Final Population Pharmacokinetic Model for Observations of Elinzanetant and M30/34

Elinzanetant



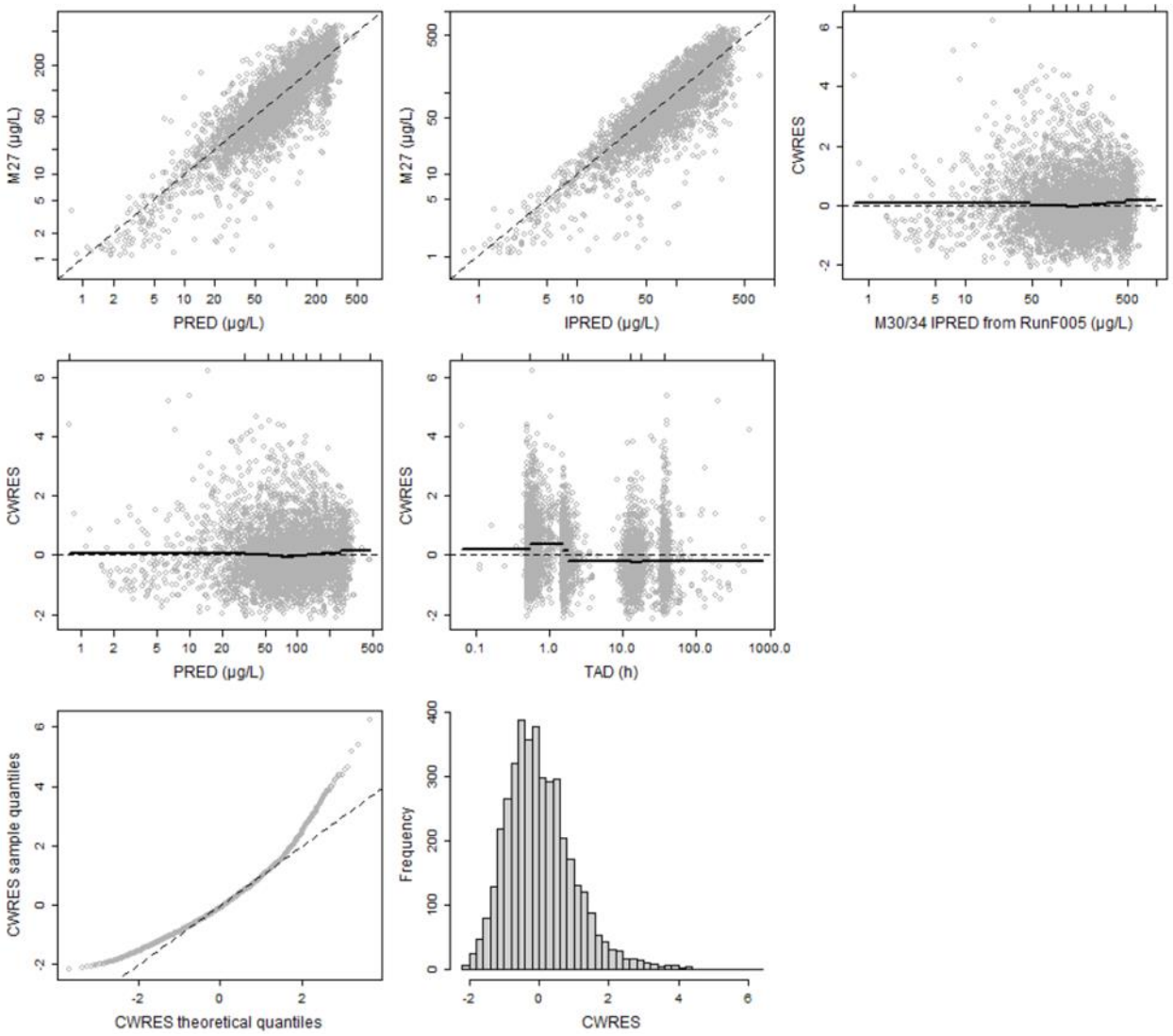
M30/34



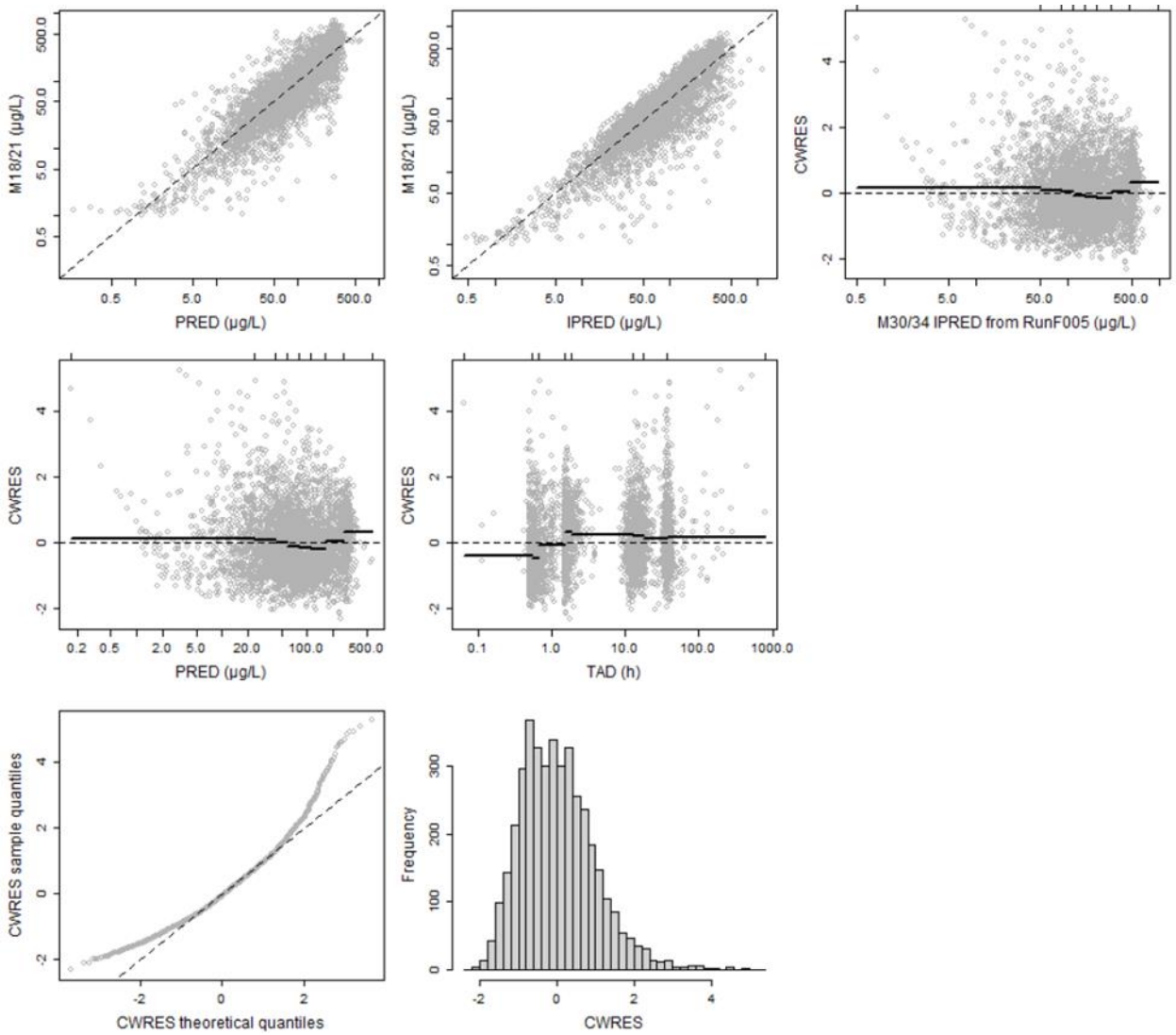
Source: Applicant's Population PK report, Figures 16-11 and 16-15.
Bold horizontal lines show arithmetic mean CWRES within each bin of the independent variables. Each bin contains the same proportion of the data and clearer bin limits are displayed as tick marks along the top of each plot.
Abbreviations: CWRES, conditional weighted residuals; IPRED, individual prediction; M, metabolite; PRED, prediction generated from model fitting; TAD, time after dose

Figure 65. Goodness-of-Fit Plots for Metabolite Correlation Model for Observations of M27 and M18/21

M27



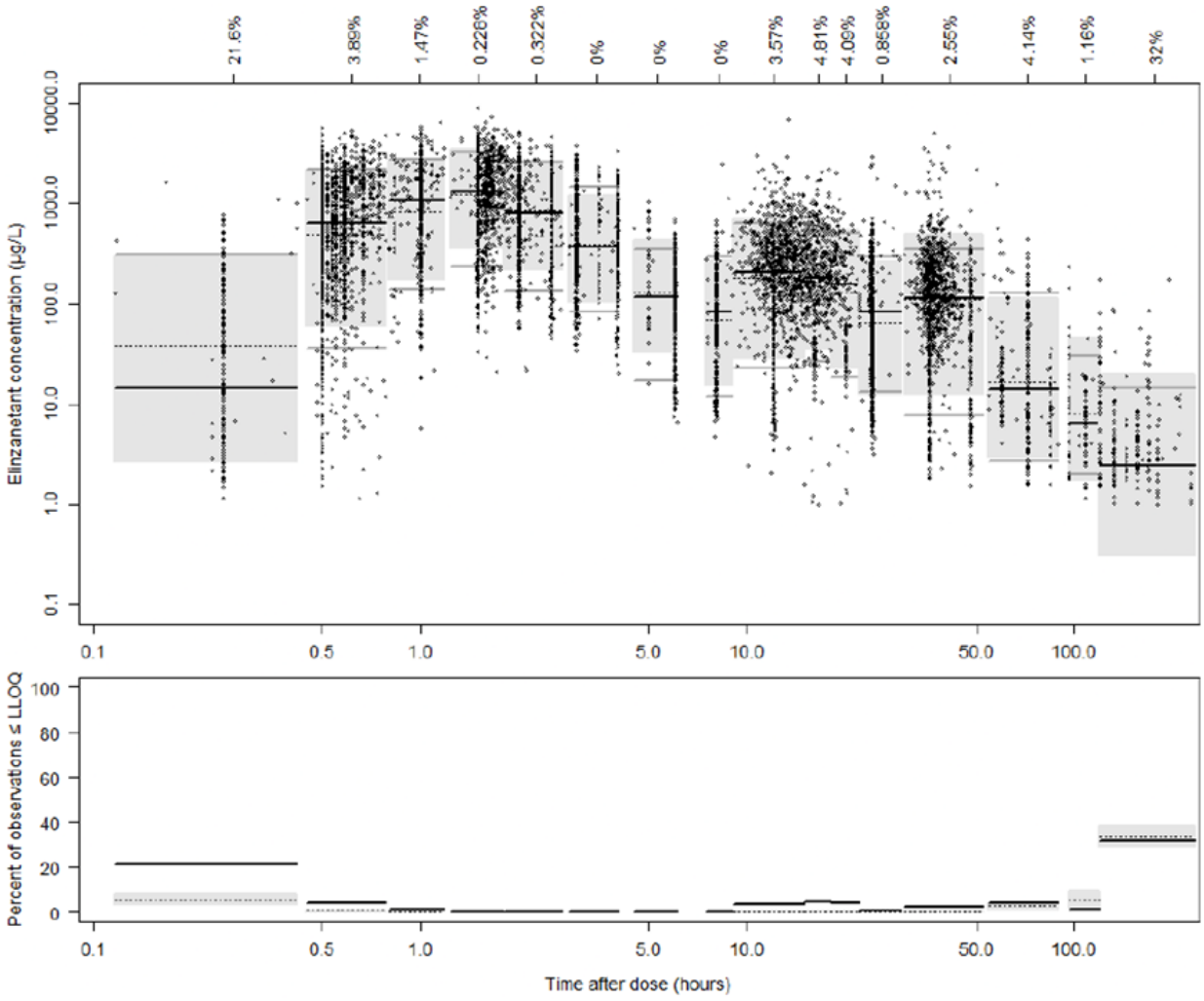
M18/21



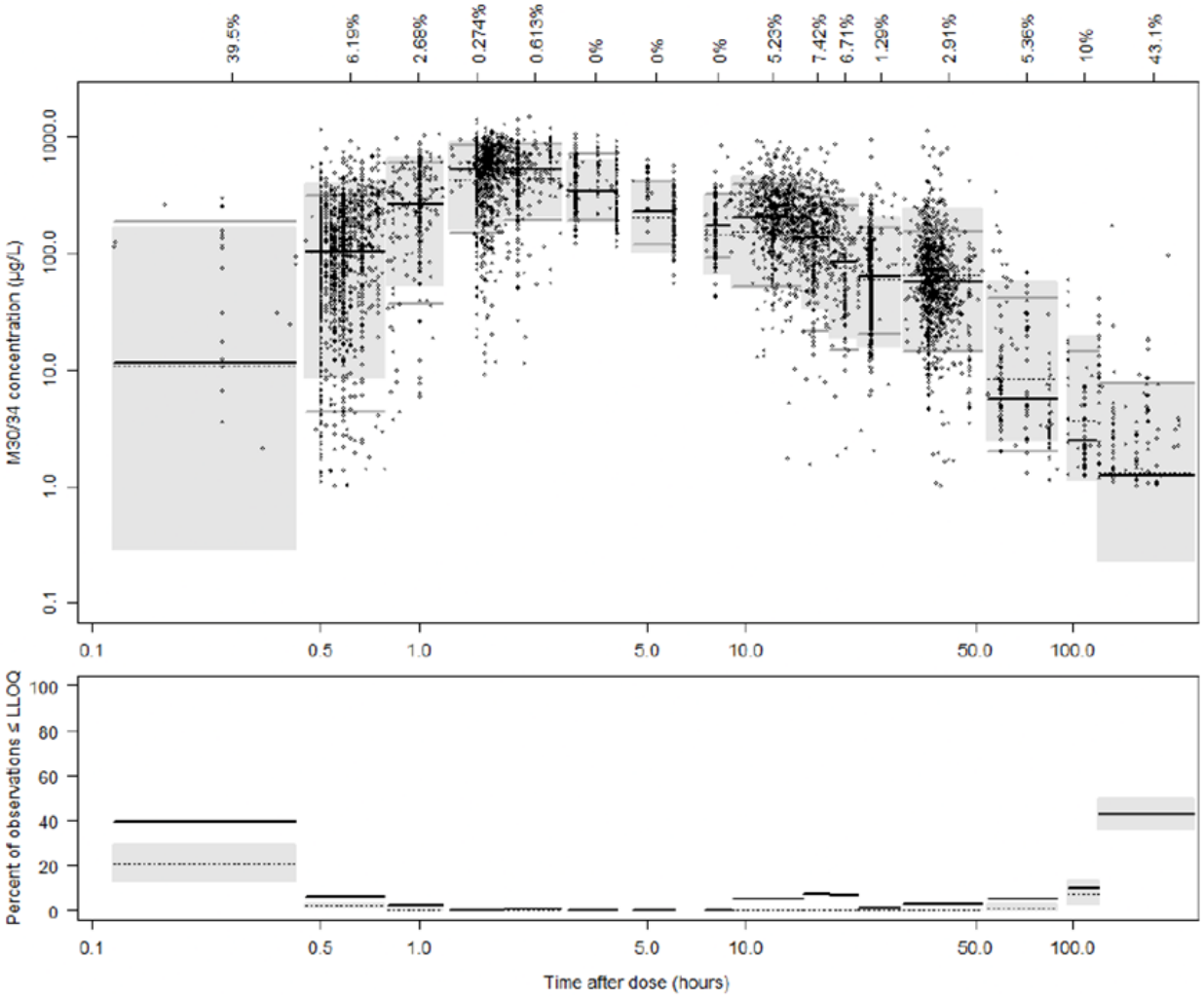
Source: Applicant's Population PK report, Figures 16-20, 16-22
Bold horizontal lines show arithmetic mean CWRES within each bin of the independent variables. Each bin contains the same proportion of the data and clearer bin limits are displayed as tick marks along the top of each plot.
Abbreviations: CWRES, conditional weighted residuals; IPRED, individual prediction; M, metabolite; PRED, prediction generated from model fitting; TAD, time after dose

Figure 66. Visual Predictive Check for Observations of Elinzanetant and M30/34 From Final Population Pharmacokinetic Model

Elinzanetant



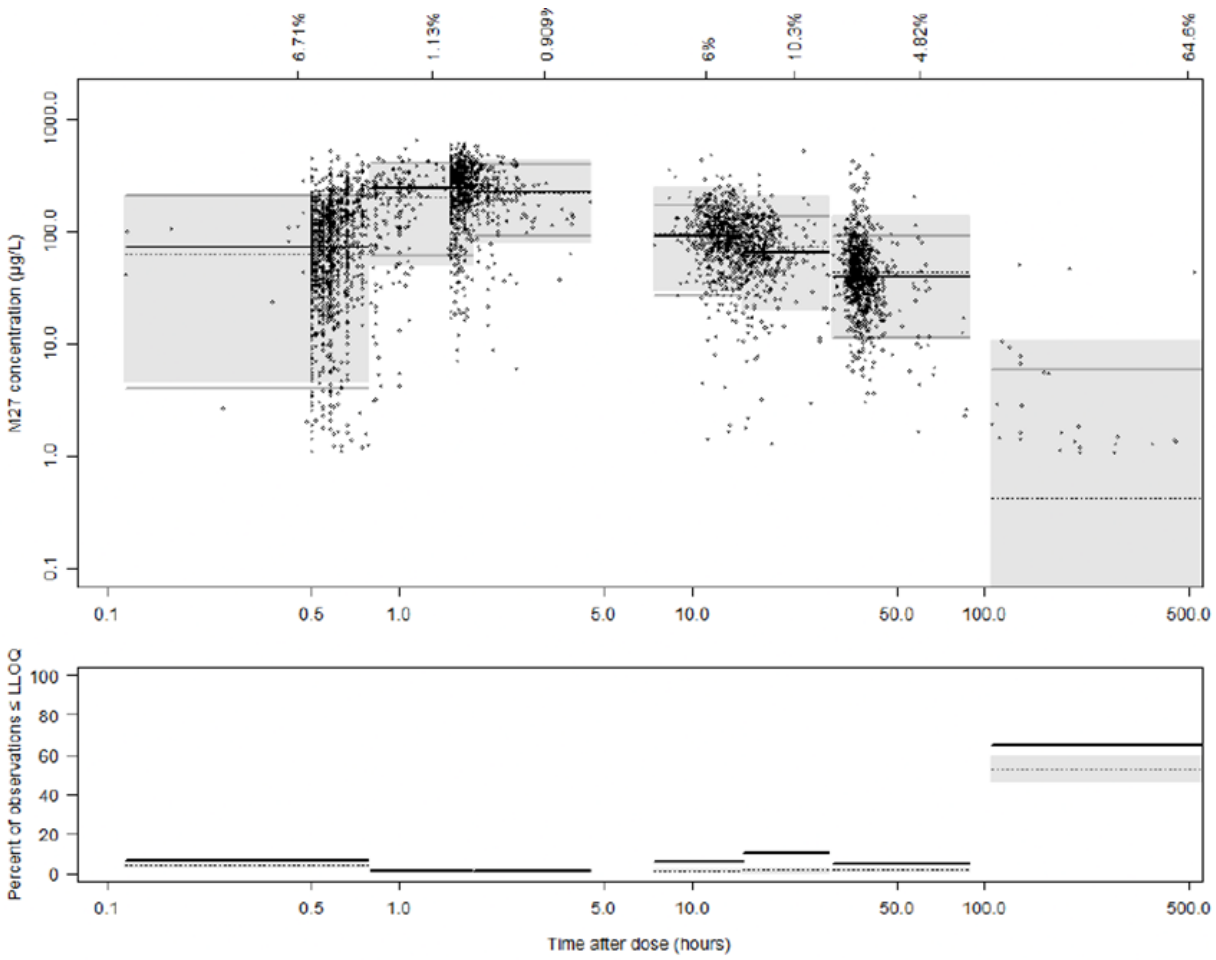
M30/34



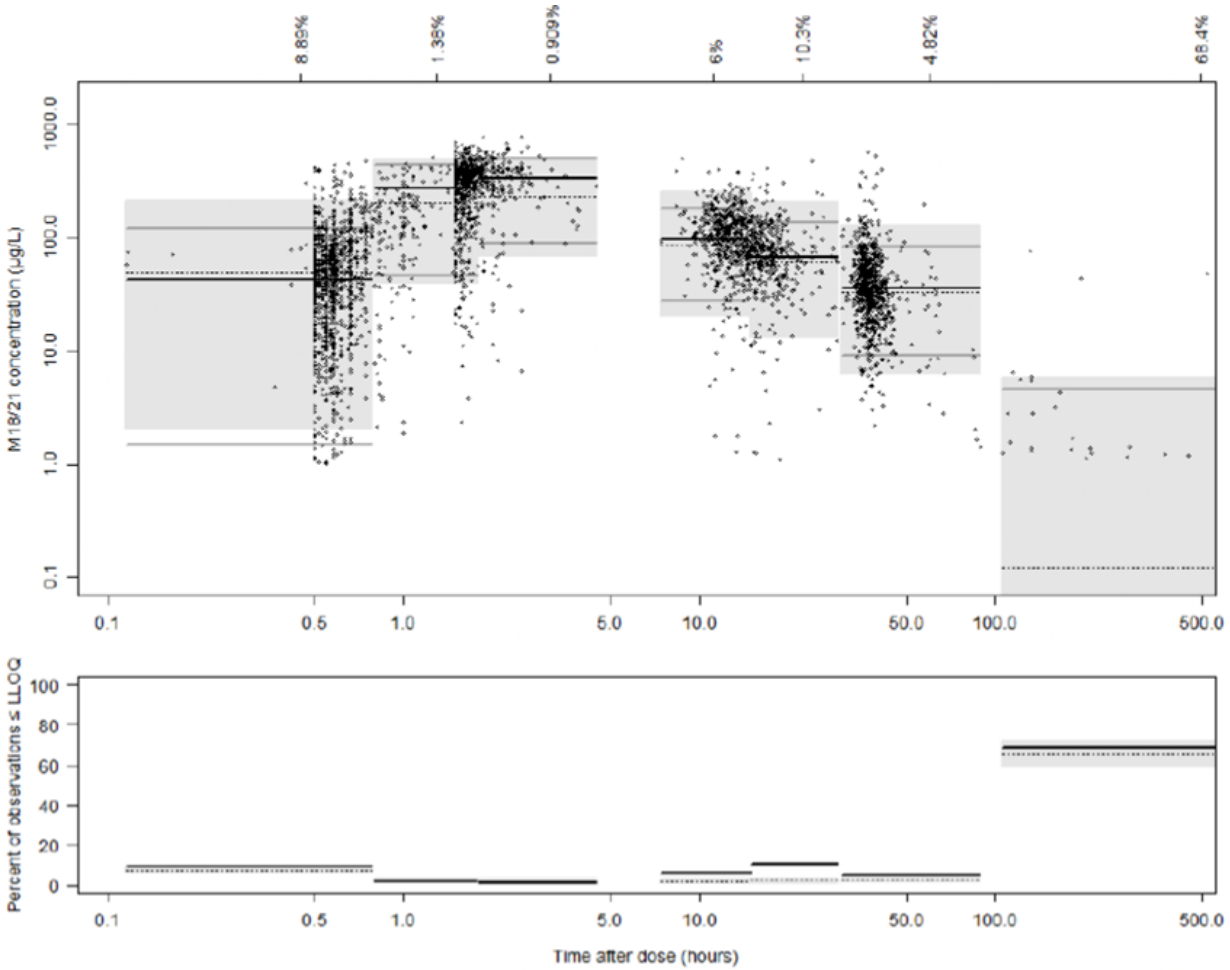
Source: Applicant's Population PK report, Figures 18-3 and 18-6.
In the top panel, black circles represent concentration observations that are > LLOQ; black solid horizontal lines represent 50th percentile of concentration observations in bin of TAD; gray solid horizontal lines represent 10th and 90th percentiles of concentration observations in bin of TAD; black dotted horizontal lines represent 50th percentile of simulated concentration values in bin of TAD; grey shaded areas represent range between 10th and 90th percentiles of simulated concentration values in bin of TAD; numbers along top of plot represent percentage of concentration observations in bin of TAD that are < LLOQ.
In the bottom panel, black solid horizontal lines represent 50th percentile of the percent of concentration observations that are < LLOQ in bin of TAD; black dotted horizontal lines: 50th percentile of the percent of simulated concentration values that are < LLOQ in bin of TAD; grey shaded areas: Range between 10th and 90th percentiles of the percent of simulated concentration values that are < LLOQ in bin of TAD.
Abbreviations: LLOQ, lower limit of quantitation; M, metabolite; PK, pharmacokinetic; TAD, time after dose

Figure 67. Visual Predictive Check for Observations of M27 and M18/21 From Metabolite Correlation Model

M27



M18/21



Source: Applicant's Population PK report, Figures 18-9, 18-10
In the top panel, black circles represent concentration observations that are > LLOQ; black solid horizontal lines represent 50th percentile of concentration observations in bin of TAD; gray solid horizontal lines represent 10th and 90th percentiles of concentration observations in bin of TAD; black dotted horizontal lines represent 50th percentile of simulated concentration values in bin of TAD; grey shaded areas represent range between 10th and 90th percentiles of simulated concentration values in bin of TAD; numbers along top of plot represent percentage of concentration observations in bin of TAD that are < LLOQ.
In the bottom panel, black solid horizontal lines represent 50th percentile of the percent of concentration observations that are < LLOQ in bin of TAD; black dotted horizontal lines: 50th percentile of the percent of simulated concentration values that are < LLOQ in bin of TAD; grey shaded areas: Range between 10th and 90th percentiles of the percent of simulated concentration values that are < LLOQ in bin of TAD.
Abbreviations: LLOQ, lower limit of quantitation; M, metabolite; PK, pharmacokinetic; TAD, time after dose

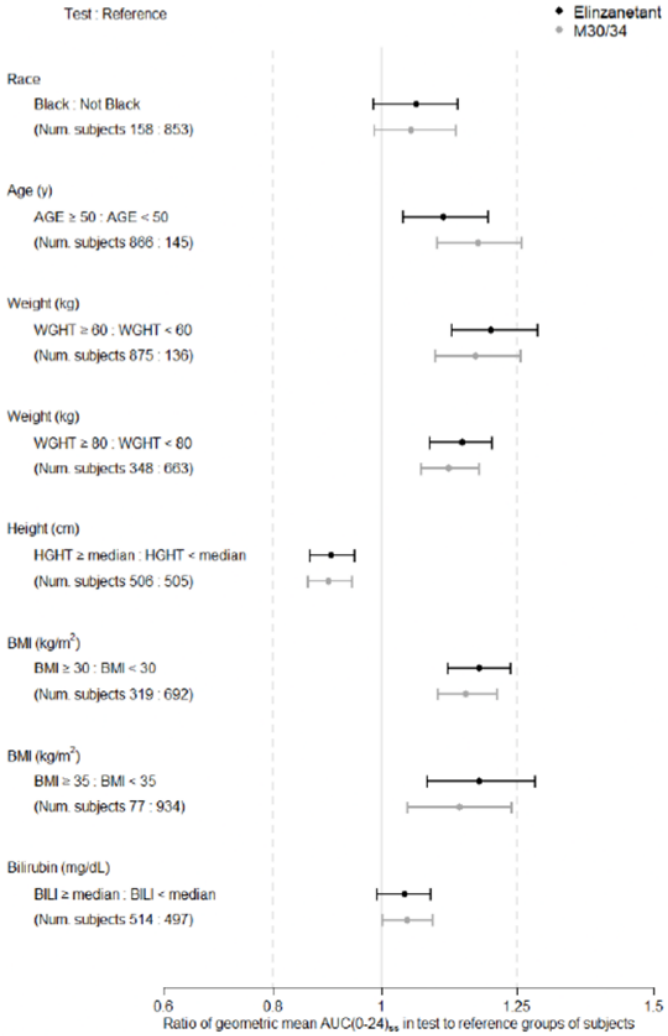
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Table 207. Summary Statistics of Individual Exposure Variables for Elinzanetant

Statistic[a]	$AUC(0\text{-}24)_{sd}$ [h·µg/L]	$C_{max,sd}$ [µg/L]	$C_{min,sd}$ [µg/L]	$C_{trough,sd}$ [µg/L]	$AUC(0\text{-}24)_{ss}$ [h·µg/L]	$C_{max,ss}$ [µg/L]	$C_{min,ss}$ [µg/L]	$C_{trough,ss}$ [µg/L]	$T_{1/2}$ [h]
N	1011	1011	1011	1011	1011	1011	1011	1011	1011
Minimum	883.6	223.0	1.49	1.49	950.2	229.7	2.90	2.90	12.4
Maximum	11267.8	2593.3	192.9	192.9	50586.3	4238.6	1651.4	1723.0	217.0
Median	5254.8	1351.1	47.0	47.0	8807.8	1503.2	152.5	153.0	45.0
Arithmetic mean	5249.9	1320.4	49.5	49.5	9422.0	1496.3	178.5	179.8	46.8
Geometric mean	5064.2	1264.3	43.9	43.9	8572.0	1422.7	142.8	143.5	45.3
Geometric SD	1.33	1.38	1.72	1.72	1.56	1.40	2.03	2.04	1.27
Geometric CV (%)	29.0	32.7	58.2	58.2	46.7	34.8	81.0	81.3	24.5

Source: Applicant's Population PK report, Table 21-3
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{trough}, trough plasma concentration; CV, coefficient of variation; SD, standard deviation; sd, single dose; ss, steady state; $T_{1/2}$, effective terminal half-life

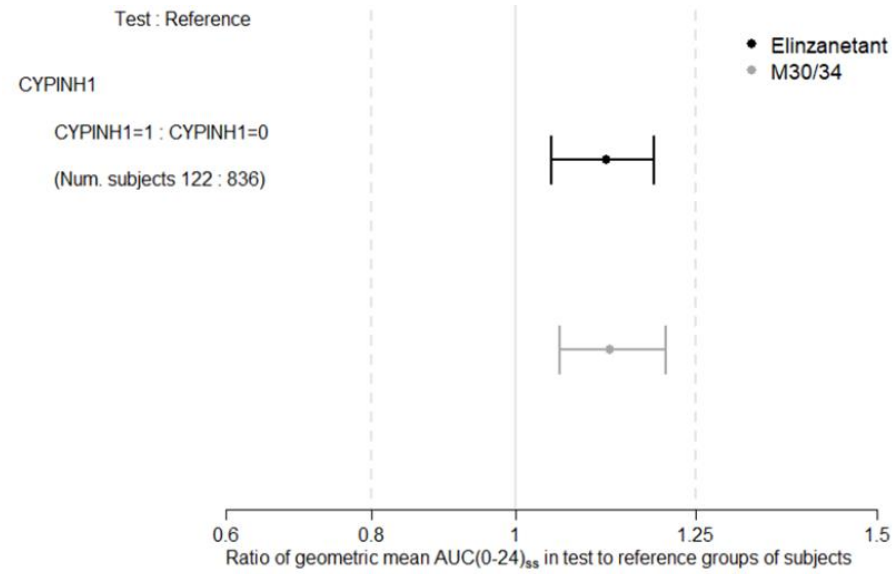
Figure 68. Forest Plot for Covariate Effects on Elinzanetant and M30/34 $AUC_{(0-24),ss}$ Relative to a Reference Subject



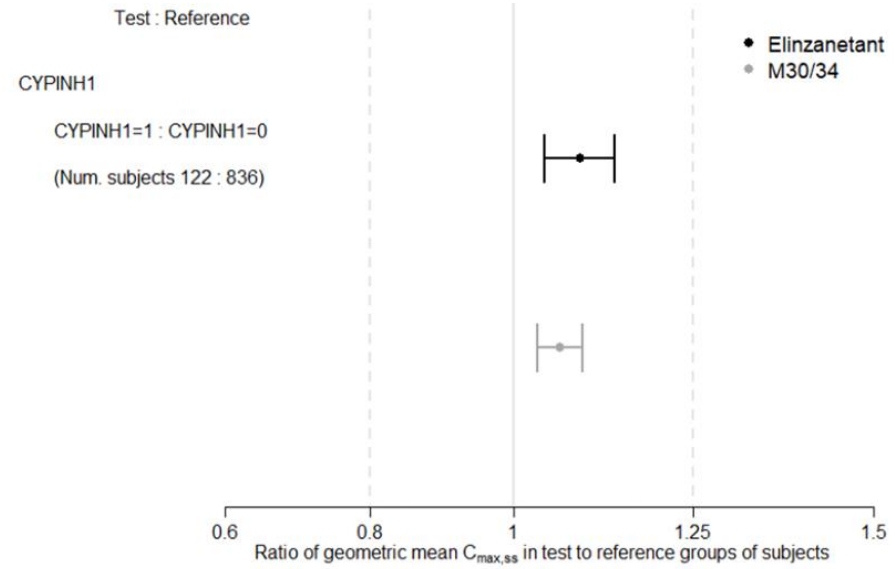
Source: Applicant's Population PK report, Figure 22-1.
The horizontal black (gray) bars indicate the 90% CI of the ratio (test to reference covariate categories) of geometric means of elinzanetant (M30/34) $AUC_{(0-24),ss}$. The 90% CI were derived by resampling individual $AUC_{(0-24),ss}$ values with replacement 1000 times from each subject subgroup. The vertical lines indicate the position of geometric mean $AUC_{(0-24),ss}$ ratios of 0.8, 1 and 1.25.
Abbreviations: AUC, area under the concentration-time curve; BMI, body mass index; C_{max}, maximum plasma concentration; M, metabolite; PK, pharmacokinetic

Figure 69. Forest Plot for Weak CYP3A4 Inhibitors on Exposure Metrics of Elinzanetant and M30/34 for Subjects From OASIS 1, OASIS 2, and OASIS 3

$AUC_{(0-24),ss}$

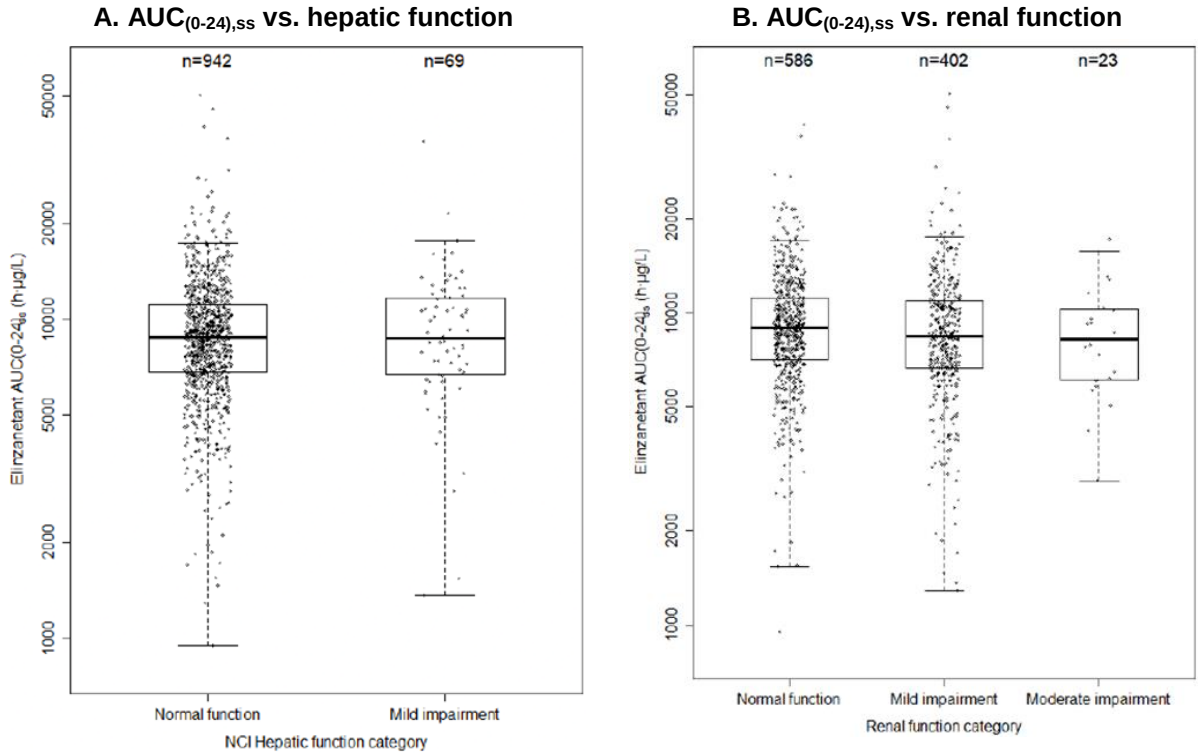


$C_{max,ss}$



Source: Applicant's Population PK report, Figures 23-3 and 23-4
The horizontal black (gray) bars indicate the 90% CI of the ratio (coadministration of weak CYP3A4 inhibitors to no coadministration) of geometric means of exposure. The 90% CI were derived by resampling the corresponding individual exposure values with replacement 1000 times from each subject subgroup. The vertical lines indicate the position of geometric mean exposure ratios of 0.8, 1 and 1.25.
$AUC_{(0-24)\ ss}$, simulated area under the plasma concentration-time curve (of elinzanetant or metabolite) from zero to 24 hours after the 14th dose in a sequence of 14 once daily elinzanetant doses of 120 mg administered at 21:00; $C_{max,ss}$, maximal simulated plasma concentration (of elinzanetant or metabolite) during a 24 h period following the 14th dose in a sequence of 14 once daily elinzanetant doses of 120 mg administered at 21:00
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CYP, cytochrome; M, metabolite; PK, pharmacokinetic

Figure 70. Box Plot of Elinzanetant $AUC_{(0-24),ss}$ Stratified by Categories of Hepatic Function (A) and Renal Function Based on eGFR (B), OASIS 1, OASIS 2, and OASIS 3 (FAS)



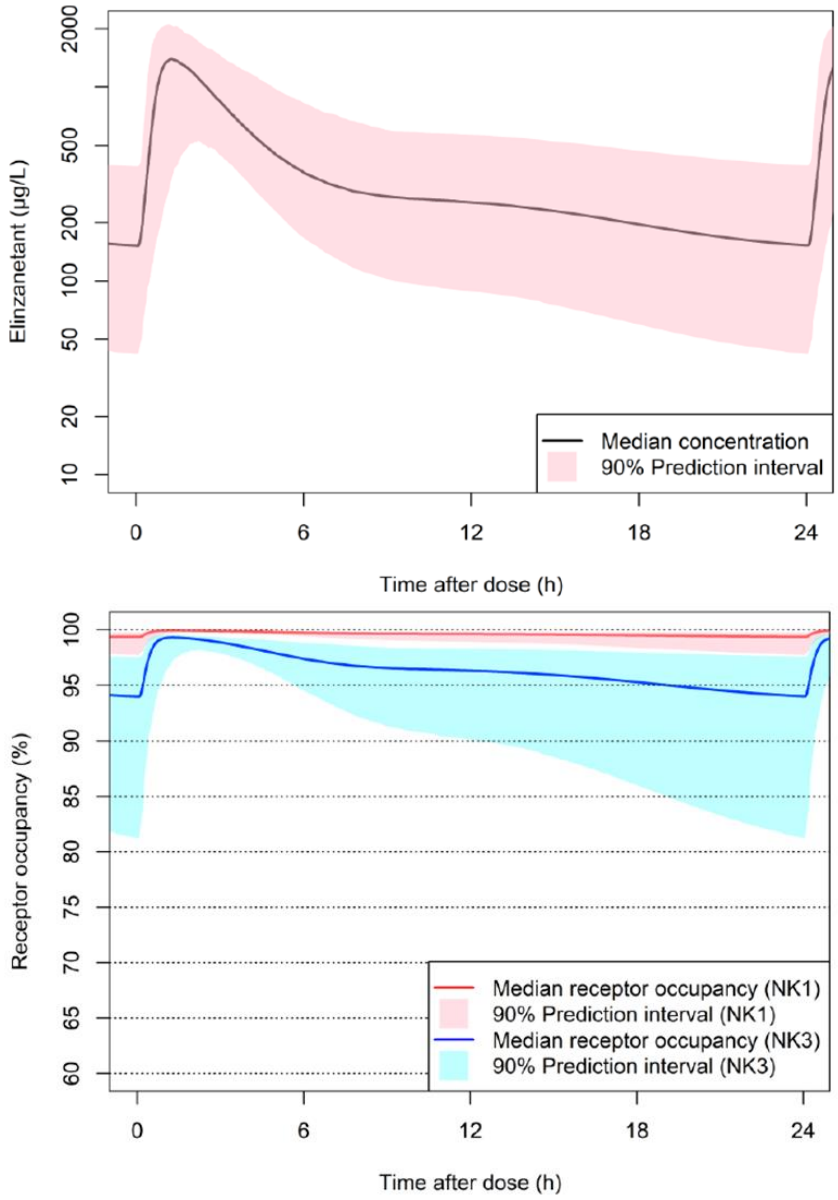
Source: Applicant's Population PK report, Figure 22-5.
Each box covers the interquartile range (IQR) with the median shown as a bold horizontal line inside each box. Whiskers extend to the lowest and highest points that lie within a distance of 1.5 times the IQR from the lower and upper limits of the IQR. P-values are from one-way analysis of variance. Counts of subject from OASIS 1, 2, and 3 studies within each renal function category are listed on the plot.
$AUC_{(0-24),ss}$, simulated area under the plasma concentration-time curve (of elinzanetant or metabolite) from zero to 24 hours after the 14th dose in a sequence of 14 once daily elinzanetant doses of 120 mg administered at 21:00.
Abbreviations: AUC, area under the concentration-time curve; eGFR, estimated glomerular filtration rate; FAS, full analysis set; n, number of subjects; PK, pharmacokinetic

14.5.1.5. Exploratory PK/PD Assessment

After the popPK model was developed, the plasma concentrations of elinzanetant across a 24-hour dosing interval (once-daily dosing at 120 mg) at steady-state in subjects from the three Phase 3 studies (OASIS 1, OASIS 2, and OASIS 3) were simulated using the final popPK model and individual EBE parameter estimates. Based on the simulated plasma concentrations of elinzanetant in these subjects, the NK1 and NK3 receptor occupancy in the human brain were simulated using a standard occupancy model. In this model, Occupancy (%) =100*Celin/(Celin + EC_{50}), where Celin is the simulated plasma concentration of elinzanetant at steady state and EC_{50} is a parameter describing the plasma concentration of elinzanetant at which the NK1 or NK3 receptor is 50% occupied. The in vivo EC_{50} for NK1 in the brain of healthy adult males (N=4) was previously estimated to be 0.97 µg/L. The EC_{50} for NK3 receptor was approximated to be 9.7 µg/L based on the EC_{50} for NK1 and the 10-fold difference in in vitro affinity between NK1 and NK3.

The simulation results suggested that >95% of subjects are expected to have >95% occupancy of the NK1 receptor across the dosing interval (Figure 71). For NK3 receptor, due to approximately 10-fold lower affinity of elinzanetant, >95% of subjects are expected to have >80% occupancy across the dosing interval (Figure 71). Of note, the EC_{50} for NK1 was estimated using data from limited number of subjects, and EC_{50} for NK3 was approximated based on EC_{50} for NK1 and difference in in vitro affinity between NK1 and NK3. Given the uncertainty in the estimate of EC_{50} for NK1 and NK3, the results of the PK/PD simulations should be interpreted with caution.

Figure 71. Simulated Elinzanetant Concentration and Occupancy of NK1 and NK3 Receptors in Human Brain Across a 24 Hour Dosing Interval at Steady-State



Source: Applicant's Population PK report, Figure 24-1
Abbreviations: NK1, neurokinin 1; NK3, neurokinin 3; PK, pharmacokinetic

14.5.1.6. Simulation of Missed Dose Scenarios

The elinzanetant exposure metrics ($AUC_{(0-24)}$, C_{min}, C_{trough} and C_{max}) and time-averaged average receptor occupancies (NK1 and NK3) over consecutive 24-hour periods under different dose scenarios for missing up to two doses (Table 208) were simulated for all subjects (who contributed PK data) in FAS from the OASIS 1, OASIS 2 and OASIS 3 studies using the selected popPK covariate model (with use of individual parameter estimates and subject covariates).

In the 24-hour period following a single missed dose (miss a single dose, resume dose intake the following evening), the median $AUC_{(0-24)}$ reduces to approximately 40% of its value at steady-state, however the median of time-averaged receptor occupancies for NK1 and NK3 reduce by less than 0.3% and 3% of steady-state levels, respectively (Table 209, Figure 72). A further reduction is observed in the 24-hour period following two consecutive missed doses (miss two consecutive doses, resume dose intake the following evening); the median $AUC_{(0-24)}$ reduces to approximately 28% of its value at steady-state, and the median of time-averaged receptor occupancies for NK1 and NK3 reduce by less than 1% and 5.5% of steady-state levels, respectively (Table 210, Figure 73).

Table 208. Missed Dose Scenarios

Scenario	Details
Scenario A	Miss a single dose, resume dose intake (120 mg once daily) the following evening (21:00)
Scenario B	Miss a single dose, take an additional dose (120 mg) the following morning (09:00), then resume dose intake (120 mg once daily) in the evening (21:00)
Scenario C	Miss a single dose, take a double dose (240 mg) the following evening (21:00), then resume dose intake (120 mg once daily) the subsequent evening (21:00)
Scenario D	Miss two consecutive doses, resume dose intake (120 mg once daily) the following evening (21:00)
Scenario E	Miss two consecutive doses, take an additional dose (120 mg) the following morning (09:00), then resume dose intake (120 mg once daily) in the evening (21:00)
Scenario F	Miss two consecutive doses, take a double dose (240 mg) the following evening (21:00), then resume dose intake (120 mg once daily) the subsequent evening (21:00)

Source: Applicant's Population PK report, page 49-50
Abbreviation: PK, pharmacokinetic

Table 209. Median PK and PD Metrics (With 90% Prediction Interval) for a Series of 24-Hour Periods Following a Single Missed Dose (Scenarios A, B and C)

Metric [units]	Scenario[a]	Start of 24 hour period relative to first missed dose			
		-24 hours (steady-state)	0 hours (missed dose)	+24 hours	+48 hours
AUC(0-24) [h•µg/L]	A	8794 (4025 - 16530)	3553 (962.6 - 9250)	7724 (3638 - 14630)	8064 (3795 - 15150)
	B	8794 (4025 - 16530)	9073 (4602 - 16180)	9324 (4335 - 17290)	9151 (4197 - 17200)
	C	8794 (4025 - 16530)	3553 (962.6 - 9250)	12980 (6701 - 22020)	9158 (4182 - 17260)
C_{max} [µg/L]	A	1502 (746.4 - 2165)	171.3 (49.82 - 425.2)	1454 (712.4 - 2088)	1468 (725.2 - 2109)
	B	1502 (746.4 - 2165)	1924 (984.5 - 2556)	1526 (760.6 - 2200)	1518 (753.2 - 2195)
	C	1502 (746.4 - 2165)	171.3 (49.82 - 425.2)	2806 (1380 - 3932)	1517 (760.1 - 2194)
C_{min} [µg/L]	A	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	120.1 (31.44 - 330.7)	130.4 (36.05 - 348.2)
	B	152.6 (42.07 - 394.2)	149.2 (40.88 - 387.6)	167.5 (49.16 - 419)	163.5 (46.42 - 418)
	C	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	166.4 (48 - 413.7)	163.5 (46.17 - 418.3)
C_{trough} [µg/L]	A	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	120.7 (32.25 - 330.7)	130.8 (36.22 - 348.2)
	B	152.6 (42.07 - 394.2)	180.5 (57.47 - 438.3)	167.5 (49.16 - 419)	163.5 (46.42 - 418)
	C	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	167.6 (49.34 - 420.3)	163.5 (46.17 - 418.3)
Time-averaged NK1 RO [%]	A	99.41 (98.66 - 99.62)	99.13 (97.34 - 99.54)	99.32 (98.33 - 99.59)	99.36 (98.49 - 99.6)
	B	99.41 (98.66 - 99.62)	99.34 (98.33 - 99.6)	99.45 (98.81 - 99.63)	99.44 (98.75 - 99.63)
	C	99.41 (98.66 - 99.62)	99.13 (97.34 - 99.54)	99.46 (98.84 - 99.64)	99.44 (98.75 - 99.63)
Time-averaged NK3 RO [%]	A	96.16 (89.8 - 98.15)	93.55 (79.86 - 97.32)	95.33 (87.41 - 97.86)	95.64 (88.52 - 97.95)
	B	96.16 (89.8 - 98.15)	95.51 (87.34 - 97.94)	96.46 (91 - 98.23)	96.38 (90.47 - 98.22)
	C	96.16 (89.8 - 98.15)	93.55 (79.86 - 97.32)	96.62 (91.31 - 98.32)	96.38 (90.51 - 98.23)

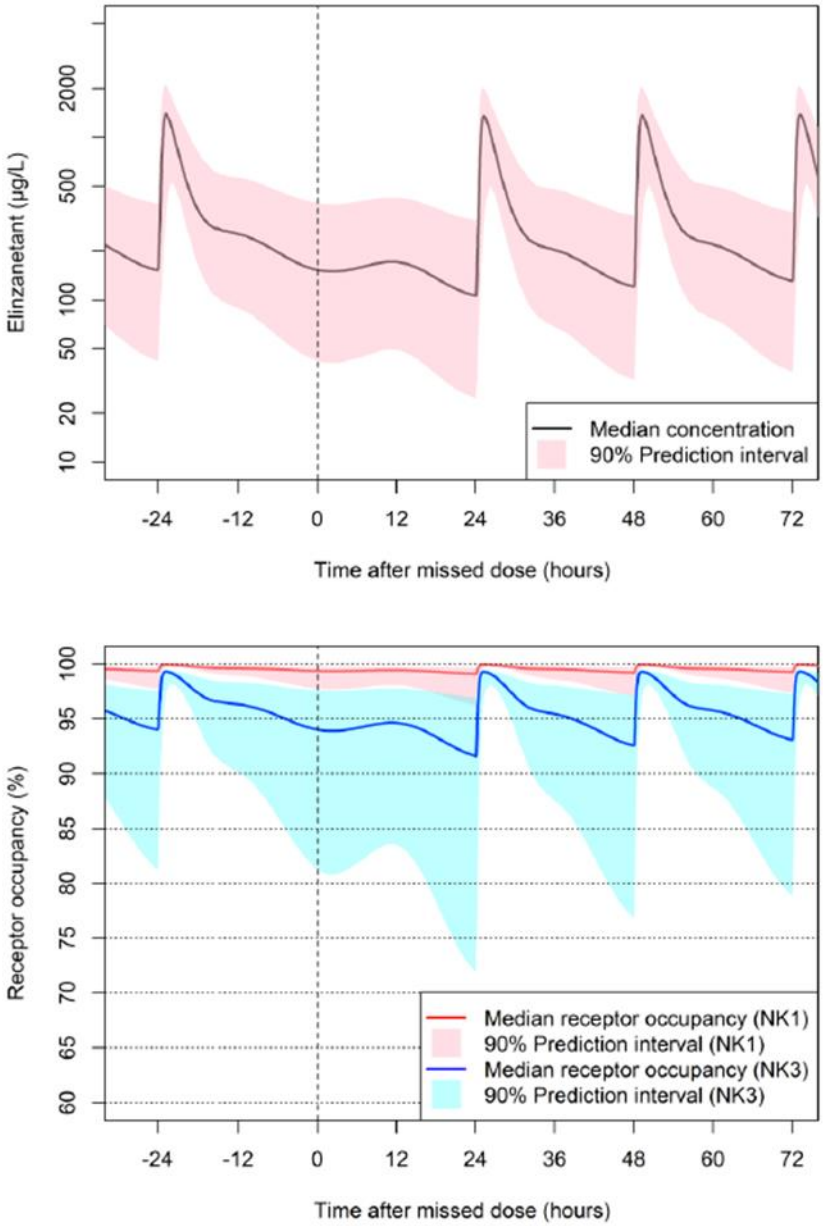
Source: Applicant's Population PK report, Table 24-2
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; NK1, neurokinin 1; NK3, neurokinin 3; PD, pharmacodynamic; PK, pharmacokinetic; RO, receptor occupancy

Table 210. Median PK and PD Metrics (With 90% Prediction Interval) for a Series of 24-Hour Periods Following Two Consecutive Missed Doses (Scenarios D, E and F)

Metric [units]	Scenario[a]	Start of 24 hour period relative to first missed dose				
		-24 hours (steady-state)	0 hours (1st missed dose)	+24 hours (2nd missed dose)	+48 hours	+72 hours
AUC(0-24) [h•µg/L]	D	8794 (4025 - 16530)	3553 (962.6 - 9250)	2469 (575.6 - 7233)	6957 (3407 - 13030)	7541 (3656 - 13920)
	E	8794 (4025 - 16530)	3553 (962.6 - 9250)	7993 (4178 - 14110)	8565 (4100 - 15690)	8632 (4058 - 15960)
	F	8794 (4025 - 16530)	3553 (962.6 - 9250)	2469 (575.6 - 7233)	12210 (6470 - 20410)	8634 (4044 - 16020)
C_{max} [µg/L]	D	1502 (746.4 - 2165)	171.3 (49.82 - 425.2)	119.1 (29.52 - 332.5)	1423 (693.8 - 2032)	1446 (710.4 - 2065)
	E	1502 (746.4 - 2165)	171.3 (49.82 - 425.2)	1876 (965.3 - 2472)	1491 (738.1 - 2136)	1493 (738.9 - 2145)
	F	1502 (746.4 - 2165)	171.3 (49.82 - 425.2)	119.1 (29.52 - 332.5)	2775 (1372 - 3865)	1495 (743.2 - 2144)
C_{min} [µg/L]	D	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	73.25 (14.91 - 241.1)	97.7 (25.49 - 277.1)	114.7 (32.42 - 307.1)
	E	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	103.7 (24.21 - 303.1)	145.2 (43.09 - 365.8)	147.7 (42.79 - 376.4)
	F	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	73.25 (14.91 - 241.1)	144.1 (41.12 - 361.9)	147.8 (42.54 - 377.2)
C_{trough} [µg/L]	D	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	73.25 (14.91 - 241.1)	98.19 (26.15 - 278.1)	115.2 (32.73 - 307.1)
	E	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	148 (47.2 - 370.1)	145.2 (43.09 - 365.8)	147.9 (42.79 - 376.4)
	F	152.6 (42.07 - 394.2)	106.1 (24.91 - 308.3)	73.25 (14.91 - 241.1)	145.1 (43.24 - 367.7)	147.8 (42.54 - 377.2)
Time-averaged NK1 RO [%]	D	99.41 (98.66 - 99.62)	99.13 (97.34 - 99.54)	98.84 (95.76 - 99.47)	99.22 (98.02 - 99.56)	99.3 (98.36 - 99.58)
	E	99.41 (98.66 - 99.62)	99.13 (97.34 - 99.54)	99.18 (97.57 - 99.56)	99.4 (98.69 - 99.61)	99.4 (98.67 - 99.62)
	F	99.41 (98.66 - 99.62)	99.13 (97.34 - 99.54)	98.84 (95.76 - 99.47)	99.42 (98.72 - 99.62)	99.4 (98.67 - 99.62)
Time-averaged NK3 RO [%]	D	96.16 (89.8 - 98.15)	93.55 (79.86 - 97.32)	91.04 (70.49 - 96.65)	94.46 (85.35 - 97.53)	95.15 (87.56 - 97.73)
	E	96.16 (89.8 - 98.15)	93.55 (79.86 - 97.32)	94.1 (82.4 - 97.51)	96.01 (90.03 - 98.03)	96.06 (89.89 - 98.06)
	F	96.16 (89.8 - 98.15)	93.55 (79.86 - 97.32)	91.04 (70.49 - 96.65)	96.18 (90.35 - 98.13)	96.06 (89.88 - 98.08)

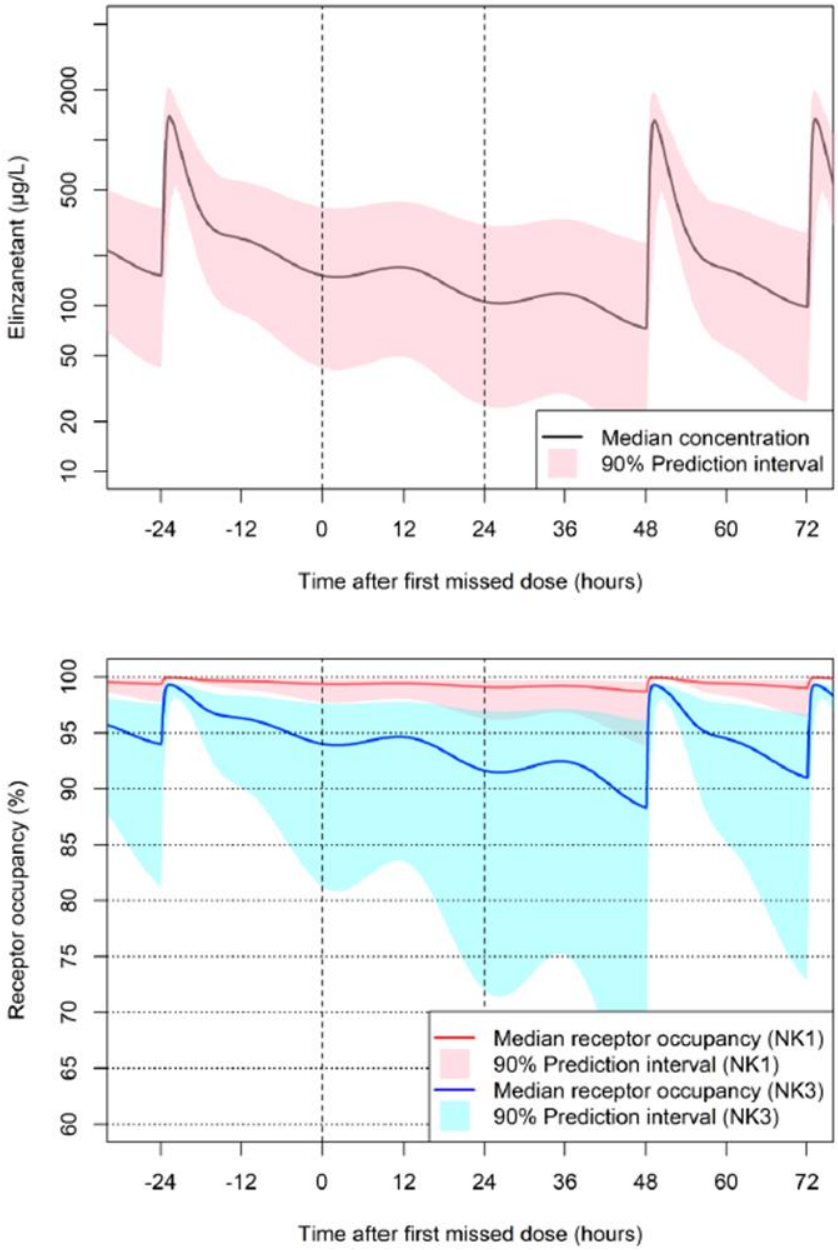
Source: Applicant's Population PK report, Table 24-3
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; NK1, neurokinin 1; NK3, neurokinin 3; PD, pharmacodynamic; PK, pharmacokinetic; RO, receptor occupancy

Figure 72. Simulated Elinzanetant PK, Receptor Occupancy (NK1 And NK3) Profiles for Missed Dose Scenario A



Source: Applicant's Population PK report, Figure 24-2
Top panel: median elinzanetant plasma concentration (solid black line) and 90% PI (pink shaded area). Bottom panel: median (solid red line) and 90% PI (shaded pink area) of NK1 receptor occupancy, and median (solid blue line) and 90% PI (shaded blue area) of NK3 receptor occupancy.
Abbreviations: NK1, neurokinin 1; NK3, neurokinin 3; PK, pharmacokinetic

Figure 73. Simulated Elinzanetant PK, Receptor Occupancy (NK1 And NK3) Profiles for Missed Dose Scenario D



Source: Applicant's Population PK report, Figure 24-5
Top panel: median elinzanetant plasma concentration (solid black line) and 90% PI (pink shaded area). Bottom panel: median (solid red line) and 90% PI (shaded pink area) of NK1 receptor occupancy, and median (solid blue line) and 90% PI (shaded blue area) of NK3 receptor occupancy.
Abbreviations: NK1, neurokinin 1; NK3, neurokinin 3; PK, pharmacokinetic

14.5.2. Exposure-Response Analysis

14.5.2.1. Review Summary

There was a positive relationship between elinzanetant C_{trough} at steady state and reduction in hot flash frequency and severity. This relationship was adequately described by the E-R model. The exploratory E-R analysis for safety did not identify a significant relationship between elinzanetant exposure and elevated AST/ALT and AE of special interest. The Applicant's analyses were verified by the reviewer.

14.5.2.2. Introductions

The primary objectives of Applicant's E-R analysis were to:

(1) Evaluate E-R relationship of HF frequency and HF severity.

(2) Evaluate E-R relationship of responder who had at least 50% reduction in HF frequency.

(3) Explore the occurrence of (i) abnormal elevations in AST or ALT, and (ii) fatigue, somnolence or dizziness reported as AE and the relationship to treatment with elinzanetant and exposure and other intrinsic or extrinsic factors.

PK exposure metrices at steady-state ($AUC_{(0-24),ss}$, $C_{avg,ss}$, $C_{trough,ss}$, $C_{max,ss}$, $C_{min,ss}$) were predicted based on post hoc parameter estimates from the final population PK model. Due to the high correlation between exposure metrics, only $C_{trough,ss}$, $C_{max,ss}$ were selected as exposure candidates to be evaluated in the E-R analyses.

14.5.2.3. E-R Analysis for Efficacy

The efficacy E-R analysis was based on data from Phase 3 studies OASIS 1, OASIS 2, and OASIS 3. The primary efficacy endpoints were HF frequency and severity, and HF responder. HF responders were defined as subjects which reported at least 50% reduction in HF frequency at Week 12 compared to baseline.

NONMEM (Version 7.3.0) and R software (Version 4.2.1) were used for the E-R analysis.

The analysis data included 16,539 HF frequency records and 16.539 severity records from 1,418 subjects, of which 1,108 subjects could be classified as HF responder or nonresponder.

Longitudinal HF frequency and severity was analyzed by means of (non)linear mixed effects modeling. The E-R relationship for HF frequency was described using the following structural model.

Equation 9. E-R Relationship for HF Frequency (or severity)

$$Y_{ij} = BL_i \cdot \left((1 - eff_i) + eff_i \cdot exp\left(-\frac{log(2)}{eff_{t1/2}} t_j \right) \right)$$

$$eff_i = \left(\theta_{plc} + \mathbb{1}_{verum} \cdot \theta_{verum} \right) \cdot e^{\eta_{eff,i}}.$$

Abbreviations: Yij, HF frequency (or severity) of subject i at time tj; BLi, (model-derived) individual baseline HF frequency; $effi$, (model-derived) individual placebo (or later treatment) and drug effect; $efft1/2$, typical time required to reach 50% of the effect size ($effi$); $\theta verum$, elinzanetant treatment effect; $\mathbb{1}verum$,'1' for verum-treated subjects and '0' for placebo-treated subjects

Where: Yij is the HF frequency (or severity) of subject i at time tj; BLi describes the (model-derived) individual baseline HF frequency; $effi$ describes the (model-derived) individual placebo (or later treatment) and drug effect; $efft1/2$ describes the typical time required to reach 50% of the effect size ($effi$); $\theta verum$ describes the elinzanetant treatment effect; $\mathbb{1}verum$ is '1' for verum-treated subjects and '0' for placebo-treated subjects.

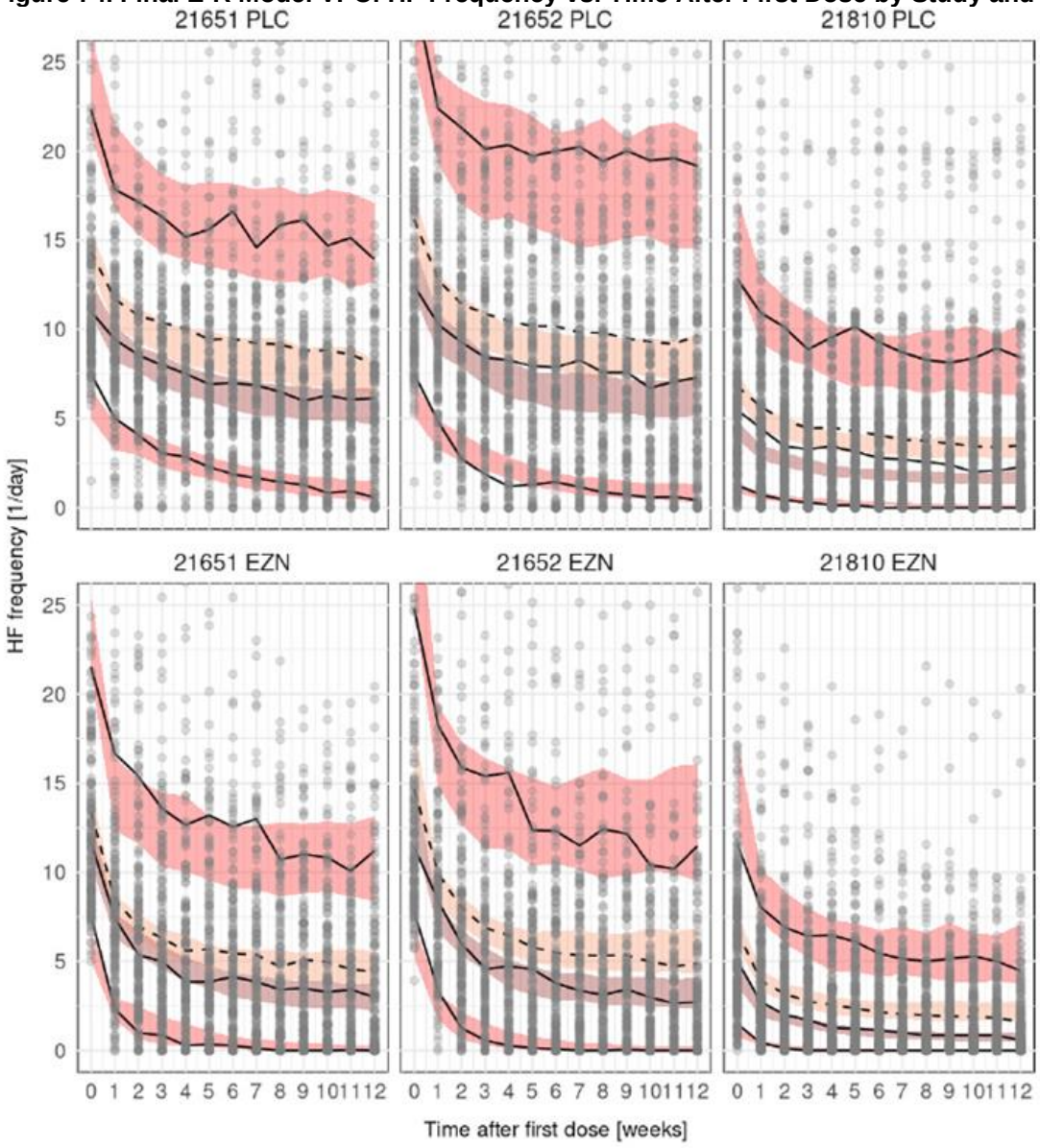
The E-R model for HF frequency started with the building of the placebo base model. Any placebo-effect was assumed to be also present in the verum-treated subjects. In the model, $C_{trough,ss}$ was added as covariate using E_{max} model to the treatment effect in EFFSS. The final model adequately predicted HF frequency (Table 211, Figure 74, and Figure 75). The E-R relationship for HF severity could be adequately described using the same (fixed) EC_{50} estimate as for the HF frequency E-R model. Additionally, the E-R model was externally qualified with data from the Phase 2b dose ranging study (SWITCH-1), which was an adaptive design study on elinzanetant doses of 40 mg, 80 mg, 120 mg and 160 mg, and placebo for 12 weeks (Figure 76). None of the covariates (age, race, body mass index, body weight, time since last amenorrhea, oophorectomy status, Menopause-specific Quality of Life Questionnaire) were likely to have clinically meaningful impact on the effectiveness of elinzanetant in reducing HF frequency or severity. The simulation based on E-R model and projected $C_{trough,ss}$ at different dose levels showed the reduction of HF frequency approaching a plateau at the studied dose of 120 mg (Figure 77).

Table 211. Parameter Estimates of Selected E-R Model

Parameter	Unit	Estimate	CV%	RSE	Shrinkage	Description
BL_OASIS.1	[1/day]	12.2		3.14		BL HF frequency OASIS-1
BL_OASIS.2	[1/day]	13.6		3.38		BL HF frequency OASIS-2
BL_OASIS.3	[1/day]	4.7		4.19		BL HF frequency OASIS-3
BL_ID203	[1/day]	178		fixed		BL ID 203 - estimate from O8/run051
BL_ID524	[1/day]	78.5		fixed		BL ID 524 - estimate from O8/run051
BL_ID457	[1/day]	44		fixed		BL ID 457 - estimate from O8/run051
BL_ID492	[1/day]	122		fixed		BL ID 492 - estimate from O8/run051
BL_ID1151	[1/day]	64		fixed		BL ID 1151 - estimate from O8/run051
BL_ID444	[1/day]	44.1		fixed		BL ID 444 - estimate from O8/run051
HL_PLC_OASIS.1	[days]	16.9		2.6		PLC effect half-life OASIS-1
HL_PLC_OASIS.2	[days]	12.5		1.82		PLC effect half-life OASIS-2
HL_PLC_OASIS.3	[days]	11.9		2.07		PLC effect half-life OASIS-3
HL_EZN_OASIS.1	[days]	14.4		2.32		EZN effect half-life OASIS-1
HL_EZN_OASIS.2	[days]	10.9		1.84		EZN effect half-life OASIS-2
HL_EZN_OASIS.3	[days]	11		1.78		EZN effect half-life OASIS-3
EFFFAST_PLC	[-]	0.127		10.3		PLC fast effect
EFFFAST_EMAX	[-]	0.202		13.6		EMAX fast effect (for Ctrough,ss)
EFFSS_PLC_OASIS.1.2	[-]	0.512		7.51		PLC steady-state effect OASIS-1/2
EFFSS_PLC_OASIS.3	[-]	0.468		7.89		PLC steady-state effect OASIS-3
EFFSS_EMAX	[-]	0.291		17.3		EMAX steady-state effect (for Ctrough,ss)
COV_EFFSS_MENQVM	[-]	-0.164		-34		Covariate effect: PLC steady-state effect ~ MENQVM (<=6 vs. > 6)
COV_EFFSS_AGE	[-]	-0.172		-31.7		Covariate effect: PLC steady-state effect ~ AGE (<=54 vs. > 54)
lgt_prob_mix1	[-]	-4.6		-11.7		mixture population parameter 1
lgt_diff_mix12_PLC	[-]	-1.14		-51.6		mixture population parameter 2
prob_ir_resp_EMAX	[-]	-1.8		-22.5		EMAX for mixture population parameter 2 (for Ctrough,ss)
SLP_mix2	[1/years]	4.86		61.2		nuisance parameter - time-slope for SUBPOP=2
IIV_BL_OASIS.1	[-]	0.476	50.4	4.03	4.51	IIV BL HF frequency OASIS-1 (sd, exp)
IIV_BL_OASIS.2	[-]	0.535	57.6	3.8	4.83	IIV BL HF frequency OASIS-2 (sd, exp)
IIV_BL_OASIS.3	[-]	0.86	105	2.77	4.07	IIV BL HF frequency OASIS-3 (sd, exp)
IIV_EFFSS	[-]	1.79		3.2	19.3	IIV steady-state effect (sd, logit)
IIV_SLP_mix2	[-]	0.651	72.6	59.6	33.1	nuisance parameter - IIV time-slope for SUBPOP=2 (sd, exp)
IIV_RUV_prop	[-]	0.001	0.1	fixed	72.3	nuisance parameter - IIV RUV proportional RUV term (fixed)
RUV_prop_OASIS.1.2	[-]	0.262	26.2	0.426	5.07	proportional RUV term OASIS-1/2 (sd)
RUV_prop_OASIS.3	[-]	0.465	46.5	0.673	6.13	proportional RUV term OASIS-3 (sd)
RUV_add_OASIS.1.2	[1/day]	0.595		1.18	5.07	additive RUV term OASIS-1/2 (sd)
RUV_add_OASIS.3	[1/day]	0.0875		1.59	6.13	additive RUV term OASIS-3 (sd)

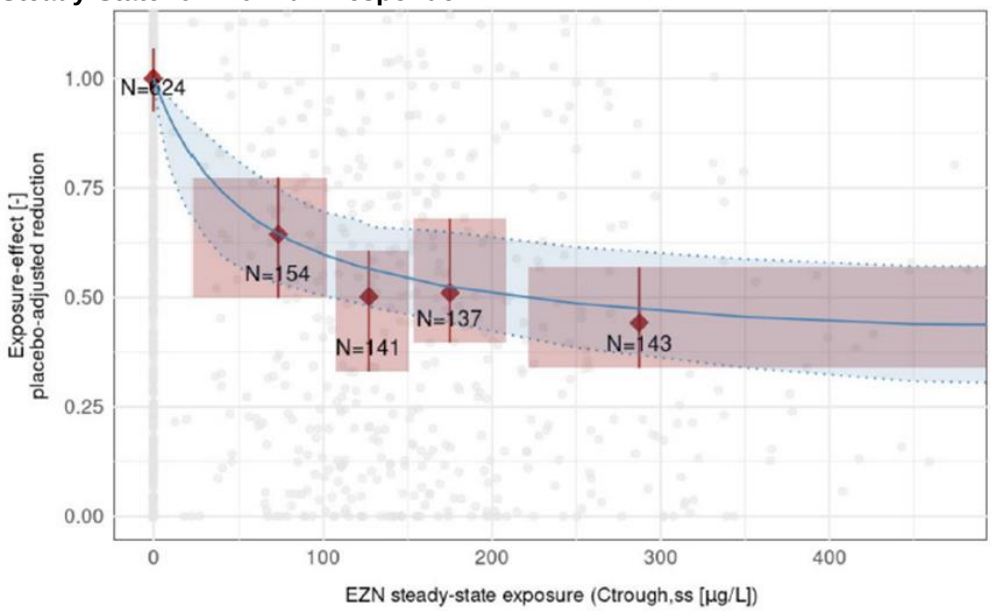
Source: Applicant's E-R report, Table 15.11
CV% of log-normal omegas = sqrt(exp(estimate) − 1) 100
Abbreviations: BL, baseline; CV, coefficient of variation; EFFFAST, efficiency fasting; EFFSS, efficiency steady state; EMAX, maximum induction effect; E-R, exposure response; EZN, elinzanetant; HF, hot flash; IIV, interindividual variability; PLC, placebo; RSE, relative standard error; RUV, residual unexplained variability

Figure 74. Final E-R Model VPC: HF Frequency vs. Time After First Dose by Study and Treatment



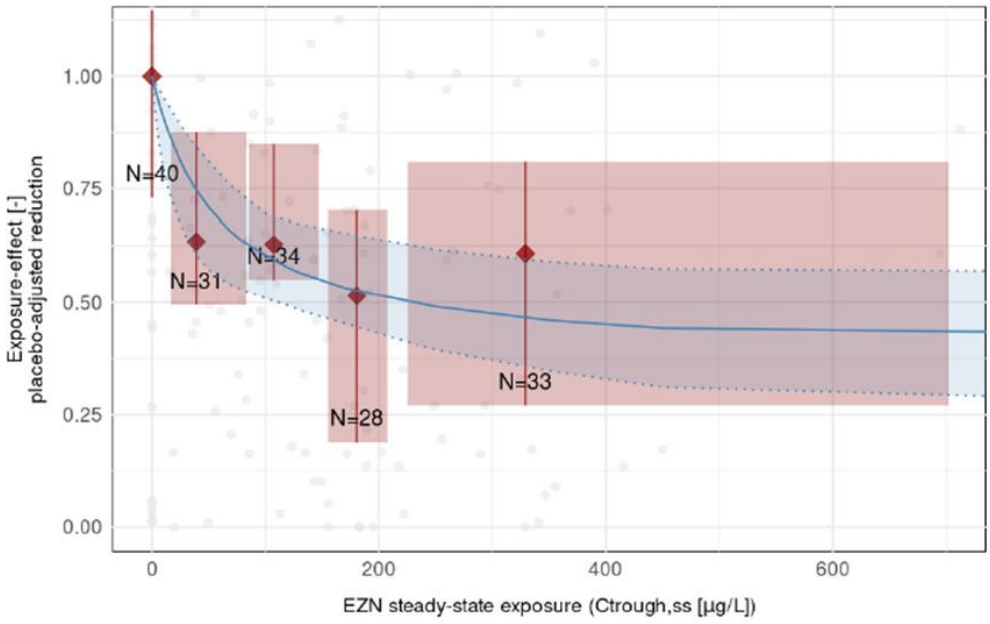
Source: Applicant's E-R report, Figure 15.48
Red shaded area: 95% CI of predicted 10th and 90th percentiles; orange shaded area: 95% CI of predicted mean; brown shaded area: 95% CI of predicted median; solid line: median, 10th and 90th percentiles of observed data; dashed line: mean of observed data.
Abbreviations: E-R, exposure response; EZN, elinzanetant; HF, hot flash; PI, prediction interval; PLC, placebo; VPC, visual predictive check

Figure 75. Exposure-Response HF Frequency~$C_{trough,ss}$ Relationship at (Approximate) Effect Steady-State for 'Normal'-Responder



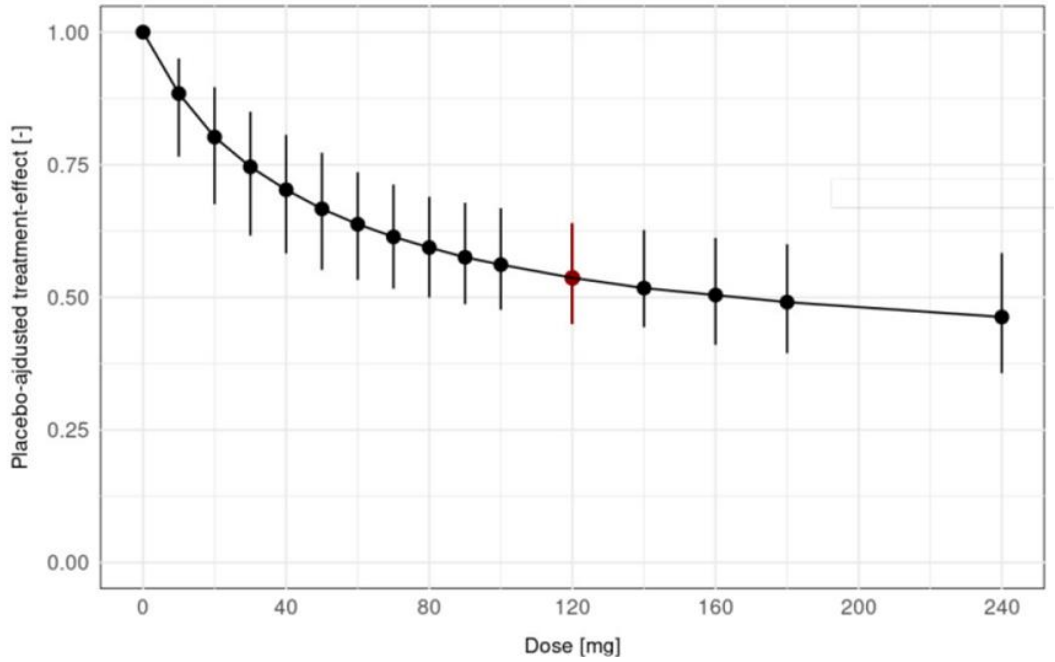
Source: Applicant's E-R report, Figure 9-12
Gray dot represents median of DV (Week 7-12)/BL; blue line (shaded area) represents simulations (95% CI); red diamond, bar, and area represent median, 95% CI, and 90% range in exposure quartile. X-axis was truncated at upper 97.5% of exposure.
Abbreviations: BL, baseline; $C_{trough,ss}$, trough concentration at steady state; E-R, exposure response; EZN, elinzanetant; DV, observed value; HF, hot flash; N, number of subjects

Figure 76. External Qualification–E-R, SWITCH-1



Source: Applicant's Population PK report, Figure 16.7
Gray dot represents median of DV (Week 7-12)/BL; blue line (shaded area) represents simulations (95% CI); red diamond, bar, and area represent median, 95% CI, and 90% range in exposure quartile. X-axis was truncated at upper 97.5% of exposure.
Abbreviations: BL, baseline; $C_{trough,ss}$, trough concentration at steady state; E-R, exposure response; EZN, elinzanetant; DV, observed value; N, number of subjects; PK, pharmacokinetic

Figure 77. Simulated Dose-Response Curve for HF Frequency



Source: Applicant's E-R report, Figure 16.9
Black dot and error bar: median, 2.5th, 97.5th percentiles of the simulated typical response per study (bootstrap run)
Simulation was performed using the E-R model for HF frequency based on $C_{trough,ss}$. Exposure at each dose level is scaled assuming dose-proportional linearity (e.g., $C_{trough,ss}$ (100 mg) = $C_{trough,ss}$ (120 mg)/120*100).
Abbreviations: $C_{trough,ss}$, trough concentration at steady state; E-R, exposure-response; HF, hot flash

14.5.2.4. E-R Analysis for Safety

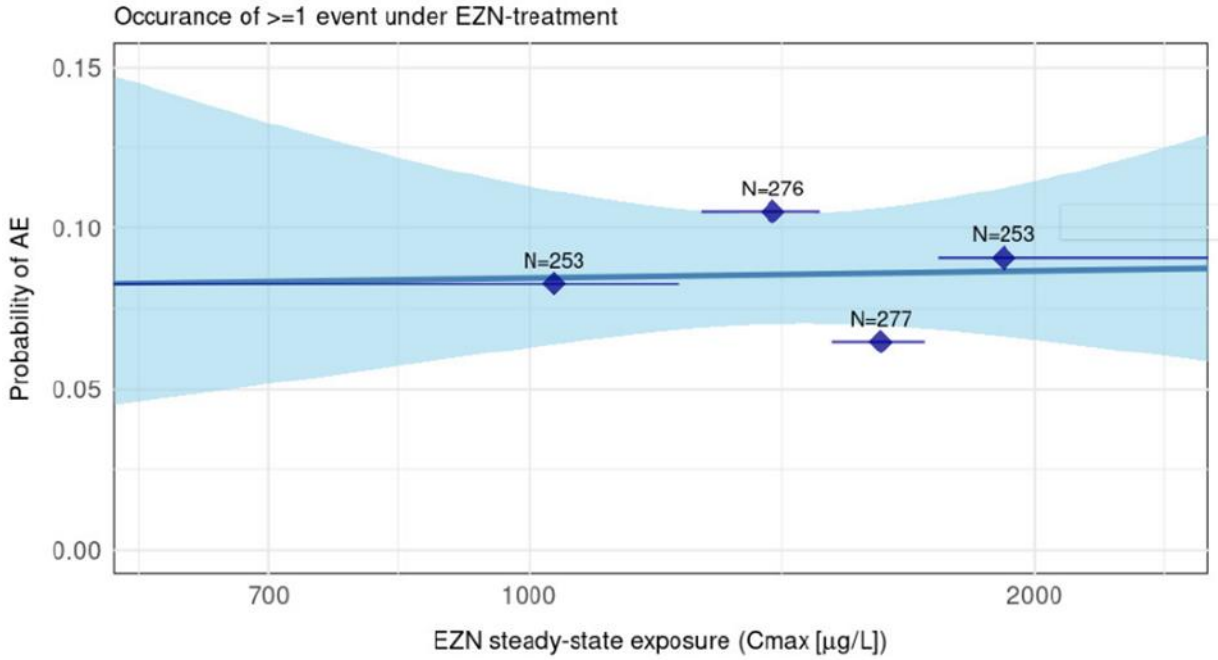
The safety E-R analysis was based on data from Phase 3 studies OASIS 1, OASIS 2, and OASIS 3. The safety endpoints included AST, ALT, and AEs of special interest (fatigue, somnolence, or dizziness).

The analysis data included a total of 11,527 ALT records and 11,684 AST records from N=1,420 subjects, and records for AESI from 1,059 subjects who received elinzanetant.

A regression analysis testing the influence of exposure on the maximum AST and ALT value per subject and on the occurrence of elevations >1xULN was performed. For both AST and ALT, a visual exploration of the time-trajectories revealed no differences between the study arms across the three studies. An exploratory regression analysis of the maximum observed value per subject under treatment with elinzanetant revealed no association with elinzanetant exposure for both liver markers.

The E-R for AESI was explored visually by comparing the incidence rates across exposure quartiles followed by a logistic regression analysis of occurrence of ≥1 event of interest versus no event of interest under elinzanetant treatment. No association between the risk for an AE of special interest and individual elinzanetant steady-state exposure could be identified within the subjects treated with 120 mg elinzanetant (Figure 78).

Figure 78. Exposure-Response Relationship for AEs of Special Interest and Steady-State C_{max}



Source: Applicant's E-R report, Figure 19.5
Solid line (shaded area): logistic regression fit (95% CI)
Abbreviations: AE, adverse event; E-R, exposure response; EZN, elinzanetant; C_{max}, maximum plasma concentration; N, number of subjects

14.5.3. PBPK Analysis

Excusive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK analyses to evaluate the DDI potentials of elinzanetant with CYP3A4 inhibitors.

The Division of Pharmacometrics has reviewed the PBPK report CPMX50214, Responses to FDA's request for information dated October 30 and December 17, 2024, and supporting modeling files, to conclude the following:

- PBPK analysis predicts that a moderate CYP3A4 inhibitor such as erythromycin could increase AUC and C_{max} of elinzanetant by 3.0 and 2.0-fold, respectively.
- PBPK analysis predicts that the exposure to 60 mg elinzanetant following administration of a moderate CYP3A4 inhibitor, such as erythromycin, is comparable to the exposure of 120 mg elinzanetant, with an increase in AUC and C_{trough} by 1.39-fold and 1.91-fold, respectively.
- PBPK analysis predicts no clinically significant effect on elinzanetant exposure when coadministered with a weak CYP3A inhibitor such as cimetidine.

Background

Elinzanetant (LYNKUET, BAY3427080, NT-814) is developed for the treatment of vasomotor symptoms associated with menopause. The proposed dosing of elinzanetant is 120 mg orally (two 60 mg capsules) once daily at bedtime with or without food.

Dose-exposure relationships were slightly greater than dose proportional in the dose range of 40 to 120 mg and dose proportional increase at doses >120 mg (Applicant's Summary of Clinical Pharmacology Studies). Human mass balance study (Study 21664) reported approximately 15% of administered [^{14}C] NT-814 was excreted in feces (ranges 0 to 40% of administered dose) in the first 48 hours and >90% by Day 15, while <1% drug was detected in urine by Day 15. The Applicant considered the drug eliminated in feces within the first 48 hours as unabsorbed, given the low solubility of NT-814 in aqueous solution. The parent compound was the major circulating component in plasma, accounting for 31% of the total drug-related exposure. M30/34, an active metabolite, was the only major metabolite, contributing approximately 10% of the total drug-related material in plasma.

The Applicant reported that the mean apparent oral clearance in subjects ranged from 15.5 to 23.2 L/h (as observed in Study 21756 and Study 21669, Clinical Pharmacology Studies) following a single 120 mg dose of elinzanetant. Similar terminal half-lives of elinzanetant were observed after both single and multiple dose administrations. Elinzanetant is highly bound to human plasma proteins (99.7%). The plasma fraction unbound was reported to be higher (within a two-fold increase) under fed conditions and in subjects with renal impairment (Study 21669). However, the plasma fraction unbound was reduced in subjects with hepatic impairment (Study 21668).

In vitro DDI data suggested that elinzanetant is mainly metabolized by CYP3A and minorly by UGT and is a substrate of P-gp. Elinzanetant is an inducer and competitive and mechanistic-based inhibitor for CYP3A and an inhibitor for P-gp and BCRP/OATP in vitro. Several clinical DDI studies were conducted to evaluate the DDI potential of elinzanetant as a CYP3A substrate or as a perpetrator for CYP3A, P-gp and BCRP/OATP. Results of clinical DDI studies indicated that elinzanetant (120 mg QD) does not impact the exposure of dabigatran etexilate (P-gp substrate), and rosuvastatin (BCRP/OATP substrate). Additionally, the Applicant measured endogenous biomarker data for 4β-hydroxycholesterol and coproporphyrin-I. Changes in 4β-hydroxycholesterol and coproporphyrin-I levels following elinzanetant administration were less than 20%. Therefore, the in vivo DDI potential of elinzanetant as a CYP3A inducer and OATP1B inhibitor is likely low. Table 212 summarizes the results of clinical DDI studies evaluating elinzanetant as a CYP3A substrate and as a CYP3A inhibitor.

Table 212. Clinical DDI Effects of Elinzanetant as CYP3A Substrate or as an Inhibitor

CYP3A Substrate (dose)	Perpetrator (Dose)	Substrate's C_{max} Ratio*	Substrate's AUC_{inf} Ratio*
Elinzanetant (40 mg SD)	Itraconazole (200 mg QD, fasted)	3.31 (2.74, 4)	4.84 (4.02, 5.83)
Elinzanetant (120 mg SD)	Carbamazepine (600 mg QD)	0.56 (0.50-0.62)	0.36 (0.31-0.41)
M18/M12		0.78 (0.68-0.88)	0.41 (0.30-0.46)
M27		0.63 (0.56-0.72)	0.35 (0.30-0.40)
M30/M34		0.63 (0.56-0.72)	0.30 (0.26-0.34)
Midazolam (1 mg SD)	Elinzanetant (120 mg SD)	1.14 (1.06-1.23)	1.45 (1.37-1.53)
Midazolam (1 mg SD)	Elinzanetant (200 mg QD)	1.71 (1.4-2.10)	1.90 (1.62-2.23)
Tamoxifen [#] (20 mg SD)	Elinzanetant (120 mg QD)	1.23 (1.14-1.32)	1.52 (1.46-1.58)

Source: Applicant's Summary of Clinical Pharmacology Studies
*Values as geometric mean (GM) (90% CI)
[#] Tamoxifen is a dual CYP2D6 and CYP3A
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CYP, cytochrome; DDI, drug-drug interaction; M, metabolite; SD: single dose; QD, once daily

The Applicant developed the PBPK modeling analysis (Study CPMX50214) to predict the changes in exposure of elinzanetant and M30/34 with erythromycin (a CYP3A moderate inhibitor) and cimetidine (a weak CYP3A inhibitor). The PBPK simulated results are used to inform the DDI dosing in the USPI. Additionally, the Applicant conducted a PBPK analysis (Study CPMX50217) to evaluate the effects of elinzanetant on the pharmacokinetics of tamoxifen and its metabolites. Given the absence of a DDI dosing recommendation for tamoxifen when coadministered with a moderate CYP3A inhibitor, the PBPK study report CPMX50217 was not reviewed.

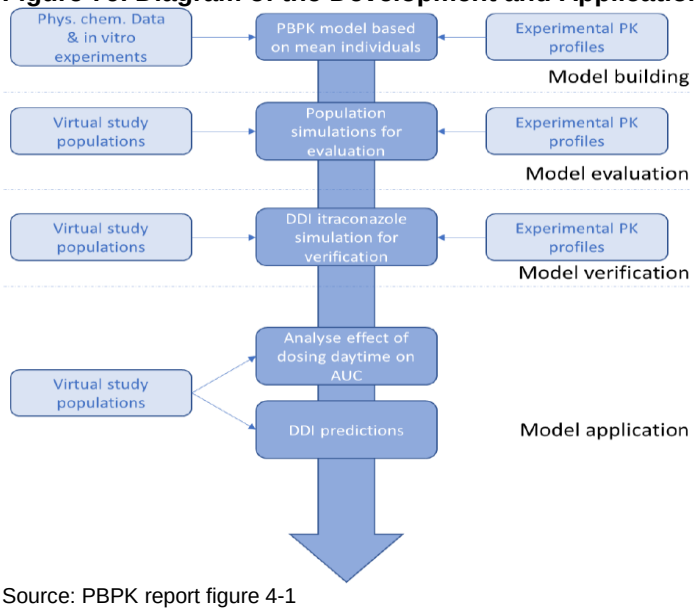
Methods

Model Development

The PBPK analyses were performed using PKsim and MoBi softwares (Open Systems Pharmacology 2025b).

A based model was first built where drug specific physicochemical properties, solubility, baseline fu, pathway-specific intrinsic clearances of elinzanetant and metabolite M30/34, and CYP3A inhibition parameters were obtained from relevant in vitro experiments. The Applicant noted that circadian fluctuations of fu informed by clinical data was also included in the model. During the model development, the parameter identification tool in MoBi was used to estimate selected model parameters. PBPK parameters such as dissolution parameters, scaling factor for the elinzanetant metabolism (v_{max}_factor) and M30/34 catalytic constant (kcat), UGT clearance, permeability, and the extent of gut wall metabolism were optimized using clinical dataset. Figure 79 presents a diagram of the overall modelling strategy for elinzanetant. Table 213 presents the list of PBPK input parameters.

Figure 79. Diagram of the Development and Application of Elinzanetant PBPK Model



Source: PBPK report figure 4-1
Abbreviations: AUC, area under the concentration-time curve; DDI, drug-drug interaction; PBPK, physiologically-based pharmacokinetic; phys. chem. data, physicochemical data; PK, pharmacokinetic

Table 213. Input Parameters for Elinzanetant and M30/34 PBPK Model

Elinzanetant

Parameter [Unit]	Value	Reference
Molecular weight [g/mol]	668.64	PIx
pKa (base)	6.4	measured; in-house information
pKa (base)	4.8	measured; in-house information
solubility [mg/l] (FaSSGF)	1247	CRM/CSM report
major binding partner in plasma	albumin	Report PH-42081, version 3.0
Plasma fraction unbound baseline [%]	0.302	Report PH-42081, version 3.0
Plasma fraction unbound shift [h]	11.10	see section 4.3.1.2.3
Plasma fraction unbound amplitude	0.25	see section 4.3.1.2.3
$K_{m,u}$ to M30/34 [nmol/l]	319	Report PH-42629, version 2.0
v_{max} to M30/34 [pmol/min/mg mic. protein]	282	Report PH-42629, version 2.0
$K_{m,u}$ to M27 [nmol/l]	293	Report PH-42629, version 2.0
v_{max} to M27 [pmol/min/mg mic. protein]	127	Report PH-42629, version 2.0
$K_{m,u}$ to other [nmol/l]	206	Report PH-42629, version 2.0
v_{max} to other metabolites [pmol/min/mg mic. protein]	34.81	see section 4.3.1.2.4
UGT Cl_{spec} [1/min]	17.35	see section 4.3.1.2.4
CYP3A4 inhibition - k_{inact} [min/l]	0.013	see section 4.3.1.2.6
CYP3A4 inhibition - K_I[a] [µmol/l]	0.64	see section 4.3.1.2.6
CYP3A4 inhibition – K_i [µmol/l]	0.21	see section 4.3.1.2.6
CYP3A4 induction - E_{max}	5.22	see section 4.3.1.2.7
CYP3A4 induction - EC_{50} [µmol/l]	1.27	see section 4.3.1.2.7

M30/34

Parameter [Unit]	Value	Reference
Molecular weight [g/mol]	684.64	PIx
pKa (base)	5.08	PIx
pKa (base)	3.55	PIx
pKa (acid)	12.34	PIx
solubility [mg/l]	91.74	PIx
major binding partner in plasma	albumin	assumed from parent molecule
Plasma fraction unbound baseline [%]	0.4945	Report PH-42138, version 1.0
Plasma fraction unbound shift [h]	13.39	see section 4.3.1.2.3
Plasma fraction unbound amplitude	0.13	see section 4.3.1.2.3
$K_{m,u}$ [nmol/l]	128	Report PH-42629, version 2.0
v_{max} [pmol/min/mg mic. protein]	76	Report PH-42629, version 2.0
CYP3A4 inhibition – k_{inact} [min/l]	0.017	see section 4.3.1.2.6
CYP3A4 inhibition - K_I[a] [µmol/l]	0.60	see section 4.3.1.2.6
CYP3A4 inhibition - K_i [µmol/l]	0.46	see section 4.3.1.2.6
CYP3A4 induction - E_{max}	4.19	see section 4.3.1.2.7
CYP3A4 induction - EC_{50} [µmol/l]	0.55	see section 4.3.1.2.7

Source: PBPK report Table 4-7 and 4-8
Abbreviations: CRM, conventional risk model; CSM, Content and Structure Model; CYP, cytochrome; EC50, half-maximal effective concentration; E_{max}, maximum induction effect; FaSSGF, fasted state simulated gastric fluid; Ki, K_{inact}, rate of enzyme inactivation; KIa, infusion rate constant; inhibition constant; $K_{m,u}$, unbound Michaelis-Menten constant; PBPK, physiologically-based pharmacokinetic; PIx, pharmacophorInformatics, pKa, Acid dissociation constants; UGT, uridine diphosphate glucuronosyl transferase; V_{max}, maximal rate of metabolism

FDA Analysis

Although in vitro data suggested that elinzanetant is a P-gp substrate, the Applicant did not include P-gp mediated clearance in elinzanetant PBPK model. The Applicant's rational is that (1) elinzanetant has a good in vitro permeability and (2) the efflux ratio is less than one in Caco 2 assay. The reviewer noted that the recovery rate of elinzanetant is very low in the Caco 2 in vitro study (KINE 240041-ELB) and it could impact the interpretation of the efflux ratio data. In

addition, the absolute bioavailability of 52%, and approximately parallel concentration-time profiles with or without coadministered itraconazole (Study 21679 figures in Section 14.2) could suggest a significant P-gp elimination. However, given a mean of 16% of total radiolabel elinzanetant was found in feces in the first 48 hours after elinzanetant oral administration (Study 21664), P-gp mediated pathway of elinzanetant could be much less than CYP3A-mediated clearance.

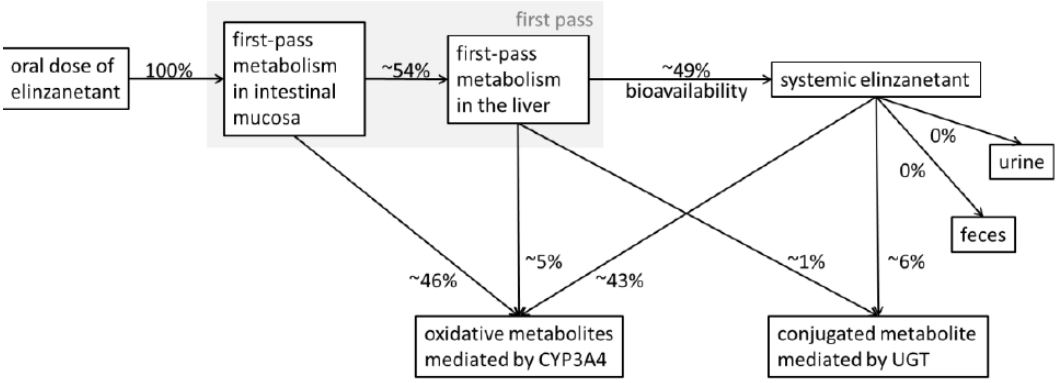
Another concern is that the elimination pathway of M30/M34 was not well characterized. The reviewer issued an information request to the Applicant to assess and discuss the impact of concomitant use of CYP3A4 inhibitors and inducers on the total pharmacological activity of elinzanetant, including the parent drug and its metabolites.

The Applicant stated that they assume M30/M34 being cleared primarily via the CYP3A pathway based on: (1) in vitro study suggesting that M30/M34 undergoes oxidative biotransformation and (2) the relative decrease in M30/M34 exposure similar to that observed with elinzanetant when coadministered with carbamazepine, indicating that the production and elimination pathway of M30/M34 is likely mediated mainly by CYP3A. Figure 80 presents the metabolism pathways of elinzanetant in the PBPK model.

The reviewer found the Applicant's assumption that CYP3A is the main pathway for M30/M34 elimination to be uncertain due to the following reasons: (1) No metabolite data were collected in the itraconazole DDI study and (2) Carbamazepine is known to induce multiple enzymes and transporters, complicating pathway characterization.

Despite these uncertainties, given that the production of M30/M34 is expected to be reduced when coadministered with a CYP3A inhibitor, the DDI effects on elinzanetant exposure serve as a reasonable surrogate for its total pharmacological activity. The uncertainty in the clearance pathway of M30/M34 may be more relevant when PBPK modeling is used to assess the effect of CYP inducers (such as efavirenz) on the exposure of elinzanetant and M30/M34. The reviewer noted that no simulations were conducted for the coadministration of elinzanetant with a moderate inducer.

Figure 80. Mass Balance of Elinzanetant in the PBPK Model



The percentages are derived from an individual simulation of 120mg PO SD in a 55-year-old woman.
Source: PBPK report figure 4-2
Abbreviations: CYP, cytochromeDDI, drug-drug interaction; Geo., geometric; M, metabolite; PBPK, physiologically based pharmacokinetic; PO, by mouth; SD, single dose; UGT, uridine diphosphate glucuronosyltransferase

Model Validation

Clinical PK and DDI dataset were used to support the model building, evaluation and verification. Table 214 presents the selected dataset used for model evaluation or validation.

Table 214. Selected Clinical Data on Elinzanetant and M30/34 Used in Model Evaluation and/or Validation

Study	Description	Elinzanetant Dose	M30/34	Usage
22050	Relative bioavailability of new and old soft-gel capsule	120 mg SD/MD	Yes	Model evaluation
21666	DDI study with rosuvastatin	120 mg MD	Yes	Model evaluation
21667	Carbamazepine DDI study	120 mg SD	Yes	Model evaluation
21668	Hepatic impairment (control arm only)	120 mg SD/MD	Yes	Model evaluation
21669	Renal impairment (control arm only)	120 mg SD	Yes	Model evaluation
21670	Single ascending dose	240, 360, 480, 600 mg SD	Yes	Model evaluation
21678	Food interaction study	40, 80. 120, 160 mg MD	No	Model evaluation
21679	Itraconazole DDI study	40 mg SD	No	Model evaluation and verification
21686	Phase II study	40, 80. 120, 160 mg MD	No	Model verification
21772	Absolute bioavailability	120 mg SD	Yes	Model evaluation
21840	DDI study with midazolam	120 mg SD/MD	Yes	Model evaluation
22004	DDI study with tamoxifen	120 mg MD	Yes	Model evaluation

Source: PBPK report Table 4-2
Abbreviations: DDI, drug-drug interaction; M, metabolite; MD, multiple dose; PBPK, physiologically based pharmacokinetic; SD, single dose

The Applicant noted that only clinical studies involving IV or soft gel capsule administration were included in the development and validation of the PBPK analysis.

Sensitivity Analysis

The Applicant conducted a sensitivity analysis for parameters governing: (1) the fraction metabolized by UGT (fmUGT), which subsequently impacts the fmCYP3A4 values, and (2) the gut wall metabolism factor, which describes the ratio between metabolism by CYP3A4 in the liver and the gut wall (kcat_GI_factor).

fmUGT: Under the assumption that UGT is only expressed in the liver, the fmUGT was set to be 6.3% after oral administration in elinzanetant PBPK model. The values of the fraction metabolized of UGT for testing were determined as 0% and 11.9% total UGT contribution.

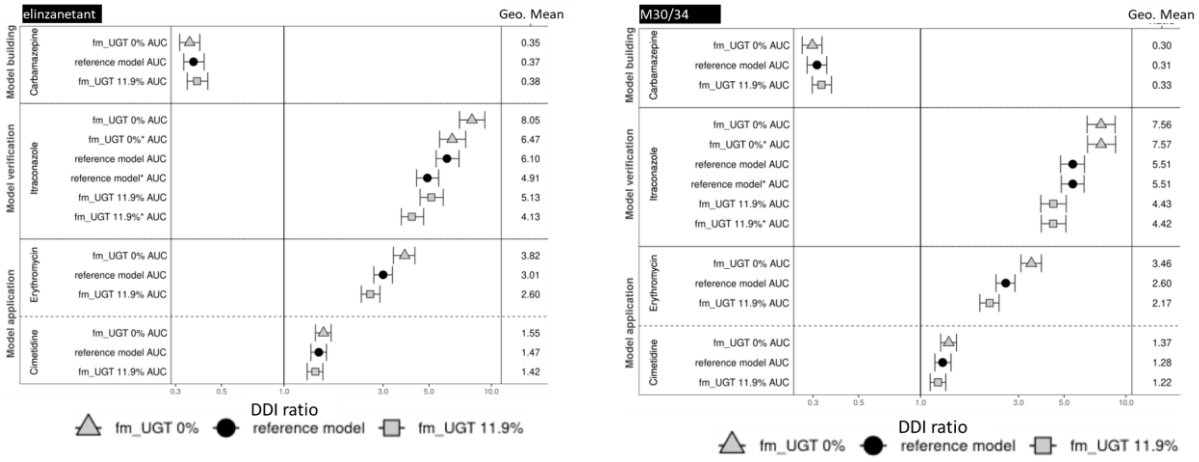
kcat_GI_factor: The initial model simulations showed that the extent of gut wall metabolization (kcat_GI_factor) was too low in the PBPK model. Thus, kcat_GI_factor was optimized to fit clinical PK and carbamazepine DDI data. The value of kcat_GI_factor is 25 in elinzanetant PBPK model. The values of kcat_GI_factor for testing were ranging 0.01 to 10-fold of the reference value of 25.

Figure 81 and Figure 82 present the sensitivity of the AUC ratio (AUCR) and C_{max} ratio (C_{max}R) of elinzanetant and M30/34 to changes in the values of fmUGT and kcat_GI_factor when coadministered with various CYP3A percipients. Figure 81 shows the effect of different fmUGT

on AUCR of elinzanetant and M30/34 in comparison to the reference PBPK model. Figure 82 shows the effect of kcat_GI_factor on the AUCR and $C_{max}R$ of elinzanetant and M30/34.

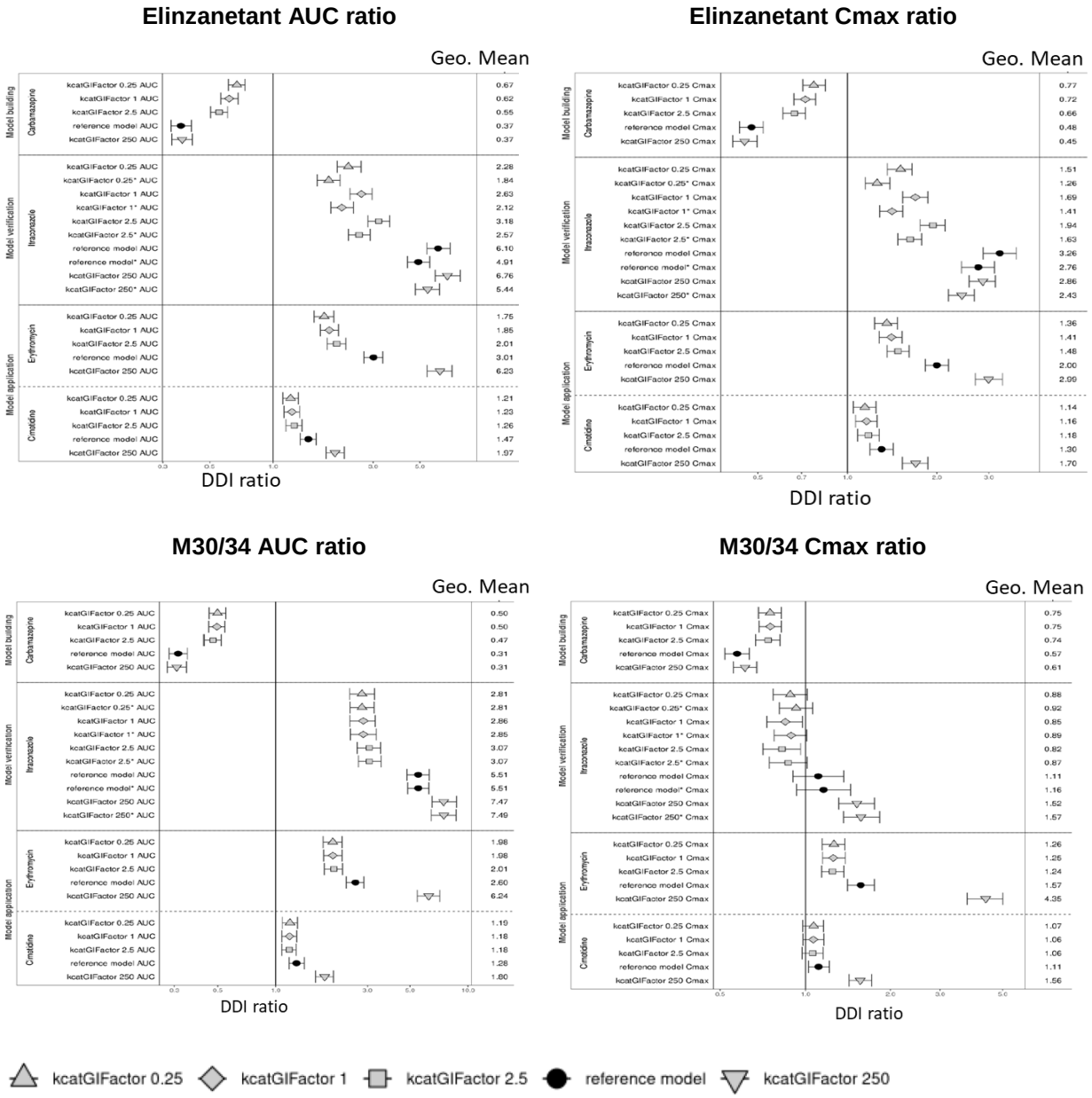
Figure 81. Simulated AUC Ratios of Elinzanetant and M30/34 for Varying UGT Contributions

Elinzanetant AUC ratio **M30/34 AUC ratio**



Source: PBPK report figure 5-40 and 42
Abbreviations: AUC, area under the concentration-time curve; Cmax, maximum plasma concentration; DDI, drug-drug interaction; Geo., geometric; M, metabolite; PBPK, physiologically based pharmacokinetic; UGT, uridine diphosphate glucuronosyltransferase

Figure 82. Simulated AUC and C_{max} Ratios of Elinzanetant and M30/34 for Varying Contributions of Gut Metabolism



Source: PBPK report figure 5-43 to 46
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; DDI, drug-drug interaction; Geo., geometric; M, metabolite; PBPK, physiologically based pharmacokinetic

FDA Analysis

As shown in Figure 81, changing the values of fmUGT and fmCYP3A has modest effect on predicted DDI with CYP inhibitors and inducer. For example, the predicted DDI effect with a moderate CYP3A inhibitor, erythromycin, is about 30% higher (AUCR 3.82 versus 3.01) when assuming the highest contribution of CYP3A-mediated clearance (i.e., fmUGT =0). Similar sensitivity was predicted for M30/34 (results not shown).

As shown in Figure 82, a lower DDI effects were simulated for elinzanetant and M30/34 when a lower contribution of gut metabolism was assumed. However, the predicted DDI of elinzanetant with erythromycin could be 2-fold higher than the reference PBPK model (AUCR 3.01 versus 6.23) when assuming a higher contribution of gut metabolism (kcat_GI_factor =250). This setting (10-fold of reference kcat_GI_factor value) is considered less possible as the model would significantly underestimate the observed C_{max} in clinical PK studies and is inconsistent with observed IV PK data.

As previously discussed, there is uncertainty regarding the extent of P-gp-mediated clearance for elinzanetant. The need to assign a higher contribution of gut metabolism in the final elinzanetant PBPK model (kcat_GI_factor of 25) may be due to P-gp involvement. Consequently, the model might overestimate rather than underestimate the contribution of gut metabolism. When the kcat_GI_factor value is reduced by 100-fold from the reference value, as shown in Figure 82, the predicted DDI effect with the moderate CYP3A inhibitor erythromycin is approximately 30% lower (AUCR 1.78 versus 3.01).

For this application, the PBPK analysis is used to inform elinzanetant DDI dosing recommendation when coadministered with a moderate CYP3A inhibitor. The reviewer concluded that the changes in fmUGT (0–11%) or a lower kcat_GI_factor (0.25–25) affect the predicted DDI effects of elinzanetant and M30/34 by about 30%. This impact is not expected to affect the applicability of using this PBPK model to support DDI dosing recommendations for moderate CYP3A inhibitors.

Supportive Compound Files

The evaluation reports for various PKsim PBPK models of CYP modulators can be found on (Open Systems Pharmacology 2025a)

FDA Analysis

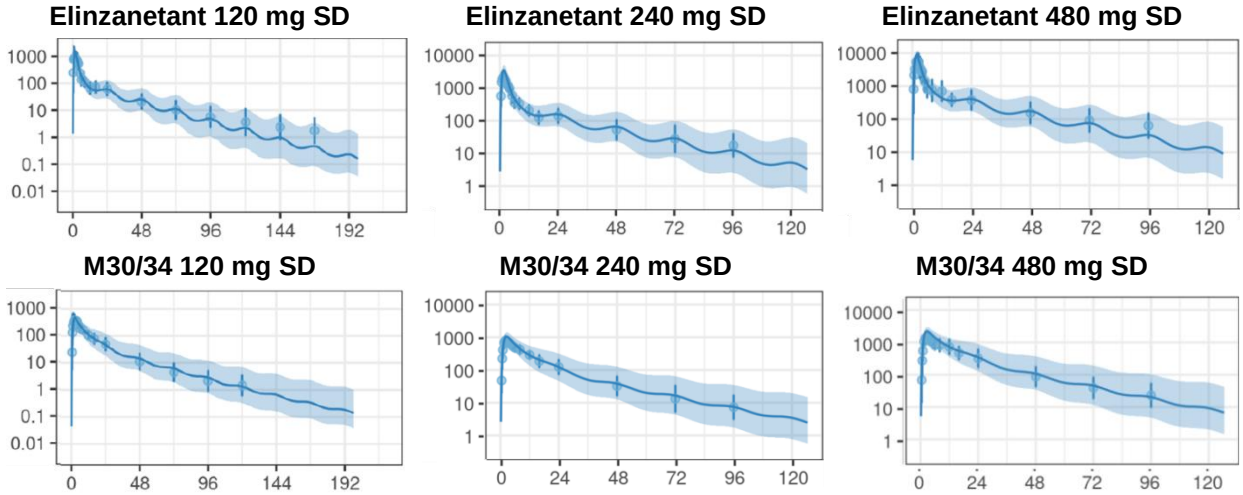
The reviewer notes that although a detailed evaluation of reports for all PBPK models supporting the development of a new drug is preferred, the extent of this evaluation can be guided by model risk, as recommended in the ICH guidance for industry *M15 General Principles for Model-Informed Drug Development* (December 2024). In the case of elinzanetant, given the extensive clinical PK and DDI studies available, and considering that the magnitude of DDI for elinzanetant with a moderate CYP3A inhibitor can be interpolated from the clinical DDI data with a strong CYP3A inhibitor and inducer, only a high-level review was conducted for key supportive PBPK models, including those for itraconazole, erythromycin, cimetidine, carbamazepine, and midazolam. The reviewer also notes prior evaluation of model reports and regulatory experience with PK-Sim PBPK modeling for predicting CYP3A DDI has been reported (e.g., NDA 215341 and NDA 214133).

Results

Can PBPK Analyses Provide a Reasonable Description of the Pharmacokinetics of Elinzanetant and M30/34?

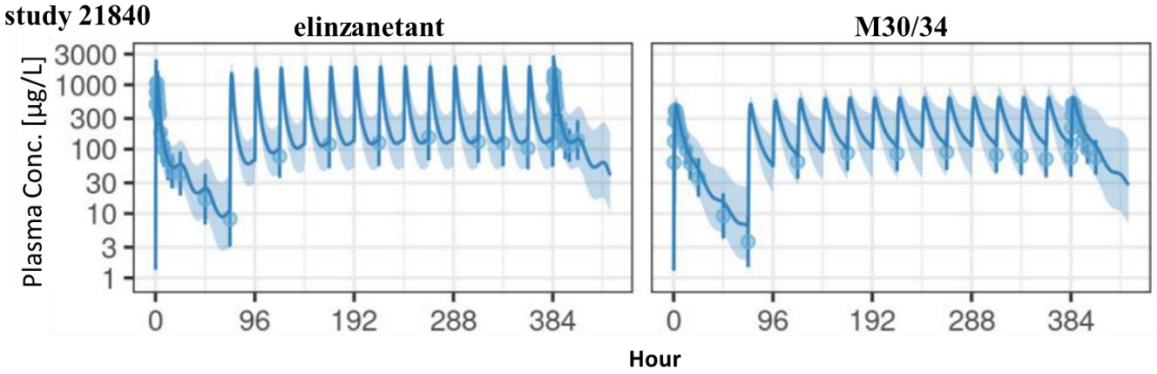
Yes. The Applicant's elinzanetant PBPK model was able to describe elinzanetant pharmacokinetics following a single and multiple doses of elinzanetant. The model was able to describe the concentration-time profile of elinzanetant and M30/34 across difference dosing regiments. The comparison of the predicted and the observed pharmacokinetics from selected clinical studies are presented in Figure 83, Figure 84, and Figure 85. Refer to Table 214 for details on the clinical dataset presented in the tables and figures of the results section.

Figure 83. Comparison of Simulated and Observed Concentration-Time Profiles of a Single Dose of Elinzanetant and M30/34



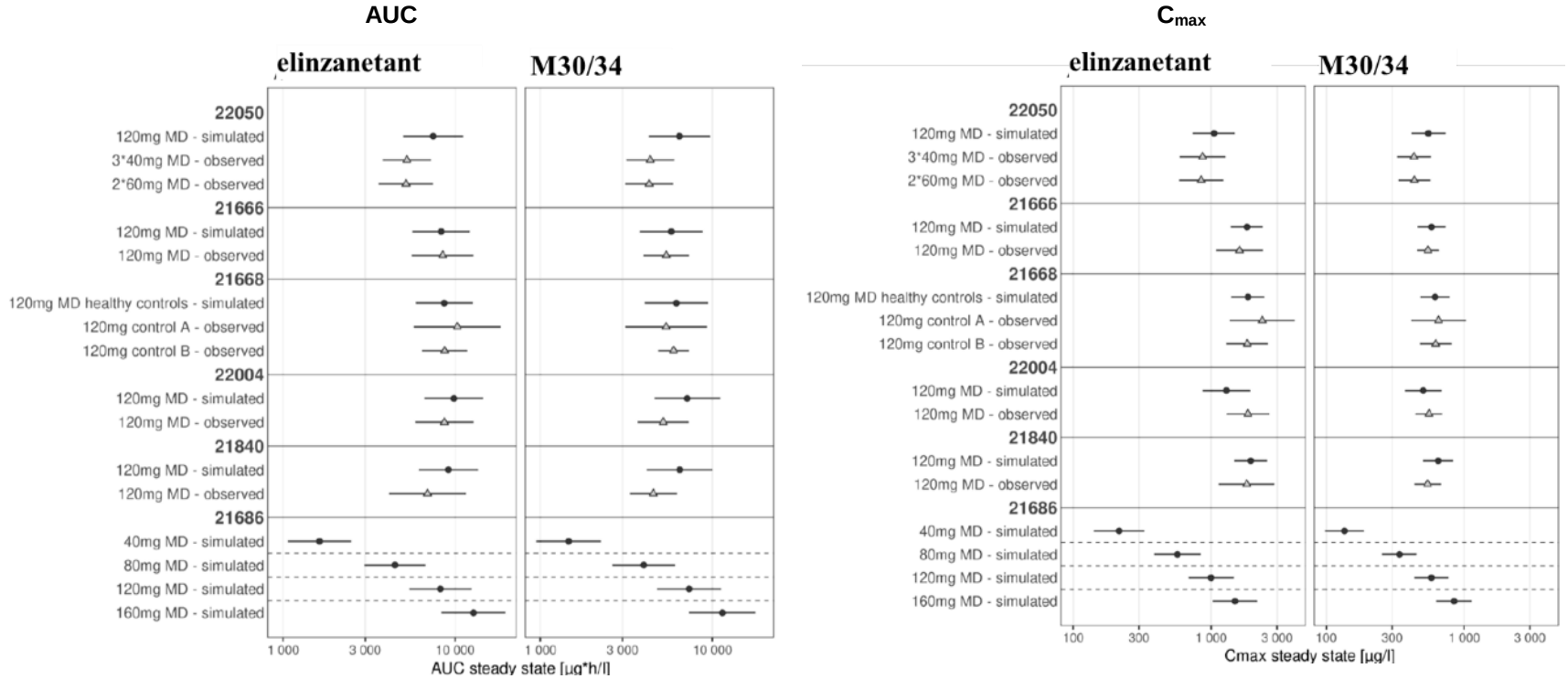
Source: PBPK report figure 5-7 and 5-12 based on study 21679 and 21670
Observed data (circles ○) shown as geometric mean with geometric standard deviation; Solid line and shade represent simulated mean and 5th-95th percentile
Abbreviations: M, metabolite; PBPK, physiologically based pharmacokinetic; SD, single dose; QD, once daily

Figure 84. Comparison of Simulated and Observed Concentration-Time Profiles of Elinzanetant and M30/34 Following Elinzanetant 120 mg QD



Source: PBPK report figure 5-15 and study 21840
Observed data (○) shown as geometric mean with geometric standard deviation. Solid line and shade represent simulated mean and 5th-95th percentile
Abbreviations: Conc., concentration; M, metabolite; PBPK, physiologically based pharmacokinetic; QD, once daily

Figure 85. Summary of the Comparison of Simulated and Observed Exposure of Elinzanetant and M30/34 Following Multiple Doses of Elinzanetant

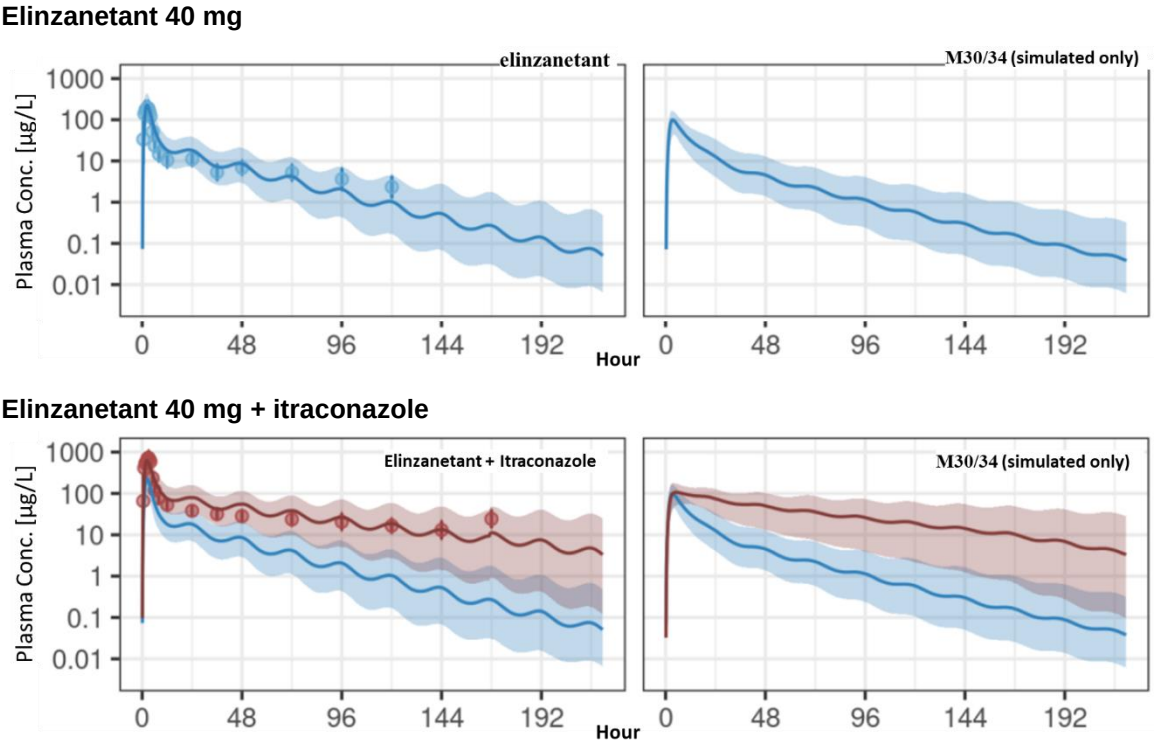


Source: PBPK report figure 8-118 and 8-119
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; MD, multiple dose; PBPK, physiologically based pharmacokinetic

Can PBPK Analyses be Used to Inform the Elinzanetant's Dosing Recommendation When Coadministered With Moderate CYP3A Inhibitors?

Yes, the final PBPK model adequately describes the observed effects of CYP3A inhibitors and inducers on the pharmacokinetics of elinzanetant and M30/34. It can be used to inform dosing recommendations for elinzanetant when coadministered with moderate CYP3A inhibitors. Figure 86 and Figure 87 compared the simulated and observed DDI effects of itraconazole and carbamazepine, respectively.

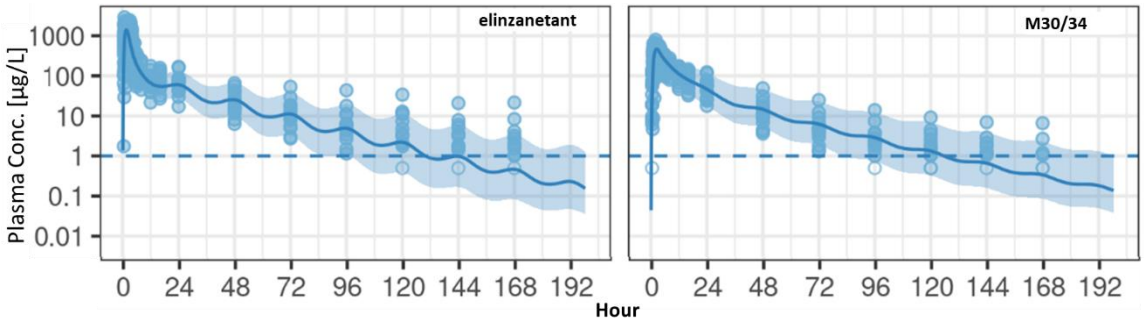
Figure 86. Comparison of Simulated and Observed Concentration-Time Profiles of Elinzanetant With or Without Itraconazole



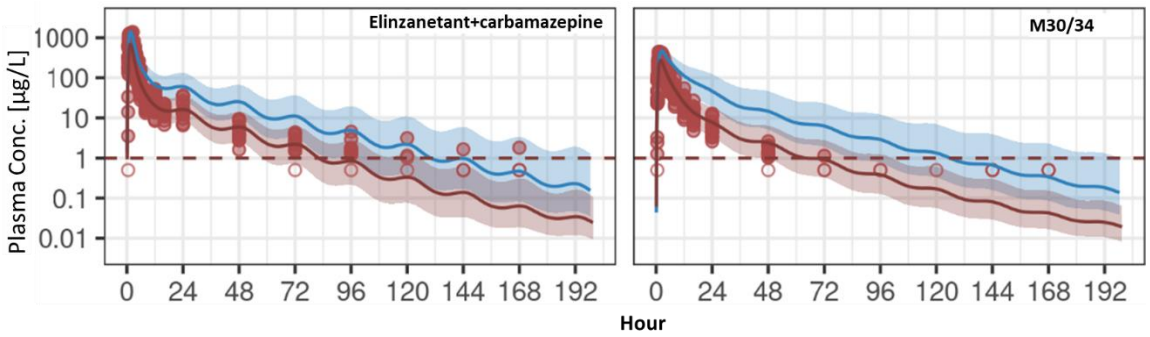
Source: PBPK report figure 5-32 and Study 21679
Observed data (○) shown as geometric mean with geometric standard deviation. Solid line and shade represent simulated mean and 5th-95th percentile.
Abbreviations: Conc., concentration; PBPK, physiologically based pharmacokinetic.

Figure 87. Comparison of Simulated and Observed Concentration-Time Profiles of Elinzanetant and M30/34 With or Without Carbamazepine

Elinzanetant 120 mg



Elinzanetant 120 mg + carbamazepine



Source: PBPK report figure 8-98 and Study 21667
Observed data (○) shown as geometric mean with geometric standard deviation. Solid line and shade represent simulated mean and 5th-95th percentile.
Abbreviations: Conc., concentration; PBPK, physiologically based pharmacokinetic

The PBPK model predicted a AUCR and C_{max} ratio of 3.0 and 2.0 for elinzanetant, respectively, when coadministered with erythromycin (500 mg three times daily) The PBPK model predicted a AUCR and C_{max} ratio of 1.47 and 1.30 for elinzanetant, respectively, when coadministered with cimetidine (800 mg BID). See Table 215 for predicted DDI effects of erythromycin and cimetidine.

Table 215. Predicted DDI Effect of Erythromycin and Cimetidine on the Exposure of Elinzanetant

CYP3A Substrate (Dose)	Precipitator (Dose)	Substrate's C_{max} Ratio*	Substrate's AUC_{inf} Ratio*
elinzanetant (120 mg SD)	erythromycin (500 mg TID)	2.00 (1.83 – 2.19)	3.01 (2.71, 3.33)
elinzanetant (120 mg SD)	cimetidine (800 mg BID)	1.30 (1.19-1.43)	1.47 (1.35-1.60)

Source: PBPK report figure 5-37
Values displayed as geometric mean and 90% confidence interval
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; Cmax, maximum plasma concentration; CYP, cytochrome; DDI, drug-drug interaction; PBPK, physiologically based pharmacokinetic; SD, single dose; TID, three times daily

An information request was sent on December 17, 2024, requesting the simulated $C_{trough,ss}$ and AUC_{ss} of elinzanetant following elinzanetant 60 mg QD at steady state with concomitant use of the moderate CYP3A inhibitor erythromycin. In the presence of erythromycin, the geometric mean AUC_{ss} and $C_{trough,ss}$ ratios of elinzanetant were 1.39 and 1.91, respectively. The Applicant

stated that the efficacy would be maintained at the simulated $C_{trough,ss}$ level based on the E-R analysis (Study CPMX50130). Dosing reduction to 60 mg QD is then recommended with coadministration of a moderate CYP3A inhibitor. No dosing modification of elinzanetant was considered necessary with coadministration of a weak CYP3A inhibitor, based on the predicted DDI effect with cimetidine.

Similarly, simulations assessed the AUC_{ss} and $C_{trough,ss}$ of elinzanetant following elinzanetant of 120 mg QD at steady state with concomitant use of the strong CYP3A inducer carbamazepine (300 mg BID). In the presence of carbamazepine, the geometric mean AUC_{ss} and $C_{trough,ss}$ of elinzanetant reduced by 68% and 81%. Exposure reduction with carbamazepine was considered clinically relevant. Refer to clinical pharmacology review for further discussion.

Conclusions

The PBPK modeling analysis can predict the effect of weak and moderate CYP3A inhibitors on the pharmacokinetics of elinzanetant and serve as the regulatory basis for DDI risk management recommendations in the prescribing information.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

Study/trial design and efficacy are discussed in Sections 1 through 4 and Section 6 through 7 in this review.

16. Efficacy

16.1. Handling of Missing Data in Primary Analyses of Coprimary Endpoints, OASIS 1, OASIS 2, and OASIS 3

In the prespecified primary analysis of the coprimary endpoints in OASIS 1, OASIS 2, and OASIS 3, the nonmonotone (intermittent) missing data and (2) the monotone missing data after the discontinuation of randomized treatment were imputed using the following two steps.

Step (1): Imputation of Nonmonotone (Intermittent) Missing Data

Monte Carlo Markov Chain MI method was used to impute intermittent missing baseline and postbaseline missing values (missing baseline values were imputed together with intermittent missing values). For the baseline value to be imputed, at least two out of the four postbaseline values (i.e., Weeks 1, 4, 8, and 12) need to be available. If not, the subject with missing baseline value was removed from the study. In OASIS 1, all subjects in the FAS had baseline values. In OASIS 2, one subject in the FAS with missing baseline value was removed from the analysis because she had only one (Week 8) out of the four postbaseline values. In OASIS 3, one subject

had missing baseline value; however, she was kept in the analysis because she had three (Weeks 1, 4, and 8) out of the four postbaseline values.

Step (2): Imputation of Monotone Missing Data After the Discontinuation of Randomized Treatment

MI method was used to impute the monotone missing data after the discontinuation of randomized treatment. The MI imputation model included auxiliary variables indicating (yes/or) whether the subject has permanently discontinued from the randomized treatment at each visit of Week 1, 4, 8, and 12. In addition, baseline measurement of frequency/severity of VMS, region and treatment as well as previous postbaseline endpoint values were also included in the imputation model. Per the statistical analysis plan, when there were less than 10 subjects (who permanently discontinued the randomized treatment) across both treatment groups with available postdiscontinuation data at any intermediate time point, the indicator variable was not included in the imputation model for that time point.

Note, in both steps (1) and (2), the imputed negative values were set to zero since VMS frequency and severity values cannot be negative.

After the completion of imputation steps, each imputed dataset was analyzed using the MMRM model specified for the primary analysis of four coprimary endpoints. The results were combined using the Rubin's rule (Rubin 1987) to obtain an overall estimated treatment effect. A total of 500 multiple imputed datasets was generated. Seed numbers 21651, 21652, and 21653 were used for multiple imputations for OASIS 1, OASIS 2, and OASIS 3, respectively.

16.2. Efficacy Sensitivity Analyses for Coprimary Endpoints, OASIS 1 and OASIS 2

This section presents results from FDA's SA1 as described in Section 6.2.4.2. These results were consistent with findings in the primary analyses for OASIS 1 and OASIS 2.

Table 216. Change From Baseline in Mean Daily Frequency of Moderate to Severe Hot Flashes, MMRM Analysis Without Missing Data Imputation Based on Weeks 1 to 12, OASIS 1 and OASIS 2 (FAS)

	OASIS 1		OASIS 2	
Visit/Statistics	Elinzanetant 120 mg (N=199)	Placebo (N=197)	Elinzanetant 120 mg (N=200)	Placebo (N=200)
Baseline				
n	199	197	199	200
Mean (SD)	13.38 (6.57)	14.26 (13.94)	14.66 (11.08)	16.16 (11.15)
Change from Baseline to Week 4				
LS-Mean (SE)	-7.58 (0.43)	-4.33 (0.44)	-5.00 (0.39)	-3.34 (0.39)
Difference vs. Placebo (95% CI)	-3.25 (-4.45, -2.06)		-3.01 (-4.37, -1.65)	
p-Value (one-sided)	<0.0001		<0.0001	

Visit/Statistics	OASIS 1 Elinzanetant 120 mg (N=199)	OASIS 1 Placebo (N=197)	OASIS 2 Elinzanetant 120 mg (N=200)	OASIS 2 Placebo (N=200)
Change from Baseline to Week 12				
LS-Mean (SE)	-8.53 (0.62)	-5.56 (0.63)	-9.77 (0.52)	-6.79 (0.52)
Difference vs. Placebo (95% CI)	-2.96 (-4.69, -1.24)		-2.97 (-4.43, -1.51)	
p-Value (one-sided)	0.0004		<0.0001	

Source: Table 1/2 (for OASIS 1) (page 14) and Table 1/2 (for OASIS 2) (page 22), "response-to-ir" pdf document (Applicant's IR response dated July 25, 2024), verified by the FDA reviewer.
The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week (1-12), and region (United States versus the rest of the world) as factors, with baseline severity as covariates, as well as an interaction of treatment by week and an interaction of baseline frequency by week.
Abbreviations: FAS, full analysis set; IR, information request; LS, least squares; MMRM, mixed-effect model for repeated measures; N, number of subjects in treatment arm; n, number of subjects at Baseline; SD, standard deviation; SE, standard error

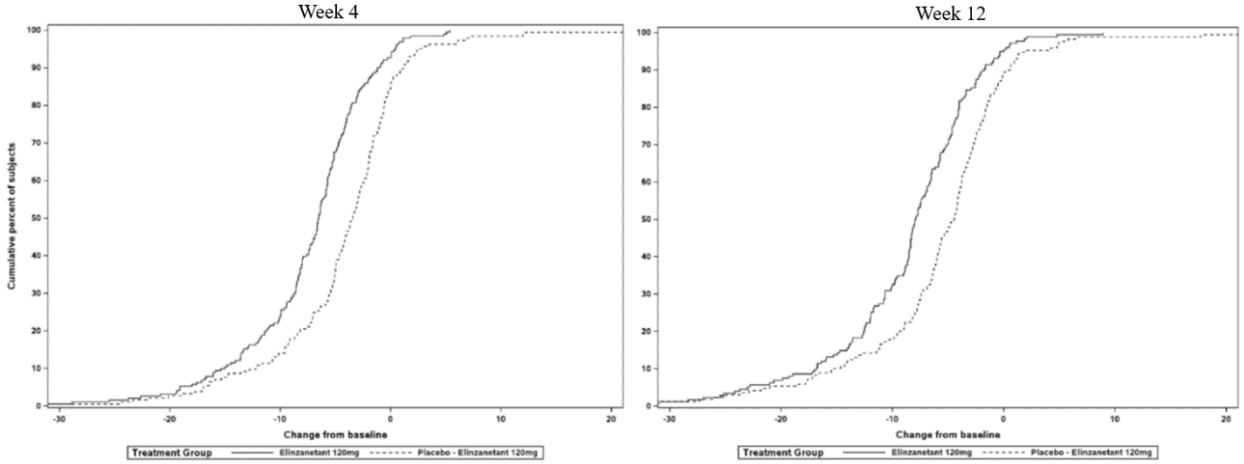
Table 217. Change From Baseline in Mean Daily Severity of Moderate to Severe Hot Flashes, MMRM Analysis Without Missing Data Imputation Based on Weeks 1 to 12, OASIS 1 and OASIS 2 (FAS)

Visit/Statistics	OASIS 1 Elinzanetant 120 mg (N=199)	OASIS 1 Placebo (N=197)	OASIS 2 Elinzanetant 120 mg (N=200)	OASIS 2 Placebo (N=200)
Baseline				
n	199	197	199	200
Mean (SD)	2.56 (0.22)	2.53 (0.23)	2.53 (0.24)	2.54 (0.24)
Change from Baseline to Week 4				
LS-Mean (SE)	-0.73 (0.04)	-0.39 (0.04)	-0.75 (0.04)	-0.53 (0.04)
Difference vs. Placebo (95% CI)	-0.33 (-0.44, -0.22)		-0.22 (-0.34, -0.09)	
p-Value (one-sided)	<.0001		0.0003	
Change from Baseline to Week 12				
LS-Mean (SE)	-0.93 (0.05)	-0.54 (0.05)	-0.94 (0.05)	-0.65 (0.05)
Difference vs. Placebo (95% CI)	-0.38 (-0.52, -0.24)		-0.29 (-0.44, -0.14)	
p-Value (one-sided)	<.0001		<.0001	

Source: Table 1/4 (for OASIS 1, page 18) and Table 1/4 (for OASIS 2, page 26), "response-to-ir" pdf document ((Applicant's IR response dated July 25, 2024), verified by the FDA reviewer.
The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week (1-12), and region (United States versus the rest of the world) as factors, with baseline severity as covariates, as well as an interaction of treatment by week and an interaction of baseline frequency by week.
Abbreviations: FAS, full analysis set; IR, information request; LS Means, least squares means; MMRM, mixed-effect model for repeated measures; N, number of subjects in treatment arm; n, number of subjects at Baseline; SD, standard deviation; SE, standard error

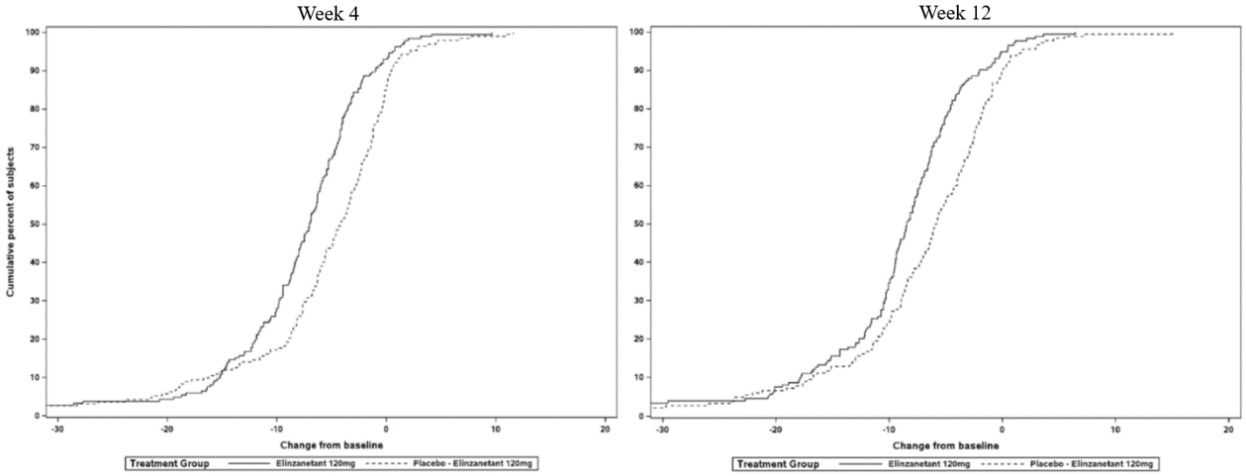
16.3. Cumulative Percent of Subject by Change From Baseline in Frequency and Severity, OASIS 1 and OASIS 2

Figure 88. Cumulative Percent of Subjects by Change From Baseline in Mean Daily Frequency of Moderate to Severe Hot Flashes at Weeks 4 and 12, OASIS 1 (FAS)



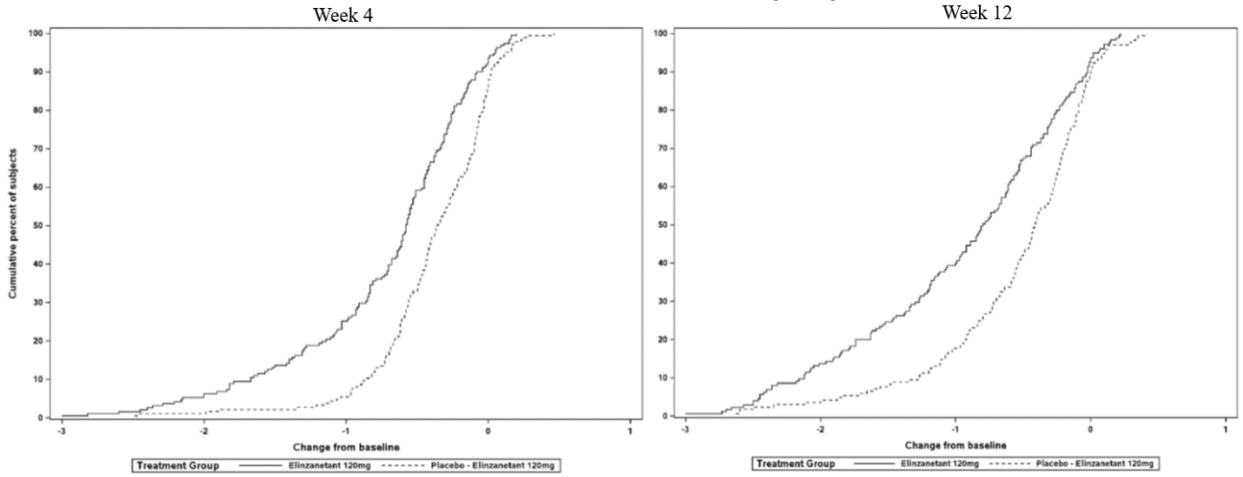
Source: Figure 8.2.3.1/1 and Figure 8.2.3.1/2 of Applicant's Clinical Study Report for OASIS 1; verified by the FDA reviewer
Abbreviations: FAS, full analysis set

Figure 89. Cumulative Percent of Subjects by Change From Baseline in Mean Daily Frequency of Moderate to Severe Hot Flashes at Weeks 4 and 12, OASIS 2 (FAS)



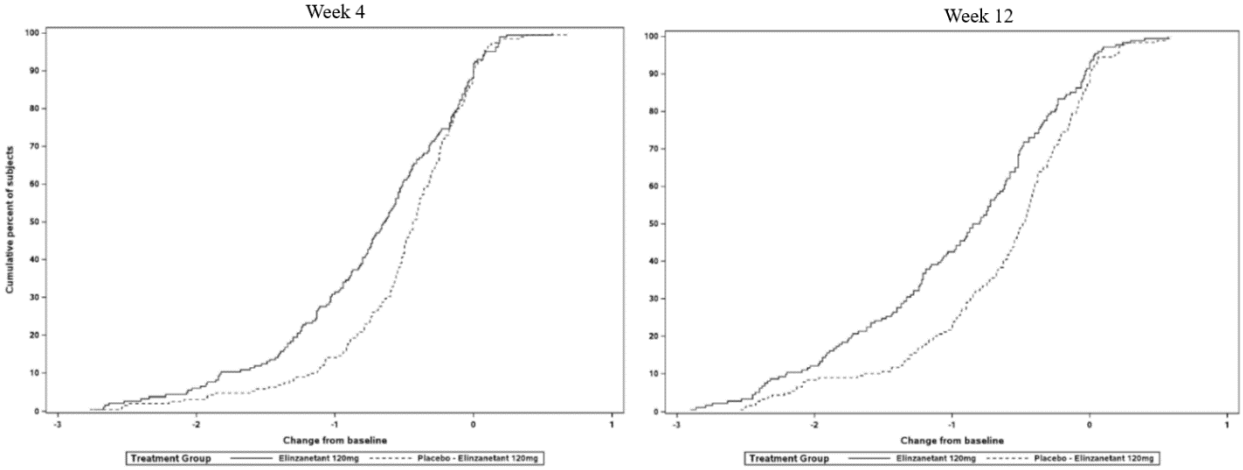
Source: Figure 8.2.3.1/1 and Figure 8.2.3.1/2 in Applicant's Clinical Study Report for OASIS 2; verified by the FDA reviewer
Abbreviations: FAS, full analysis set

Figure 90. Cumulative Percent of Subjects by Change From Baseline in Mean Daily Severity of Moderate to Severe Hot Flashes at Weeks 4 and 12, OASIS 1 (FAS)



Source: Figure 8.2.3.1/10 and Figure 8.2.3.1/11 in Applicant's Clinical Study Report for OASIS 1; verified by the FDA reviewer
Abbreviations: FAS, full analysis set

Figure 91. Cumulative Percent of Subjects by Change From Baseline in Mean Daily Severity of Moderate to Severe Hot Flashes at Weeks 4 and 12, OASIS 2 (FAS)

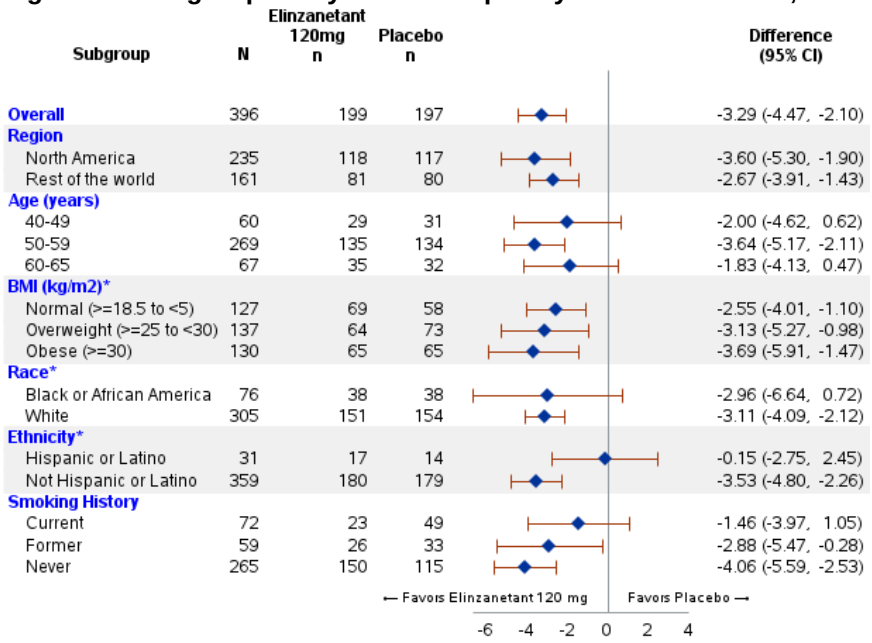


Source: Figure 8.2.3.1/10 and Figure 8.2.3.1/11 of Applicant's Clinical Study Report for OASIS 2; verified by the FDA reviewer
Abbreviations: FAS, full analysis set

16.4. Subgroup Analyses for Coprimary Endpoints, OASIS 1 and OASIS 2

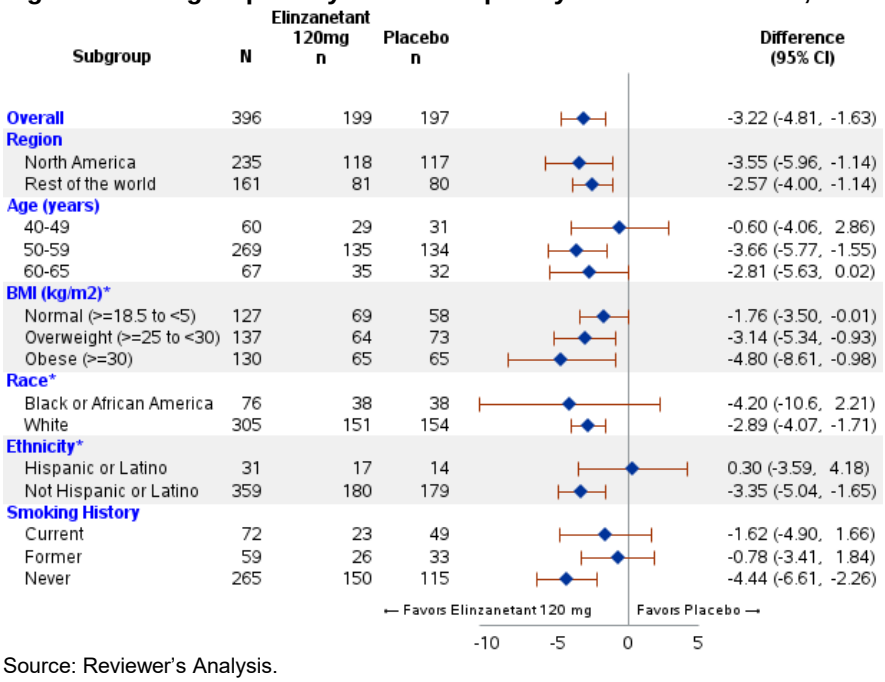
This section presents the results of the subgroup analyses for the coprimary endpoints in Figure 92 through Figure 99 for OASIS 1 and OASIS 2. The results are discussed in Section 6.2.5.3.1.

Figure 92. Subgroup Analyses on Frequency of HFs at Week 4, OASIS 1 (FAS)



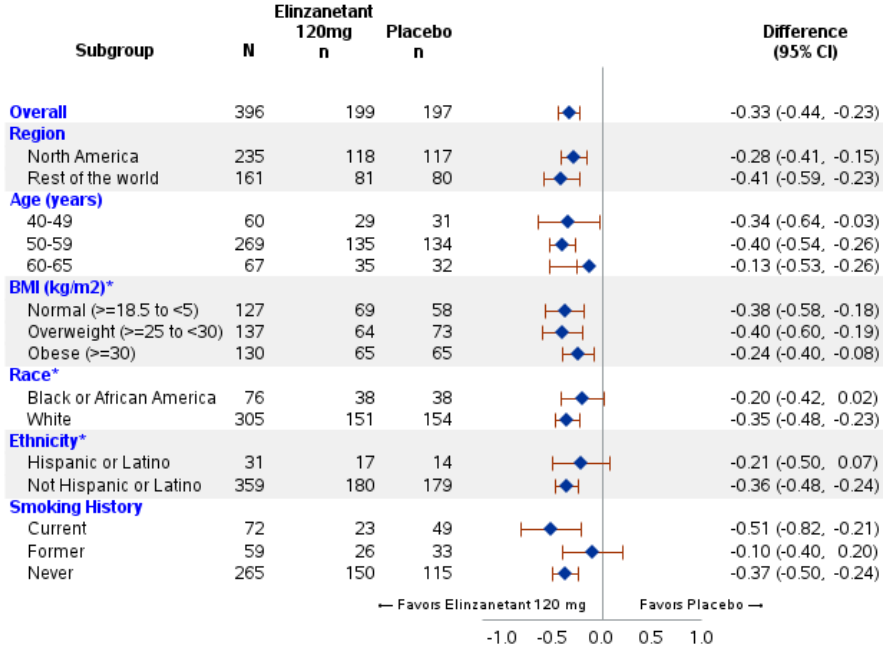
Source: Reviewer's Analysis
*Subgroups for which treatment effects could not be estimated due to small sample sizes in the category included BMI <18.5 (n=2), ethnicity not reported (n=6), Asian (n=3), American Indican or Alaska (n=2), Multiple race (n=3), race not reported (n=7).
Abbreviations: BMI, body mass index; FAS, full analysis set, HFs, hot flashes; N, number of subjects in treatment group; n, number of subjects with given characteristic

Figure 93. Subgroup Analyses on Frequency of HFs at Week 12, OASIS 1 (FAS)



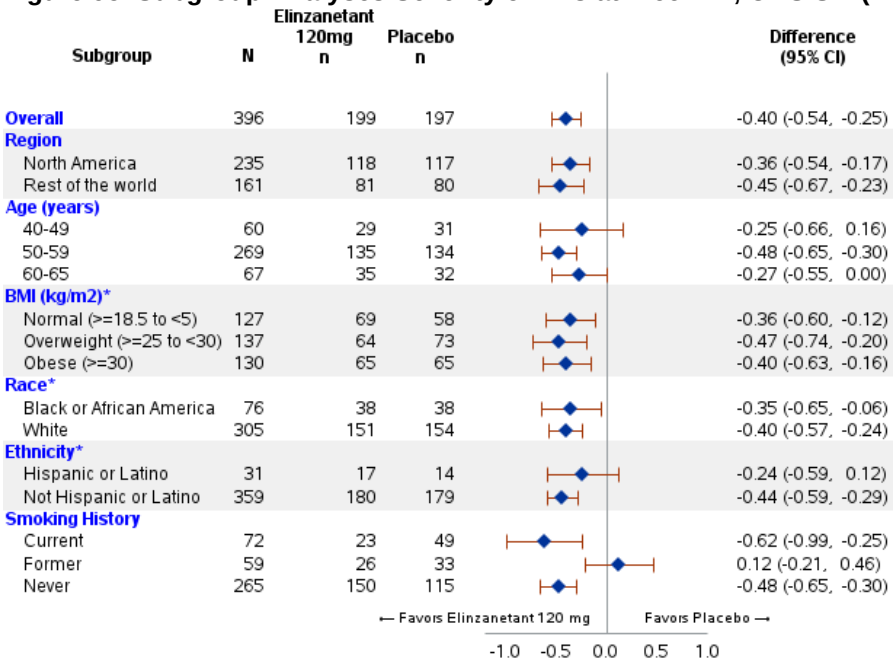
Source: Reviewer's Analysis.
*Subgroups for which treatment effects could not be estimated due to small sample sizes in the category included BMI <18.5 (n=2), ethnicity not reported (n=6), Asian (n=3), American Indican or Alaska (n=2), Multiple race (n=3), race not reported (n=7).
Abbreviations: BMI, body mass index; FAS, full analysis set; HFs, hot flashes; N, number of subjects in treatment group; n, number of subjects with given characteristic

Figure 94. Subgroup Analyses on Severity of HFs at Week 4, OASIS 1 (FAS)



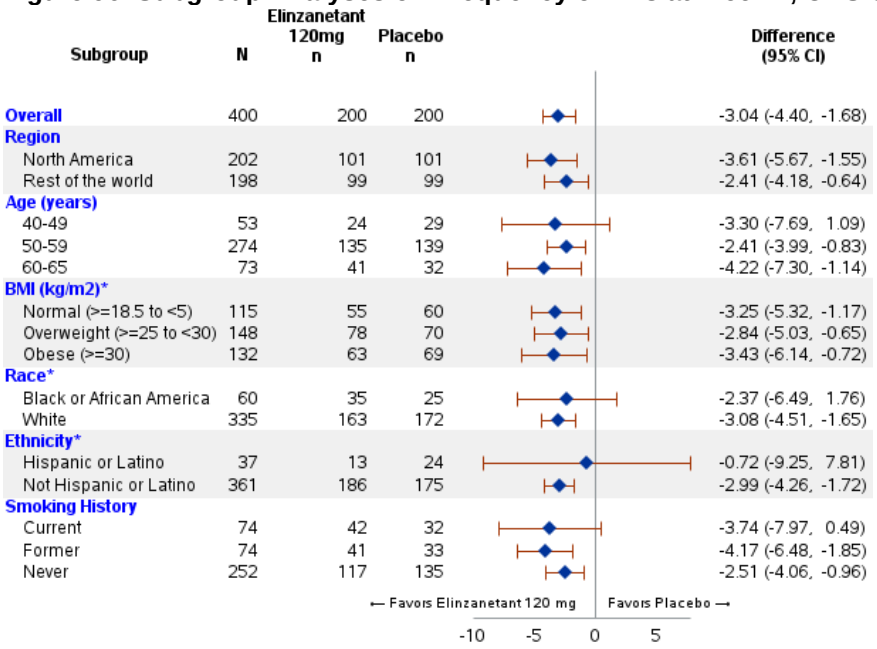
Source: Reviewer's Analysis.
*Subgroups for which treatment effects could not be estimated due to small sample sizes in the category included BMI <18.5 (n=2), ethnicity not reported (n=6), Asian (n=3), American Indican or Alaska (n=2), Multiple race (n=3), race not reported (n=7).
Abbreviations: BMI, body mass index; FAS, full analysis set; HFs, hot flashes; N, number of subjects in treatment group; n, number of subjects with given characteristic

Figure 95. Subgroup Analyses Severity of HFs at Week 12, OASIS 1 (FAS)



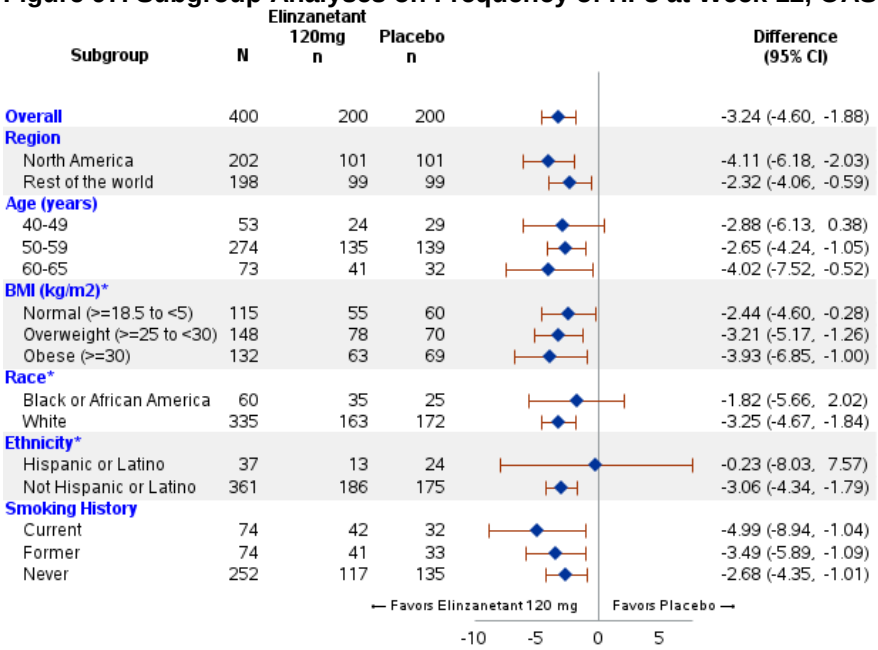
Source: Reviewer's Analysis.
*Subgroups for which treatment effects could not be estimated due to small sample sizes in the category included BMI <18.5 (n=2), ethnicity not reported (n=6), Asian (n=3), American Indican or Alaska (n=2), Multiple race (n=3), race not reported (n=7).
Abbreviations: BMI: body mass index; FAS: full analysis set; HFs, hot flashes; N, number of subjects in treatment group; n, number of subjects with given characteristic

Figure 96. Subgroup Analyses on Frequency of HFs at Week 4, OASIS 2 (FAS)



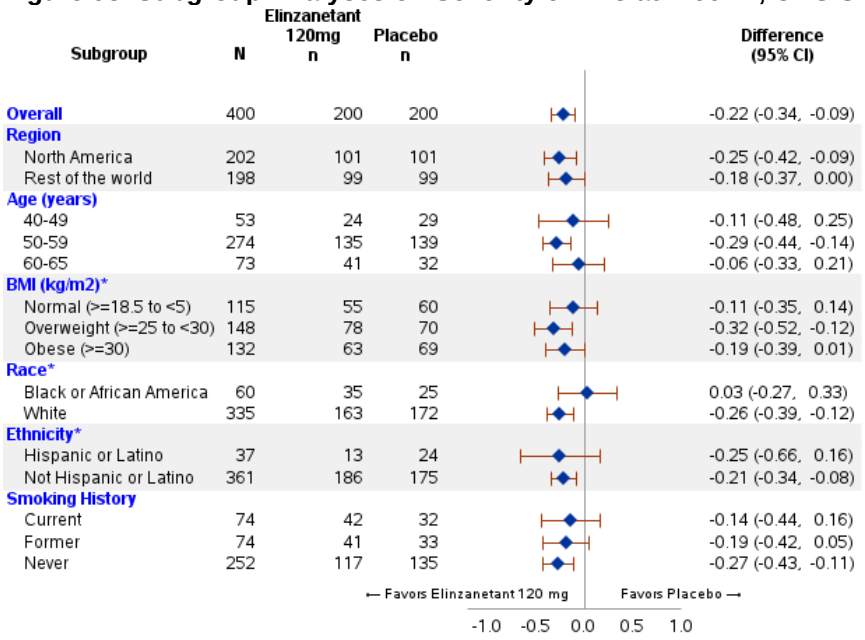
Source: Reviewer's Analysis
*Subgroups for which treatment effects could not be estimated due to small sample sizes in the category included BMI <18.5 (n=5), ethnicity not reported (n=2), Asian (n=1), American Indican or Alaska (n=2), Multiple race (n=1), race not reported (n=1).
Abbreviations: BMI: body mass index; FAS: full analysis set; HFs, hot flashes; N, number of subjects in treatment group; n, number of subjects with given characteristic

Figure 97. Subgroup Analyses on Frequency of HFs at Week 12, OASIS 2 (FAS)



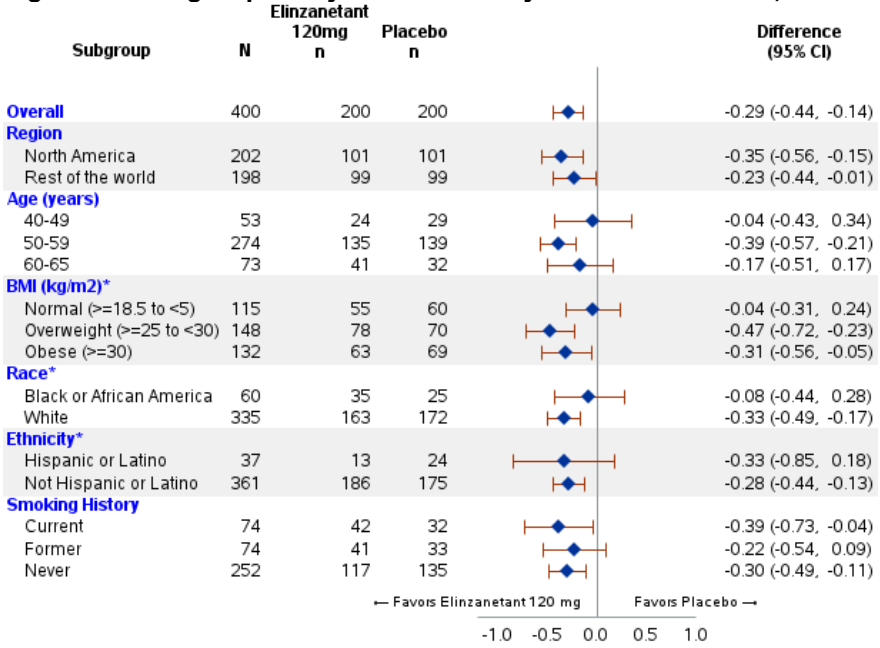
Source: Reviewer's Analysis
*Subgroups for which treatment effects could not be estimated due to small sample sizes in the category included BMI <18.5 (n=5), ethnicity not reported (n=2), Asian (n=1), American Indican or Alaska (n=2), Multiple race (n=1), race not reported (n=1).
Abbreviations: BMI, body mass index; FAS, full analysis set; HFs, hot flashes; N, number of subjects in treatment group; n, number of subjects with given characteristic

Figure 98. Subgroup Analyses on Severity of HFs at Week 4, OASIS 2 (FAS)



Source: Reviewer's Analysis
*Subgroups for which treatment effects could not be estimated due to small sample sizes in the category included BMI <18.5 (n=5), ethnicity not reported (n=2), Asian (n=1), American Indican or Alaska (n=2), Multiple race (n=1), race not reported (n=1).
Abbreviations: BMI, body mass index; FAS, full analysis set; HFs, hot flashes; N, number of subjects in treatment group; n, number of subjects with given characteristic

Figure 99. Subgroup Analyses on Severity of HFs at Week 12, OASIS 2 (FAS)



Source: Reviewer's Analysis
*Subgroups for which treatment effects could not be estimated due to small sample sizes in the category included BMI <18.5 (n=5), ethnicity not reported (n=2), Asian (n=1), American Indican or Alaska (n=2), Multiple race (n=1), race not reported (n=1).
Abbreviations: BMI, body mass index; FAS, full analysis set; HFs, hot flashes; N, number of subjects in treatment group; n, number of subjects with given characteristic

16.5. Hot Flash Daily Diary, OASIS 1, OASIS 2, and OASIS 3

Figure 100. Electronic Hot Flash Daily Diary, Morning and Evening

MORNING HOT FLASH eDIARY

1.

[Instruction 1] Please complete this diary every morning when you get up. **[Instruction 2]** Please answer each question thinking about when you went to bed last night until now. **Note**: A night-time hot flash that wakes you up (or stops you sleeping) is a severe hot flash. If you had more hot flashes once you were awake, record these too.	
Please record the number of times you woke up in the night. Total number of times you woke up last night:	⌊__⌋
Did you have any hot flashes last night (since you went to bed until now)?	Yes or No
Please record the total number of hot flashes of each severity you had during the night (since you went to bed until now). Total number of **MILD** hot flashes during the night (sensation of heat without sweating): Total number of **MODERATE** hot flashes during the night (sensation of heat <u>with</u> sweating, but able to continue activity): Total number of **SEVERE** hot flashes during the night (sensation of heat <u>with</u> sweating, causing cessation (stopping) of activity):	 ⌊__⌋ ⌊__⌋ ⌊__⌋
[Instruction if 'Did you have any hot flashes…?' = Yes, and all numbers of hot flashes = 0] You have reported that you have had hot flashes but have entered 0 for each type of hot flash severity. Tap the Next button to go back and review these entries.	
Did the hot flashes that you had last night (since you went to bed until now) disturb your sleep?	Not at all A little bit Somewhat Quite a bit Very much

2. **EVENING HOT FLASH eDIARY**

[Instruction 1] Please complete this diary every night when you go to bed. **[Instruction 2]** Please answer each question thinking about when you got up this morning until now.	
Evening Hot Flash eDiary	
Did you have any hot flashes today (since you got up this morning until now)?	Yes or No
Please record the total number of hot flashes of each severity you have had today (since you got up this morning until now). Total number of **MILD** hot flashes during the day (sensation of heat without sweating): Total number of **MODERATE** hot flashes during the day (sensation of heat with sweating, but able to continue activity): Total number of **SEVERE** hot flashes during the day (sensation of heat with sweating, causing cessation (stopping) of activity):	⌊_⌋ ⌊_⌋ ⌊_⌋
[Instruction if 'Did you have any hot flashes…?' = Yes, and all numbers of hot flashes = 0] You have reported that you have had hot flashes but have entered 0 for each type of hot flash severity. Tap the Next button to go back and review these entries.	

Source: "app-1-pro-instruments-paper-based-version-and-screenshot.pdf" document, page 1 and "app-1-pro-instruments-paper-based-version-and-screenshot.pdf" document, page 2

17. Clinical Safety

This section includes supportive information regarding safety assessment.

17.1. Additional Safety Analyses

Alcohol Considerations

In Study 21676, psychomotor and cognitive effects of alcohol plus elinzanetant were investigated in healthy subjects. The study was a single-blind, randomized, placebo-controlled, 2-period crossover, single dose study in 20 healthy subjects. Subjects participated in two treatment periods and were administered a single oral dose of elinzanetant 200 mg or matching placebo, while alcohol was administered intravenously.

(b) (4)

In comparison to alcohol plus placebo, administration of alcohol plus elinzanetant was associated with a decrease of peak velocity and increase in reaction times of saccadic eye movements, a reduction in adaptive tracking performance, an increase of the sleepiness (Epworth scale) and a decrease of alertness (Bond Lader scale), and a worsening of recognition score and recognition times in the Visual Verbal Learning Test. Changes in the PD endpoints correlated with the pharmacokinetics of elinzanetant. For sleepiness, on average, considering all time points, there was a 2-point increase, relative to a maximum score of 24 points on this scale. The largest differences were observed in the first 3 hours postdosing.

In terms of safety parameters, no vital sign abnormalities were reported as an adverse event by the investigator. Somnolence and fatigue were the most common AEs reported in the study. Fatigue was more common in placebo-treated subjects (35%) compared to elinzanetant-treated subjects (15%). In contrast, somnolence was more common in elinzanetant-treated subjects (40%) compared to placebo-treated subjects (15%). Given the small sample size and single dose nature of the study, limited conclusions are possible, however there were no new safety considerations identified in this study.

Safety Update

The 120-day safety update was submitted November 24, 2024, and is summarized as follows:

There were no deaths.

In the ongoing Phase 1 study (Study 22382: "A combined single- and multiple-dose, open-label, fixed sequence, 2 x 3 crossover study to investigate the relative bioavailability, safety and tolerability of elinzanetant in healthy female and male participants"), there was no new relevant safety information. The clinical portion of this study has been completed.

In both ongoing clinical studies (NIRVANA, a Phase 2 study in postmenopausal women and OASIS 4, a Phase 3 study in women with or at high risk of developing hormone-receptor positive breast cancer), data remain blinded. In NIRVANA, there were two SAEs: diverticulitis and basal cell carcinoma that were deemed "unrelated to study drug". No SAEs pertaining to AESIs of somnolence/fatigue, phototoxicity, and postmenopausal uterine bleeding were identified during the period covered by this report. In OASIS 4, there were nine SAEs in eight subjects including correction of breast asymmetry, pain in trigeminal nerve distribution, pulmonary embolism, deep vein thrombosis, endometrectomy, ischemic CVA, progression of breast cancer, anterior wall adhesions, and pelvic adhesions. Since both studies remain blinded causality cannot be fully assessed. OASIS 4 is further confounded by high-risk status or concurrent malignancy.

The Applicant provided a report of liver safety, another listed AESI.

The respective liver injury data (referred to as CLO by the Applicant) from the two ongoing studies, NIRVANA (Phase 2) and OASIS 4 (Phase 3) are reviewed below.

- There were two cases of liver injury in the NIRVANA study.
  - Case #1: 58-year-old woman, nonsmoker, obesity, and medical history of elevated liver enzymes (1.6 to 2.6xULN at baseline) and nonalcoholic fatty liver disease. At Week 12, liver markers were 1.2 to 5.7xULN and returned to baseline levels within 16 days after stopping (blinded) treatment. The adverse event ("worsening of elevated liver enzymes") was nonserious and of mild intensity as assessed by investigator. The external liver expert assessed the case in a blinded fashion as a case of "mild acute mixed pattern liver injury (Ratio ALT/ALP =4.5) over chronic steatosis." Causality was assessed as probable.
  - Case #2: 55-year-old woman, nonsmoker, nonalcohol drinker with type II diabetes, with mild elevation in liver markers at baseline. Following 4 weeks of blinded treatment her liver markers increased by 4 to 6xULN. She was asymptomatic. Her fibroscan findings were compatible with mild-moderate fibrosis. The evaluation is still ongoing including liver expert assessment.

For OASIS 4, four of the overall five CLO cases in this study have been assessed by the LSMB. Of these, two were assessed as unlikely and two as possibly related to elinzanetant use (cannot definitively exclude the possibility). For all four cases an alternative etiology was proposed by the LSMB. Assessment of the one case reported during the reporting period is still pending. Of note, all women in OASIS 4 study were receiving adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitor) for underlying disease of breast cancer.

Two of the five CLO cases were already reported in expedited manner to FDA (2023A147501 and 2023A157847) in 2023. Both cases were assessed as possibly related to the study drug use by the LSMB. The LSMB identified for both cases an alternative etiology, namely possible biliary obstruction at level of the ampulla and acetaminophen use, respectively.

During the reporting period of this 120-day safety update report, one subject meeting the criteria for CLO was identified. Subject (SID (b) (6)) is a 64-year-old woman, past smoker, who experienced an increase of ALT to 3.28xULN (115 U/L). The onset was 371 days at which time the subject stopped the treatment. The elevated ALT (ALT >3xULN) was assessed by the investigator as nonserious with moderate intensity. Maximal values of liver enzymes at Day 379, about 8 days after last dose were as follows: ALT =133 U/L or 3.8xULN, AST =59 U/L or 1.69xULN, and GGT 80 U/L or 1.9xULN. No signs or symptoms were reported. Her general medical history includes essential hypertension, meniscus tear left knee, breast cancer right, obesity grade 2, carpal tunnel syndrome, and allergic rhinitis. Her background therapy includes letrozole (2.5 mg Q24h) since (b) (6). The case is still under CLO monitoring. The LSMB assessment is pending.

There were two remaining nonserious CLO cases in OASIS 4 (SID (b) (6)), which were received and assessed prior to the reporting period of this 120-day safety update report. One case pertained to a 51-year-old woman, nonsmoker, with hepatic steatosis with history of alcohol abuse, and type 2 diabetes mellitus, and a medical history that included atrial fibrillation, gout, hypertension, and obesity. The subject started CLO and had maximal increase of liver parameters of: BILI Dir. =1.09xULN (5.6 µmol/L), ALT =4.2xULN (147 U/L), AST =4.46xULN (156 U/L), AP =1.03xULN (107 U/L), and GGT =9.29xULN (390 U/L). The

LSMB assessed the causal association with the study drug as unlikely and proposed an alternative etiology: nonalcoholic steatohepatitis.

The other CLO case involved a 48-year-old woman, nonsmoker, with a history of hypertension and alcohol abuse. Her maximal increase of liver parameters was ALT =5.4xULN (189 U/L), AST =3.54xULN (124 U/L), AP =1.03xULN (107 U/L), and GGT =14.71xULN (618 U/L). The subject recovered. The LSMB assessed the causal association with the study drug as unlikely and proposed an alternative etiology: nonalcoholic steatohepatitis and alcohol abuse.

Altogether, and so far, no safety concerns arose during data review by the independent data safety monitoring board (DSMB) members, last DSMB meeting took place on June 21, 2024, next was planned for December 2024 (after the date of the 120-day safety update submission).

The liver cases were confounded by underlying liver disease. The majority of the SAEs were confounded by an underlying medical diagnosis. As the data remains blinded, we agree with the DSMB, that no conclusions on causality for elinzanetant can be drawn at this stage based on the available information. No new signals were identified.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable

21. Other Drug Development Considerations

Not applicable

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

In support of this NDA, the Applicant submitted clinical data from three Phase 3 studies: OASIS 1, OASIS 2, and OASIS 3. OASIS 1 and OASIS 2 were pivotal efficacy studies and OASIS 3 was primarily a long-term safety study but also provided additional supportive efficacy data. The Applicant attested that all three clinical studies were conducted in accordance with the Code of Federal Regulations governing the protection of human subjects (21 CFR part 50), institutional review boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with GCP.

An Office of Scientific Investigation consult evaluated six study sites from the Phase 3 program. The sites chosen are shown in Table 218. Additionally, the Applicant was also inspected. Based on discussion with the Office of Scientific Investigations (OSI), the studies appear to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the Applicant appear acceptable to support this NDA. At the site of Dr. Babajide, the inspection identified six unreported AEs (alopecia, COVID-19 infection, leg cramp, shingles, face injury, and common cold). Alopecia and leg cramp were determined by Dr. Babajide as related to the investigative product. (b) (4) (b) (4) OSI recommends the review division include this case of alopecia in the safety analysis and the team reviewed the case of alopecia. The final Clinical Inspection Summary was finalized on April 22, 2025, and details are in Table 218.

Bayer Healthcare Pharmaceuticals Inc. (Bayer) was inspected to evaluate their conduct and oversight of OASIS 1, OASIS 2, and OASIS 3 as the Applicant of these clinical studies. The inspection found no compliance deficiencies in Bayer's conduct and oversight of the OASIS studies. The numbers of subjects randomized in the study and participating investigator sites were consistent with those reported in the NDA. Data management, including data capture and analyses, was found to be adequate, with no issues noted.

In summary, the inspections of the clinical sites and the Applicant did not reveal significant concerns regarding the conduct and the oversight of the clinical studies or GCP or regulatory compliance. Based on the results of these inspections, OSI concluded that the data generated by the inspected investigators and submitted by the Applicant are acceptable in support of the proposed indication.

Table 218. Summary of the Findings of Clinical Inspections by Clinical Site

Investigator/ Clinical Site	Clinical Trial(s)	Number of Subjects Enrolled/Randomized/Completed	Key Findings
Dr. Ramin Farsad (Site 14037) United States	OASIS 1	20/19/19	No significant concerns
Dr. Ondrej Mika (Site 38010) Czech Republic	OASIS 1 and 2	OASIS 1 and 2 combined: 20/20/18	Two subjects enrolled who did not meet blood pressure eligibility criteria. Safety of subjects were not negatively impacted by these protocol deviations.
Dr. Allen Dinnerstein (Site number 14001: OASIS 2 and 14002: OASIS 3) United States	OASIS 2 and 3	OASIS 2: 18/18/15 OASIS 3: 18/18/15	No significant concerns
Dr. Janusz Tomaszewski (Site number 18001) Poland	OASIS 2 and 3	OASIS 2: 54/54/44 OASIS 3: 46/46/35	No significant concerns
Dr. Dagmara Makowska-Mainka (Site number 18005) Poland	OASIS 2 and 3	OASIS 2: 16/16/13 OASIS 3: 17/17/12	For OASIS 2, the site failed to maintain ultrasound images for five subjects. However, a sub-investigator recorded the measurements taken during ultrasound, which were deemed adequate to capture the data from the source images. The results acquired at this site were considered reliable to support the application.
Dr. Abimbola Babajide (Site number 12007) United Kingdom	OASIS 3	27/27/21	The inspection identified six unreported AEs (alopecia, COVID-19 infection, leg cramp, shingles, face injury and common cold). Alopecia and leg cramp were determined by Dr. Babajide as related to the investigative product.

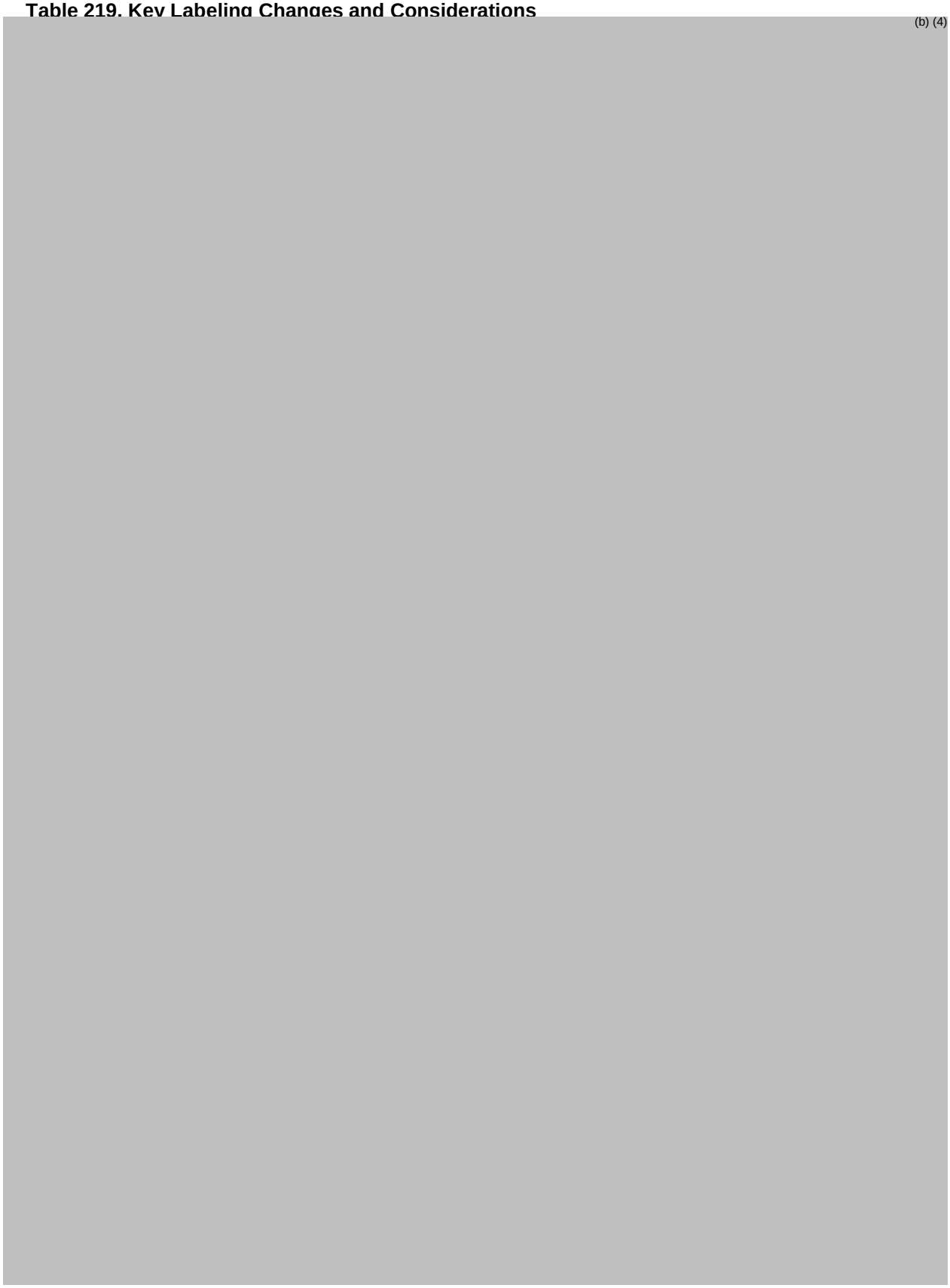
Source: Reviewer compilation
Abbreviations: AEs, adverse events; COVID-19, coronavirus disease of 2019

23. Labeling: Key Changes

This PI review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the (Table 219). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 219. Key Labeling Changes and Considerations

(b) (4)



1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing information
- Patient package insert
- Carton/container

24. Postmarketing Requirements and Commitments

None.

25. Financial Disclosure

Table 220 summarizes the financial disclosures submitted to the NDA that include OASIS 1, OASIS 2, OASIS 3, and SWITCH-1. One investigator in SWITCH-1 (b) (6) received significant payments from NeRRe Therapeutics Ltd. for consulting arrangements unrelated to SWITCH-1. NeRRe was acquired by Bayer, the current Applicant. In FDA Form 3455, Bayer stated that the "small number of subjects randomized ((b) (6) patients) by (b) (6) site represents a small percentage of the overall total of 199 patients randomized" in SWITCH-1. Bayer concluded that there was very minimal risk of bias on the trial's overall study results. The review team agrees with this conclusion.

Table 220. Financial Disclosures for Trials: OASIS 1 (Study 21651), OASIS 2 (Study 21652), OASIS 3 (Study 21810), and SWITCH-1 (Study 21686)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1,243 (OASIS 1: 430; OASIS 2: 408; OASIS 3: 380; and SWITCH-1: 25)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

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27. Review Team

Table 221. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Samantha Bell, Margaret Kober
Nonclinical reviewers	Pratistha Tamrakar, Sarah Lee, Edna Albuquerque
Nonclinical team leader	Andrea Benedict
OCP reviewer(s)	Mohammad (Ahsan) Akbar, Lin Zhou
OCP team leader(s)	Yanhui Lu, Manuela Grimstein
Clinical reviewer	Sergio Oehninger
Clinical team leader	Christina Chang
Biometrics reviewer	Yun Tang
Biometrics team leader	Solomon Chef
Cross-discipline team leader	Christina Chang
Division director (pharm/tox)	Kimberly Hatfield
Division director (OCP)	Shirley Seo
Division director (OB)	Daphne Lin
Division director (clinical)	Christina Chang
Office director (or designated signatory authority)	Janet Maynard

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 222. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Hamid Shafiei, James Laurenson, Xiaoqin Wu, Vaikunth Prabhu, Mesfin Abdi, Tapash Ghosh, Kalpana Paudel, Hitesh Shroff, Friedrich Burnett, Lawrence Perez, Julia Pinto
OPDP	Montherson Saint Juste, James Dvorsky
OSI	Regina Zopf, Michele Fedowitz
OSE/DEPI	Huei-Ting Tsai, Adebola Ajao
OSE/DMEPA	Rina Patel, Stephanie DeGraw
OSE/DRISK	Christopher Booze, Yasmeen Abou-Sayed
OSE/DPV	Lynda McCulley, Kate McCartan

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; DPV, Division of Pharmacovigilance; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-223 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Hamid Shafiei OPQAII DPQAVII	Sections: 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hamid Shafiei			**Digitally signed by Hamid Shafiei** **Date: 10/23/2025 9:01 AM EDT** **GUID: 202510231316**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Hamid Shafiei OPQAII DPQAVII	Sections: 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hamid Shafiei			**Digitally signed by Hamid Shafiei** **Date: 10/23/2025 9:01 AM EDT** **GUID: 2025102313145**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Shirley Seo OCP DCEP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shirley Seo			**Digitally signed by Shirley Seo** **Date: 10/23/2025 9:04 AM EDT** **GUID: 2025102313422**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Huali Wu OCP DPM	Sections: 14.5.1, 14.5.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Huali Wu			**Digitally signed by Huali Wu** **Date: 10/23/2025 9:10 AM EDT** **GUID: 20251023131046**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Sergio Oehninger ORDPURM DUOG	Sections: Modules 1 and 3, and some sections of modules 5 and 12.	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	none

Signature: Sergio Oehninger

Digitally signed by Sergio Oehninger

Date: 10/23/2025 9:19 AM EDT
GUID: 2025102313196

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Mohammad Akbar OCP DCEP	Sections: Mohammad Akbar	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Mohammad Akbar

Digitally signed by Mohammad Akbar

Date: 10/23/2025 9:22 AM EDT
GUID: 20251023132224

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Huali Wu OCP DPM	Sections: 14.5.1, 14.5.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Huali Wu			**Digitally signed by Huali Wu** **Sign on behalf of Signed as proxy by Huali Wu, on behalf of Jingyu Yu** **Date: 10/23/2025 9:27 AM EDT** **GUID: 20251023132743**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Yun Tang OB DBIV	Sections: 6, 16, and 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yun Tang			**Digitally signed by Yun Tang** **Date: 10/23/2025 9:45 AM EDT** **GUID: 20251023134559**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Tsae Yun Lin OB DBIV	Sections: Worked on sections 6, 16, and 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Tsae Yun Lin			**Digitally signed by Tsae Yun Lin** **Date: 10/23/2025 9:50 AM EDT** **GUID: 20251023135035**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Yanhui Lu OCP DCEP	Sections: 5, 8,14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yanhui Lu			**Digitally signed by Yanhui Lu** **Date: 10/23/2025 10:19 AM EDT** **GUID: 2025102314199**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Reviewer	Lin Zhou OCP DCEP	Sections: Section 14.1 in vitro studies and Section 14.2.4 Clinical DDI studies	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lin Zhou			**Digitally signed by Lin Zhou** **Date: 10/23/2025 10:26 AM EDT** **GUID: 20251023142647**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Andrea Benedict ORDPURM DPTRDPURM	Sections: 5, 7, 8, 13, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Andrea Benedict			**Digitally signed by Andrea Benedict** **Date: 10/23/2025 11:13 AM EDT** **GUID: 20251023151333**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Kimberly Hatfield ORDPURM DPTRDPURM	Sections: 5, 7, 8, 13, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kimberly Hatfield			**Digitally signed by Kimberly Hatfield** **Date: 10/23/2025 11:19 AM EDT** **GUID: 20251023151953**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Secondary Reviewer	Manuela Grimstein OCP DPM	Sections: 14.5.3	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Manuela Grimstein			**Digitally signed by Manuela Grimstein** **Date: 10/23/2025 11:54 AM EDT** **GUID: 20251023155452**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Primary Reviewer	Yuching Yang OCP DPM	Sections: 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yuching Yang			**Digitally signed by Yuching Yang** **Date: 10/23/2025 2:54 PM EDT** **GUID: 20251023185430**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Christina Chang ORDPURM DUOG	Sections: 1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 15, 16, 17, 22, 23, 24, 25, 26, 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Christina Chang			**Digitally signed by Christina Chang** **Date: 10/23/2025 3:39 PM EDT** **GUID: 20251023193936**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Reviewer Discipline Secondary Reviewer	Christina Chang ORDPURM DUOG	Sections: 1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 15, 16, 17, 22, 23, 24, 25, 26, 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Christina Chang			**Digitally signed by Christina Chang** **Date: 10/23/2025 3:40 PM EDT** **GUID: 20251023194027**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Christina Chang ORDPURM DUOG	Sections: 1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 15, 16, 17, 22, 23, 24, 25, 26, 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Christina Chang			**Digitally signed by Christina Chang** **Date: 10/23/2025 3:45 PM EDT** **GUID: 20251023194556**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Reviewer Discipline Tertiary Reviewer	Christina Chang ORDPURM DUOG	Sections: 1, 2, 3, 4, 6, 7, 9, 10, 11, 12, 15, 16, 17, 22, 23, 24, 25, 26, 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Christina Chang			**Digitally signed by Christina Chang** **Date: 10/23/2025 3:46 PM EDT** **GUID: 20251023194637**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Andrea Benedict ORDPURM DPTRDPURM	Sections: 5, 7, 8, 13, 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Andrea Benedict signing as Pratistha Tamrakar.
Signature: Andrea Benedict			**Digitally signed by Andrea Benedict** **Date: 10/23/2025 3:51 PM EDT** **GUID: 20251023195142**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Reviewer Discipline Primary Reviewer	Christina Chang ORDPURM DUOG	Sections: 7	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Christina Chang			**Digitally signed by Christina Chang** **Sign on behalf of Signing on behalf of Marcea Whitaker** **Date: 10/23/2025 4:12 PM EDT** **GUID: 20251023201228**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Tsae Yun Lin OB DBIV	Sections: Worked on sections 6, 16, and 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Tsae Yun Lin			**Digitally signed by Tsae Yun Lin** **Sign on behalf of Dr. Chefo is on leave so TsaeYun Daphne Lin signs f** **Date: 10/23/2025 4:30 PM EDT** **GUID: 2025102320300**	

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTINA Y CHANG
10/23/2025 04:33:51 PM

JANET W MAYNARD
10/23/2025 04:39:50 PM

PHARMACOLOGY/TOXICOLOGY LABELING REVIEW

NDA #:	219469
Supporting Document(s):	SDN 1 (eCTD 0001), SDN 28 (eCTD 0028), SDN 30 (eCTD 0030) SDN 35 (eCTD 0035)
Submit Date:	SDN 1: 07/26/2024, SDN 28: 05/25/2025, SDN 30: 07/08/2025, SDN 35: 09/25/2025
Received Date:	07/26/2024
PDUFA Goal Date:	10/26/2025
Established/Proper Name	Elinzanetant
Trade Name	LYNKUET
Pharmacologic Class	Neurokinin (NK)1 and NK3 receptors antagonist
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Dosage form	60 mg soft gelatin capsule
Applicant Proposed Indication (s)	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

Introduction

LYNKUET or Elinzanetant [synonyms BAY 3427080, NT-814, GSK1144814] is a neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

The Applicant has submitted this NDA under the 505(b)(1) pathway as a New Molecular Entity (NME), and as such a full battery of nonclinical pharmacology, pharmacokinetic, and toxicology studies had been completed to support the nonclinical safety of this drug component has been submitted.

Labeling Review

The table below presents 1) the Applicant's proposed labeling in PLLR format (SDN 1, eCTD 0001; SDN 28, eCTD 0028; SDN 30, eCTD 0030; SDN 35, eCTD 0035), and 2) the Division's proposed labeling for the nonclinical-relevant sections of the Prescribing Information, including the Indications and Usage section in Highlights of Prescribing Information and Sections 8 [8.1, 8.2, 8.3], 11, 12 [12.1] and 13 [13.1 and 13.2].

The Applicant's originally proposed text (left column) and the final agreed upon text (right column) are noted below. The rationale for modifications of the Applicant's proposed labeling, labeling discussions, and other notable text proposals from Applicant and the Division are documented in the reviewer's comments after each section in the table.

All the nonclinical and nonclinically relevant sections were agreed upon by the Applicant in the SDN 35 (eCTD 0035) draft labeling submitted on 09/25/2025.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 5679044

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PRATISTHA TAMRAKAR
10/17/2025 01:40:28 PM

ANDREA BENEDICT
10/17/2025 01:47:40 PM
I concur with the review and recommendations of Dr. Tamrakar.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 219469
Supporting document/s:	SDN 1 (eCTD 0001)
Applicant's letter date:	07/26/2024
CDER stamp date:	07/26/2024
Product:	Elinzanetant capsule
Indication:	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
Applicant:	Bayer Healthcare Pharmaceuticals, Inc
Clinical Review Division:	Division of Urology, Obstetrics, and Gynecology
Reviewers:	Edna Albuquerque, PhD Pratistha Tamrakar, PhD Sarah Lee, PhD
Supervisor/Team Leader:	Andrea Benedict, PhD
Tertiary Reviewer:	Kimberly P. Hatfield, PhD
Division Director:	Christina Chang, MD
Project Manager:	Samantha Bell

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 219469 are owned by Bayer Healthcare Pharmaceuticals, Inc, or are data for which Bayer Healthcare Pharmaceuticals, Inc. has obtained a written right of reference.
Any information or data necessary for approval of NDA 219469 that Bayer Healthcare Pharmaceuticals, Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 219469.

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Reference ID: 5623053

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1 Executive Summary

1.1 Introduction

NDA 219469 is a 505(b)(1) application submitted by Bayer Healthcare Pharmaceuticals, Inc. for elinzanetant (BAY 3427080); as 60-mg soft gelatin capsule for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Elinzanetant is a new molecular entity that acts as a noncompetitive antagonist of both the human neurokinin (NK)1 and NK3 receptors (NK1R and NK3R, respectively). Elinzanetant has ~10-fold higher affinity to human NK1R compared to human NK3R, with mean pKi values of 9.43 and 8.42 for NK1R and NK3R, respectively. Elinzanetant has three principal metabolites M27, M30/34, and M18/21, which also act as noncompetitive antagonists at NK1R and NK3R.

NK1R and NK3R antagonists are thought to act by inhibiting the activity of KNDy (i.e., kisspeptin/neurokinin B [NKB]/dynorphin) neurons, which project to the vasomotor center in the median pre-optic nucleus to modulate neuronal activity involved in thermoregulation. This inhibition of KNDy neurons, which are thought to be in a hyperactivated state because of estrogen decline in menopause, is proposed to result in improvement of menopause-associated VMS [also called hot flushes (HFs)].

Fezolinetant [VEOZAH, approved in 2023], was the first-in-class NK3R antagonist indicated for the treatment of VMS in postmenopausal women. Antagonists of the NK1R (Aprepitant [EMED, approved in 2003], Rolapitant [VARUBI, approved in 2015], and Fosaprepitant [FOCINVEZ®; approved in 2008]) have also been approved for the indication of nausea and vomiting associated with emetogenic cancer chemotherapy.

The clinical program for elinzanetant includes 29 completed studies: There are 24 Phase 1 studies, 2 Phase 2 studies, and 3 Phase 3 studies. Safety and efficacy of elinzanetant were evaluated in 3 phase 3 studies: OASIS 1, OASIS 2, and OASIS 3.

The nonclinical program for elinzanetant includes studies of pharmacodynamics (PD), pharmacokinetics (PK), repeat dose toxicity (up to 26 weeks in rats and 39 weeks in monkeys), reproductive and developmental toxicity (in rats and rabbits), genotoxicity and carcinogenicity (in transgenic mice and rats), and phototoxicity. Since elinzanetant was established to have disproportionate human metabolite (M27) early in nonclinical development, additional nonclinical studies were also conducted with this metabolite. The main metabolites M18/21 and M30/34 were also further assessed in nonclinical studies (for example, genotoxicity studies).

In January 2024, the Applicant met with the Agency for a pre-NDA meeting under IND 129492, and it was established that the nonclinical package and nonclinical data supporting the mechanism of action of elinzanetant appeared to be adequate to support an NDA submission (see more details in Meeting Minutes in DARRTS dated 02/06/2024).

The Applicant submitted the NDA in July 2024, along with additional nonclinical studies including the rat pre-/post-natal development (PPND) study, carcinogenicity studies in rat and transgenic mice, and abuse potential studies.

1.2 Brief Discussion of Nonclinical Findings

Pharmacology

Elinzanetant is a new molecular entity that acts as a noncompetitive antagonist of both the human neurokinin (NK)1 and NK3 receptors (NK1R and NK3R, respectively). In binding assays, elinzanetant displayed high affinity for human NK1R [pKi values of 8.71 – 10.15 (mean pKi of 9.43)] and NK3R [pKi values of 8.03 – 8.8 (mean pKi of 8.42)]. Elinzanetant has ~10-fold lower affinity towards human NK3R compared to human NK1R. Additionally, elinzanetant has higher affinity for human NK1R and NK3R receptors than for human NK2 receptors (pKi values of approximately 6.0). In functional in-vitro assays, elinzanetant inhibited the activity of human NK1R and NK3R, with calculated pKB values of 9.02 - 9.1 for human NK1R and 8.17 - 8.5 for human NK3R. Ex-vivo receptor occupancy studies in human putamen showed that elinzanetant occupied NK1Rs in the human putamen in a concentration-dependent manner with a pKi of 9.44.

Each of the principal metabolites of interest – M27, M30/34 and M18/21, which accounted for 6%, 11% and 5.5%, respectively, of total radioactivity in the human biotransformation clinical study # CPMX 50130/B002427 – showed high affinity and noncompetitive antagonistic activity at the human NK1R and NK3R. The affinities and potencies of the metabolites at human NK1R and NK3R are similar to those of elinzanetant.

In-vivo pharmacodynamic activity of elinzanetant was investigated in a gerbil foot tapping model of NK1 activity and in the guinea pig wet-dog shake model of NK3 activity. After oral dosing with elinzanetant, foot tapping induced by the NK1R agonist GR73632 in male gerbils was blocked [ID_{50} (dose resulting a 50% reduction in time spent foot tapping) = 1.36 mg/kg]. Similarly, elinzanetant doses of 8.5 and 25.5 mg/kg significantly inhibited wet-dog shake behavior induced by the NK3R agonist senktide in the guinea pigs, indicating central NK3R antagonist activity. While the Applicant did not conduct studies in animal models to demonstrate the effects of elinzanetant in reducing HF-like symptoms, overall, the pharmacology data support the Applicant's therapeutic rationale for the use of elinzanetant to modulate neuronal activity in the vasomotor center.

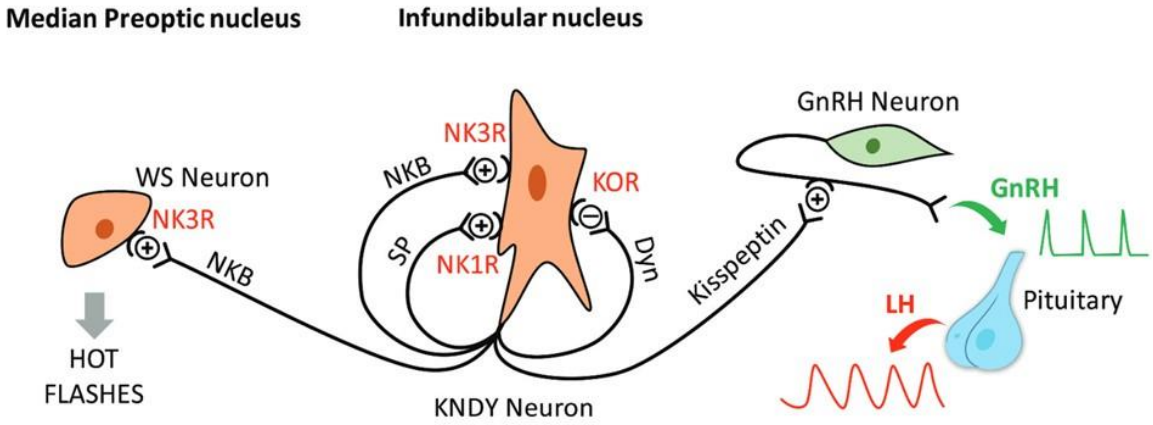
Selectivity screens (b) (4) were performed to evaluate the potential for off-target binding for elinzanetant and the 3 principal human metabolites of elinzanetant (M27, M30/34, and M18/21). Elinzanetant was >100-fold more selective for the human NK3R and >300-fold more selective for the human NK1R versus 88 other non-tachykinin human receptors, enzymes, and transporters.

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The pharmacologic class term for elinzanetant is neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist.

Mechanism of Action

NK1R and NK3R antagonists are thought to act by inhibiting the activity of KNDy (i.e., kisspeptin/neurokinin B [NKB]/dynorphin) neurons, which project to the vasomotor center in the median pre-optic nucleus to modulate neuronal activity involved in thermoregulation. This inhibition of KNDy neurons, which are thought to be in a hyperactivated state because of estrogen decline in menopause, is proposed to result in improvement of menopause-associated VMS (also called HFs).



Abbreviations: Dyn, dynorphin; GnRH, gonadotropin releasing hormone; KNDY, kisspeptin, neurokinin B, and dynorphin; KOR, kappa opioid receptor; LH, luteinizing hormone; NKB, neurokinin B; NK3R, NKB receptor; SP, substance P; WS, wide spiking

Figure 1: NK1/NK3R and schematic of the links between KNDy neurons, the regulation of GnRH secretion, and the vasomotor area in the hypothalamus.[1]

Pharmacokinetic

PK studies in rats, monkeys, and dogs demonstrated that elinzanetant is absorbed following oral administration, with its oral bioavailability being moderate in male and female rats (77% and 47%, respectively) and low in monkeys and dogs (19%).

Autoradiographic studies revealed that, following the oral administration of radiolabeled elinzanetant to different species, radioactivity distributed to major organs, including the liver and pigmented tissues (e.g., the uveal tract and the retina). In typical PK studies, elinzanetant was found to cross the blood brain barrier. In pregnant rats, the organ distribution of elinzanetant was similar to that in non-pregnant rats. In addition, elinzanetant crossed the placenta, and elinzanetant and its metabolites were detected in different fetal organs, including the brain. Collectively, these findings suggest that the

[1] Sassarini, J., & Anderson, R. A. (2024). Elinzanetant: a phase III therapy for postmenopausal patients with vasomotor symptoms. Expert Opinion on Investigational Drugs, 33(1), 19–26.

brain, the liver, pigmented tissues, and the developing fetus can be important targets for elinzanetant-related effects. Following administration of radiolabeled elinzanetant to lactating rats, approximately 6% of the elinzanetant dose was excreted in milk within 48 hours (h) post administration.

Plasma protein binding was high across all preclinical species tested (99.5 to 99.9%) and higher in humans (>99.9%) for elinzanetant and its principal metabolites (M27, M30/34 and M18/21). As such, whenever appropriate for the nonclinical safety assessments, the extent of protein binding is included in the calculations of safety and exposure margins. The nonclinical safety assessment further considers the finding that in animals, as in humans, elinzanetant is metabolized primarily by oxidation at the methyl-phenyl moiety and the morpholine ring mainly to metabolites M27, M30/34 (a major human metabolite), and M18/21.

Pivotal Chronic Repeat-dose Toxicity

- In the 26-week rat study (Study No R-13894), elinzanetant was administered orally, twice a day (BID) 6 h apart, by gavage to sexually mature rats at a dose of 0, 25, 60, or 90 mg/kg BID for a total daily dose of 0, 50, 120, or 180 mg/kg/day in males and 0, 10, 25, or 40 mg/kg BID for a total daily dose of 0, 20, 50, or 80 mg/kg/day in females. Clinical pathology changes suggesting mild impairment of hepatic function were reported in high-dose males without correlating microscopic findings of liver damage. Dose-related incidence of macrophage infiltrations in the alveoli was noted in both sexes, without increase in severity. Minimal infiltrates were noted starting in males and females at 50 and 20 mg/kg/day, respectively. Tubular basophilia, hyaline casts and cortical scars were observed in males and correlated with increased kidney weights. Systemic exposure (C_{max} and AUC) in females was >2-fold that in males at the 50 mg/kg/day level (only comparable dose level) at both Day 1 and Week 26. At Week 26, females had evidence of drug accumulation at all doses with repeat administration (e.g., 2 to 3-fold accumulation for C_{max} and AUC from Day 1 to Week 26).

  The no-observed-adverse-effect-level (NOAEL) was the high-dose of 80 mg/kg/day (females) and mid-dose of 120 mg/kg/day (males), with male $AUC_{(0-24)}$ = 76100 µg.h/L (8.8 X the maximal recommended human dose [MRHD] of 120 mg/day) and female $AUC_{(0-24)}$ = 311000 µg.h/L (36 X MRHD of 120 mg/day). Safety margins are based on the human $AUC_{(0-24)}$ of 8572 µg.h/L obtained from the MRHD in the clinical study B002427.

- In the 39-week monkey study (Study No R-13895), elinzanetant was administered orally, BID, 6 h apart, by gavage to sexually mature male and female monkeys at a dose of 0, 15, 30, or 40 mg/kg BID leading to a total daily dose of 0, 30, 60, or 80 mg/kg/day for 39 weeks. At the high-dose, adverse drug-related weight loss and gastrointestinal clinical signs were observed in females and were generally accompanied by inflammatory cell infiltrate and in one female

mild hyperplasia of the mucosa of the cecum and colon. Gastrointestinal signs of disturbances (loose and/or liquid feces) were also seen in males starting at 30 mg/kg/day. A lack of estrus cycle activity was observed in females at 60 and 80 mg/kg/day and was consistent with the expected pharmacological effects. Increased liver weight and sinusoidal compression, presenting as narrowing of the sinusoidal space was observed in males at 80 mg/kg/day and females at 60 mg/kg/day.

The NOAEL for females was the low-dose of 30 mg/kg/day, with $AUC_{(0-24)}$ = 3000 µg.h/L (<1 X MRHD) and the NOAEL for males was the high-dose of 80 mg/kg/day, with $AUC_{(0-24)}$ = 8370 µg.h/L (1 X MRHD). Safety margins are based on the human $AUC_{(0-24)}$ of 8572 µg.h/L obtained from the MRHD in the clinical study B002427.

- A 26-week rat study for the M27 metabolite (Study R-13953) was conducted to qualify the safety of this metabolite in rat [systemic exposure of M27 and M18/21 were very low in rats after administration of elinzanetant, and M27 was considered a disproportionate metabolite]. M27 was administered orally, daily, by gavage to sexually mature rats at a dose of 0, 5, 10, or 20 mg/kg/day. Bilirubin increase was noted in females but there were no correlating findings of hemolysis, cholestasis, organ weight changes, macroscopic, or microscopic changes in the liver at 13 or 26 weeks. Slightly higher incidence and severity of myofiber regeneration, degeneration, and necrosis in the tongues of males and females administered 20 mg/kg/day for 13 weeks. In the study report, this finding was considered to be related to the sublingual blood sampling, rather than the test item, based on the location and characteristics of this finding (Heimann et al, 2009). The NOAEL for both males and females was considered to be 20 mg/kg/day, with $AUC_{(0-24)}$ = 13700 µg.h/L (5.4 X MRHD) in male and $AUC_{(0-24)}$= 38300 µg.h/L (15 X MRHD in female rat). Safety margins are based on the $AUC_{(0-24)}$ of 2496.3 µg.h/L for M27 obtained from the MRHD of elinzanetant in clinical study B002427

Genotoxicity

In-vitro and in-vivo genotoxicity studies with elinzanetant and in-vitro genotoxicity studies with its three principal metabolites (M27, M30/34, and M18/21) did not reveal any evidence of a genotoxic potential.

Carcinogenicity

- There were no neoplastic findings in the 26-week transgenic mice study (B003184).
- Positive carcinogenicity findings were present in the 2-year rat study (B003186). Female rats were treated orally with elinzanetant doses ranging from 7 to 80 mg/kg/day compared to vehicle for 104 weeks. Elinzanetant dose dependently reduced body weight gain (body weights were 9%, 9%,17%, and 19% lower at 7,

20, 60, and 80 mg/kg/day, respectively, compared to control at terminal sacrifice), but had no effect on overall survival. Elinzanetant treatment resulted in neoplastic findings in the uterus and the hematolymphoid system as described below:

- Statistically significant increases in malignant lymphoma in the hematolymphoid system at 80 mg/kg/day.
- Statistically significant increases in the incidence of malignant endometrial adenocarcinoma of the uterus at ≥60 mg/kg/day.
- Statistically significant increases in the incidence of combined malignant and benign endometrial tumors of the uterus at ≥60 mg/kg/day.
- Statistically significant increases of combined malignant and benign endometrial tumors and malignant squamous cell carcinoma of the uterus at ≥60 mg/kg/day.

Safety and exposure margins:
No Observed Adverse Effect Level (NOAEL): The oral dose of 20 mg/kg/day with $AUC_{(0-24)}$ = 64000 µg.h/L was the highest test dose not associated with carcinogenic signals in female rats. Based on the elinzanetant $AUC_{(0-24)}$ of 8572 µg.h/L obtained from the MRHD in the clinical study B002427, the clinical safety margin provided by the highest noncarcinogenic dose to the MRHD is **~7.5 X.** Based on the $AUC_{(0-24)}$ for the metabolites, safety margins are ~0.2 X, 3.7 X, and 0.05 X for the metabolite M27, M30/34, and M18/21, respectively.

The oral dose of 60 mg/kg/day (elinzanetant $AUC_{(0-24)}$ = 252000) was the lowest tested dose associated with carcinogenic signals in female rats. Based on AUCs, the clinical exposure margins provided by this dose to the MRHD are **~29.4 X for elinzanetant** and ~0.8 X, 7.0 X, and 0.1 X for the metabolites M27, M30/34, and M18/21, respectively.

Of note, CNS-related signs were observed in rats during the study and are described further under the subheading 'CNS-related findings' below.

CNS-related findings

Clinically relevant CNS-related safety signals were reported in two studies – a 2-year carcinogenicity study conducted in female Sprague-Dawley (SD) rats (Envigo – formerly Harlan – USA) and a 13-week repeat-dose toxicity study conducted in male and female SD rats (Envigo, Netherlands). The substrain of SD rats from Envigo is referred to as SD:Hsd.

In the 2-year carcinogenicity study (study B003186), female SD:Hsd rats were treated with the dose of 0, 3.5, 10, 30, or 40 mg/kg, BID, by oral gavage for 104 weeks (n = 50 rats/group). Increased incidence of convulsions was noted in rats treated with doses ≥60 mg/kg/day. At doses ≥60 mg/kg/day, prodromal signs of convulsions (e.g., increased sensitivity to touch and decreased activity) generally preceded detection of

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convulsions, which were first noted around day 162 and 106 after start of treatment with the doses of 60 mg/kg/day and 80 mg/kg/day, respectively.

In the 13-week repeat-dose toxicity study (study R-13628), male SD:Hsd rats were treated with the dose of 0, 25, 60, or 150 mg/kg (highest dose decreased to 87.5 after day 9), BID, and female SD:Hsd rats were treated with the dose of 0, 10, 25, or 50 mg/kg, BID. Treatments were delivered by oral gavage for 13 weeks. Muscle spasms (lasting up to 3 min) and tremors were noted in some female rats around day 24 after start of treatments and were followed by convulsions (starting around treatment day 34) in 2 out of 16 females at 20 mg/kg, 3 out of 16 females at 50 mg/kg, and 3 out of 21 females at 100 mg/kg. Likewise, 1 out of 16 males in the groups that received the low and mid doses (50 and 120 mg/kg/day, respectively) had tremors, whole-body rigidity, spams (lasting up to 1-3 min), stiff tail, and involuntary muscle contractions (convulsions). Male rats treated with the highest tested dose (300/175 mg/kg/day) died prematurely after presenting with reduced activity, hunched posture, abnormal gait, piloerection, and prostration. There were no histopathological findings in the brain.

Reproductive and developmental toxicity

In the fertility and early embryonic developmental (FEED) study conducted in rat [study R-13611], female rats were treated with 0, 5, 25, or 100 mg/kg/day of elinzanetant via oral gavage for 22 days before cohabitation with untreated males, days 1 to 14 during cohabitation with untreated males, and on postcoital days 0 to 6. Increased percentage of pre-implantation and post-implantation embryo loss, resulting in reduced litter size, and lower fetal body weights were seen at the dose of 100 mg/kg/day (14-fold the $AUC_{(0-24)}$ at the human therapeutic dose). These effects were not observed following dosing at 25 mg/kg/day (3-fold the $AUC_{(0-24)}$ at the human therapeutic dose). Since no PK/TK parameters were collected in the FEED study, calculations of margins of exposure were done based on the 13-week exposures from the 13-week toxicity study R-13596 in rats [13-week AUCs were 32200 µg.h/mL at 25 mg/kg/day and 135000 µg.h/mL at 100 mg/kg/day in female rats].

In the embryofetal developmental (EFD) study in rat [R-13610], female rats were treated with 0, 5, 25 or 100 mg/kg/day of elinzanetant via oral gavage once daily from gestation day (GD) 6 to 17. No evidence of embryofetal lethality or teratogenicity occurred at doses ≤100 mg/kg/day, with $AUC_{(0-24)}$ = 197000 µg.h/L (23-fold the $AUC_{(0-24)}$ at the human therapeutic dose), and no maternal toxicity occurred at doses ≤25 mg/kg/day, with $AUC_{(0-24)}$ = 57200 µg.h/L (7-fold the $AUC_{(0-24)}$ at the human therapeutic dose).

In the embryofetal developmental (EFD) study in rabbit [R-13597], female rabbits were treated with 0, 30, 45, or 70 mg/kg twice daily (BID) or a total daily dose of 0, 60, 90, or 140 mg/kg/day elinzanetant administered via oral gavage from GD 7 to 19. Maternal toxicity in the form of marked body weight loss and decreased food consumption leading to early sacrifice in 4 out of 27 females was observed at the highest tested dose of 140 mg/kg/day, with $AUC_{(0-24)}$ = 10600 µg.h/L (~equivalent to the $AUC_{(0-24)}$ at the

human therapeutic dose). No evidence of embryofetal lethality or teratogenicity occurred in fetuses of surviving dams at doses up to 140 mg/kg/day.

In the pre- and postnatal development (PPND) study in rat [study B003187], female rats were treated with 0, 1.5, 5, or 15 mg/kg/day elinzanetant from GD 6 to lactation day (LD) 21. A higher incidence of still born pups, an increase in total litter loss, with a decrease of pup viability on postnatal days 0 to 4, and an increase in the number of neonatal pups without milk in the stomach were observed at doses ≥5 mg/kg/day, with $AUC_{(0-24)}$ = 8610 µg.h/L (equivalent to the $AUC_{(0-24)}$ at the human therapeutic dose).

In the same study, principle human metabolites of elinzanetant were detected in the plasma of F1 pups from dams that received once daily oral doses of elinzanetant ≥1.5 mg/kg/day, with $AUC_{(0-24)}$ = 2000 µg.h/L (elinzanetant $AUC_{(0-24)}$ below the range of human therapeutic exposure) during pregnancy and lactation.

- Metabolites M27 (code name: BAY 3462932) and M18/21(code name: BAY 3462934) were detected in the F1 pup plasma at 24-h post-dosing of the dams with elinzanetant doses ≥5 mg/kg/day on lactation day 4.
- Metabolite M30/34 (code name: BAY 3462933) was detected in the F1 pup plasma from dams treated with elinzanetant doses ≥1.5 mg/kg/day.

Phototoxicity study

Elinzanetant has several characteristics that, per the *Guidance for Industry: S10 Photosafety Evaluation of Pharmaceuticals* (January 2015), available at https://www.fda.gov/media/85076/download, make it a potential phototoxicant. Elinzanetant absorbs photons in the ultraviolet (UV) spectrum (290-700 nm). In the in-vitro Balb/c 3T3 neutral red uptake phototoxicity assay (Study Report R-13578), one peak was detected at 321.4 nm with a calculated molar extinction coefficient (MEC) of 3762.3 $L \cdot mol^{-1}$, which exceeds the threshold of 1000 $L \cdot mol^{-1}$ for phototoxicity. In the same study, elinzanetant was found to be cytotoxic with an IC_{50} of 0.845 µg/mL in presence of UV-A. Elinzanetant distributes to and accumulates in melanin-rich tissues in the rat, with radioactivity that was still present in the pigmented eye uvea at day 35 (840 h) post-dose, a finding that suggests long-term retention or irreversible tissue binding of elinzanetant in pigmented tissues (Study Report R-13624; Study Report R-14368).

Potential Safety Concerns of Clinical Relevance based on Nonclinical Findings

The main clinically relevant nonclinical safety signals were identified as: (i) central nervous system (CNS)-related signals, including tremors and convulsions in rats, (ii) skeletal muscle degeneration in rats, (iii) malignant adenocarcinoma of the uterus, the combination of malignant and benign endometrial tumors and squamous cell carcinoma of the uterus, and lymphomas of the hematolymphoid system in the 2-year rat carcinogenicity study, (iv) in-vitro phototoxic signals, (v) gastrointestinal (GI)-related signals in rats and monkeys, and (vi) reproductive and developmental toxicity signals in rat and rabbit. Some topics have been briefly described above. Refer to Section 11

Integrated Summary and Safety Evaluation for additional information and discussion of clinical relevance.

1.3 Recommendations

1.3.1 Approvability

Pharm/Tox supports the approval of elinzanetant for the treatment of moderate to severe VMS due to menopause.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

The labeling will be reviewed in a separate review.

2 Drug Information

2.1 Drug

CAS Registry Number: 929046-33-3

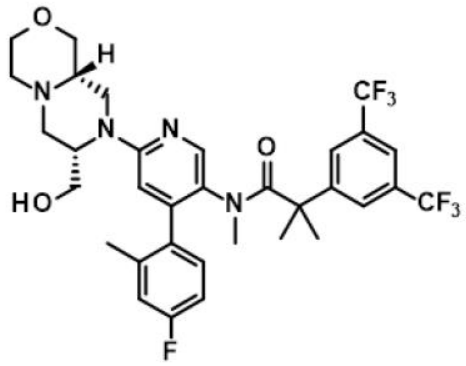
Generic Name: elinzanetant

Code Name: BAY 3427080 [NT-814 and/or GSK1144814A are previous names and still noted in some of the studies and hence also occur in this document]

Chemical Name: 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]-3-pyridinyl}-N,2-dimethylpropanamide

Molecular Formula/Molecular Weight: $C_{33}H_{35}F_7N_4O_3$ / 668.7 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Neurokinin (NK)1 and NK3 receptor antagonist

Reference ID: 5623053

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND: 129492, (b) (4)
DMF: (b) (4)

2.3 Drug Formulation

Elinzanetant capsules 60 mg are oblong, opaque red soft gelatin capsules with EZN60 imprinted on the capsule shell (b) (4)

Table 1: Composition of elinzanetant capsule, 60 mg.

Composition	Reference to standard	Function	Quantity per capsule [mg]
Drug substance			
Elinzanetant	Specification	Drug substance	60.00 [a]
Excipients fill mass			(b) (4)
all-rac-α-Tocopherol	Ph. Eur., USP-NF		
Caprylocaproyl macrogolglycerides	Ph. Eur., USP-NF		
Glycerol monocaprylocaprate	Ph. Eur., USP-NF		
Glycerol mono-oleate	Ph. Eur., USP-NF		
Polysorbate 80	Ph. Eur., USP-NF		
(b) (4)			
Weight capsule fill			**1200.00**
Excipients printed capsule shell			
Capsule shell	see Table 2–2	Soft gelatin capsule	(b) (4)
Ink white	see Table 2–3	Printing ink	
Weight capsule shell			**640.13**
Weight capsule			**1840.13**
(b) (4)			

c q.s. = quantum satis (a sufficient quantity)

Source: Table extracted from module 3.2.P.1 (Refer to table 2-2 and 2-3 in same module section for details on the excipients and printed capsule shell).

2.4 Comments on Novel Excipients

The elinzanetant drug product has no novel excipients for the oral route of administration.

Qualification of excipients

Table 2 lists the maximal daily exposures (MDEs) to the excipients considering the MRHD of 120 mg elinzanetant.

The maximal daily doses of two excipients (glyceryl monocaprylocaprate and glyceryl monooleate) exceed the MDEs in previously approved oral drug products per the FDA Inactive Ingredient Report (IIR) (Table 2).

Table 2: Drug product composition and assement of maximal daily doses of excipients

Composition	Amount (mg) per capsule	Maximal Daily Dose (mg)	MDE per FDA IIR (mg)
Elinzanetant	60.0	120.0	NA
All-rac-α-tocopherol	(b) (4)		246
Caprylocaproyl macrogoglycerides			3623
Glyceryl monocaprylocaprate			**501.9**
Glyceryl monooleate			**2.0**
Polysorbate 80			233.0

NA: not applicable.

Glyceryl monooleate

Api et al. (2021)[2] reported that the oral NOAEL for glyceryl monooleate in a repeat-dose toxicity study in rats was 1,000 mg/kg/day (the highest test dose). In this GLP-compliant, combined repeat-dose and reproductive study, Sprague Dawley rats were administered glyceryl monooleate via oral gavage (0, 100, 300, or 1000 mg/kg/day; n = 12 rats/sex/dose). Males were dosed for 42 days (starting 14 days prior to mating and continuing through the mating period); females were dosed up to lactation day 4. Additional groups of 5 Sprague Dawley rats/sex/dose were maintained for 2 weeks after dosing as a recovery group. No mortality occurred throughout the study period. There were no treatment-related effects on general condition, clinical observations, sensory reflex function test, landing leg width, grip strength, locomotor activity, body weight, food consumption, urinalysis (male only), hematology, organ weight, organ function, clinical chemistry, necropsy, or histopathology.

A permitted daily exposure (PDE) for glyceryl monooleate is estimated using the NOAEL of 1,000 mg/kg/day in rats and the formula:

$$PDE = \frac{NOAEL\ x\ 50}{F1\ x\ F2\ x\ F3\ x\ F4\ x\ F5}$$

[2] Api AM, Belsito D, Biserta S, Botelho D, Bruze M, Burton GA Jr, Buschmann J, Cancellieri MA, Dagli ML, Date M, Dekant W, Deodhar C, Fryer AD, Gadhia S, Jones L, Joshi K, Kumar M, Lapczynski A, Lavelle M, Lee I, Liebler DC, Moustakas H, Na M, Penning TM, Ritacco G, Romine J, Sadekar N, Schultz TW, Selechnik D, Siddiqi F, Sipes IG, Sullivan G, Thakkar Y, Tokura Y. RIFM fragrance ingredient safety assessment, glyceryl monooleate, CAS Registry Number 111-03-5. Food Chem Toxicol. 2021 Mar;149 Suppl 1:111992.

Reference ID: 5623053

where F1 = 5 (extrapolation from rat to human), F2 = 10 (variability between individuals), F3 = 1 (for reproductive study covering the whole period of organogenesis), F4 = 1 (no fetal toxicity associated with maternal toxicity), F5 = 1 (determined NOAEL).

$$PDE = \frac{1000\ x\ 50}{5\ x\ 10\ x\ 1\ x\ 1\ x\ 1} = 1000\ mg/day$$

The estimated PDE is (b) (4) x the maximal daily dose of glyceryl monooleate in the Applicant's product.

Per the Code of Federal Regulations 21 CFR §184.1323, glyceryl monooleate of a purity suitable for its intended use is generally recognized as safe (GRAS) as a direct human food ingredient. In addition, as described in a 1986 publication, federal regulations also allow the use of glyceryl oleate as a prior-sanctioned food ingredient (21 CFR§181.27) and as both an indirect (21 CFR §175.300, 21 CFR§75.320) and direct (21 CFR 175.515) food additive.

Based on the totality of the information, glyceryl monooleate is considered adequately qualified as an excipient in the Applicant's product.

Glyceryl monocaprylocaprate

The MDE for glyceryl monocaprylocaprate in previously approved oral products is only 501.9 mg (~ (b) (4) % the maximal daily dose of this excipient in the MRHD of elinzanetant). However, a glyceryl mono- and dicaprylocaprate mix is an excipient in a previously approved oral drug product at an MDE of 13,770 mg per the FDA IIR. According to the US Pharmacopeia, no less than 75% of the glyceryl mono- and dicaprylocaprate mix (a product also referred to as glyceryl monoprylocaprate Type I[3]) is the monoester.[4] With this consideration, the MDE to glyceryl monocaprylocaprate in the previously approved oral drug product is no less than ~10,328 mg. Therefore, glyceryl monocaprylocaprate at the amount in the Applicant's product is considered adequately qualified.

2.5 Comments on Impurities/Degradants of Concern

Drug substance

Table 3 lists the drug substance specification provided in the eCTD section 3.2.S.4. The red box highlights the specification for organic impurities.

[3] https://www.uspnf.com/notices/glyceryl-monocaprylocaprate-monograph-rs-separations-gen-annc-20200424#:~:text=The%2060%2Dmonth%20implementation%20period,official%20on%20May%201%2C%202025.&text=Should%20you%20have%20any%20questions,PGZ@usp.org%20).

[4] https://doi.usp.org/USPNF/USPNF_M6458_02_01.html.

Table 3: Drug substance specification.



Source: Drug substance specification in Module 3.2.S.4.

Table 4 lists all the potential organic impurities in the drug substance.

Table 4: Potential organic impurities in elinzanetant drug substance.

Short name / code no.	Structural formula	Origin
Chemical name (IUPAC)		
	(b) (4)	

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Source: Structure of potential organic impurities identified in Drug substance in module 3.2.S.3.2.

Reviewer's comments:

1) ***Sum of all organic impurities is set at (b) (4)%. This appears acceptable as the four organic impurities are specified individually at (b) (4)%.***
2) ***The (b) (4) is noted to be a (b) (4) impurity of the (b) (4) (b) (4) and is also controlled at (b) (4)%.***
3) ***During the previous nonclinical assessment at IND stages, (b) (4) was included in the specification. The Applicant notes that it was not detected in any of the late-stage development batches and is thus not included in the specification submitted with the NDA.***
4) ***The batch analyses [Module 3.2.S.4.4] reported that batches UN506BB, UN506BL, and UN506C6 met the specifications for the impurities.***
5) ***The clinical batches 2020 [# 20-001, 20-002, 20-003 (BXR9JVH), 20-004 (BXR9JVJ), 20-005 (BXR9JVK)] and clinical batches 2021 and 2022 [#7486-P54 / 000001 (BXR9ZRT), 7486-P54 / 000002 (BXR9ZRU), 7486-P54 / 100001 (BXRAEEP)] are also within specification; however, only 1 organic impurity is listed, (b) (4) It appears that the new code for this impurity is (b) (4)***

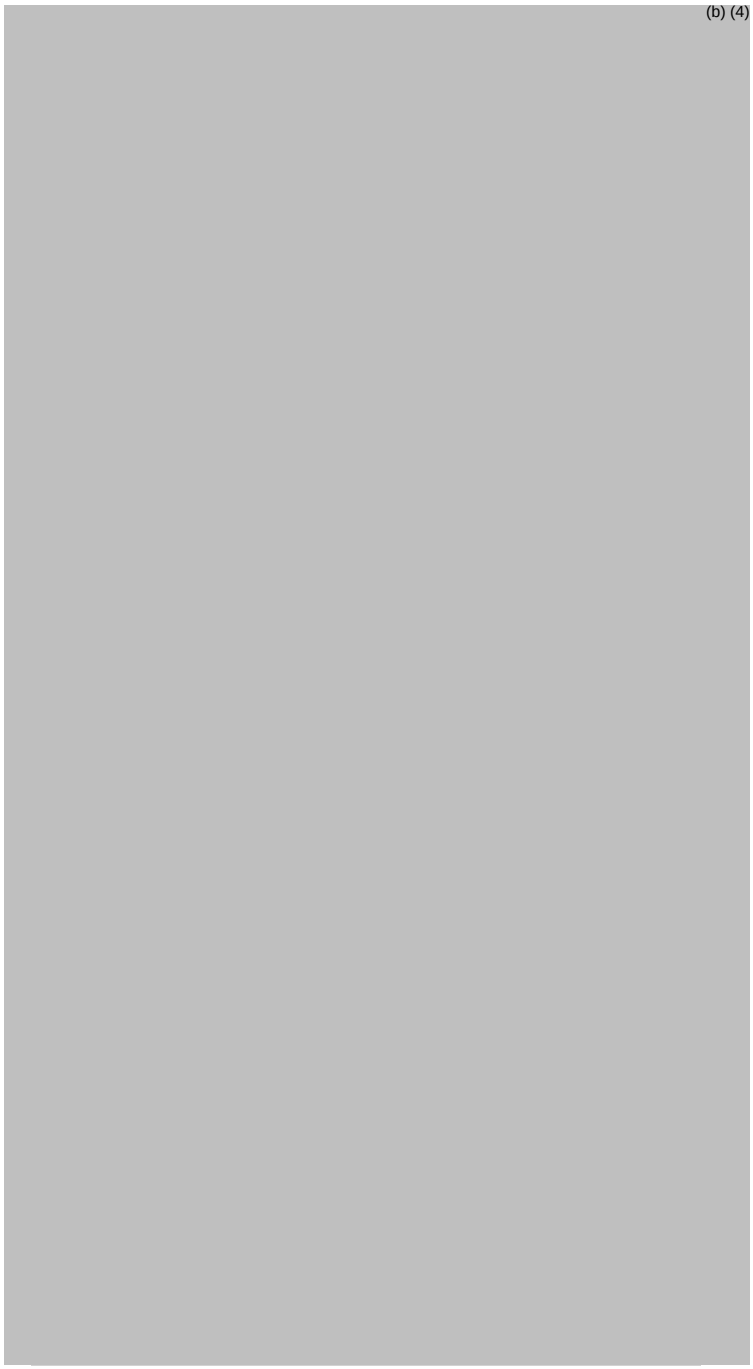
Overall Assessment and Summary (Drug Substance):
The qualification threshold of (b) (4)% set for the organic impurities and (b) (4)% for any unspecified impurities is as (b) (4) acceptable. The Applicant identified the organic impurities to have no structural alerts and designated as class 5 impurities as per ICH M7. The Nonclinical team consulted the CDER Computational Toxicology team [CDER/OTS/OCP/DARS Computational Toxicology Consultation Service] for a (Q)SAR analysis and all seven potential organic impurities of the drug substance listed by the Applicant were predicted to be negative for potential genotoxicity. Refer to the appended (Q)SAR consult report at the end of this review.

Drug product

Drug product-related impurities have been detected and characterized as degradation products. Refer to module 3.2.P.5.5 for full details on the impurities. The important aspects are highlighted below.

The Applicant has proposed a shelf life of 30 months based on available stability data [Module 3.2.P.8.1]. Drug product-related impurities have been detected and characterized as degradation products and are described below.

(b) (4)



Source: module 3.2.P.5.5.

Drug product specification

The drug product release and shelf-life specifications for the degradation products are shown in Table 5 below.

Table 5: Drug product specification for degradation products of elinzanetant.

Test	Release Specification	Shelf Life Specification
(b) (4)		

Source: Extracted from module: 3.2.P.5.6.

Qualification of degradation products

The release specifications for (b) (4) are set at (b) (4)% (b) (4). Qualification for the higher release specification limit for (b) (4) [≤(b) (4)%] and for shelf-life specifications set at higher limits [(b) (4)%] for all degradation products and are described below:

(b) (4) qualification:

(b) (4)

(b) (4) (b) (4)

Based on the NOAELs, the PDE/TDI calculation for 50-kg women is described below.

Permissible Daily Exposure/Total Daily Intake (PDE/TDI) Calculation for (b) (4) (b) (4) (as described in the (b) (4)

(b) (4)

(b) (4)

Conclusion

At the MRHD of elinzanetant (120 mg), (b) (4)% of shelf-life specification limit for the (b) (4) corresponds to a daily intake of (b) (4) mg, which is (b) (4)-fold lower than the TDI based on the more conservative PDE/TDI of (b) (4) mg/day estimated using the NOAEL from the study in monkeys. Considering the stability data provided for the clinical batches in the eCTD Module 3.2.P.8.3, the highest level of (b) (4) is within specification and the specified limit appears reasonable.

(b) (4) Qualification:

(b) (4)

A 4-week oral repeat-dose toxicity study (study# PH-42298/T105216-5) was conducted in rats using (b) (4) at doses up to (b) (4) mg/kg/day. The high dose of (b) (4) mg/kg/day was identified as the NOAEL. This corresponds to (b) (4) mg/kg based on batch purity of 96%. Based on the NOAEL, the PDE/TDI calculation for 50-kg women is described below.

Permissible Daily Exposure/Total Daily Intake (PDE/TDI) Calculation for (b) (4)

(b) (4)

(b) (4)

Conclusion for (b) (4)

The shelf-life specification limit for the (b) (4) of up to (b) (4)% at the MRHD of elinzanetant (120 mg) corresponds to a daily intake of (b) (4) mg, which is (b) (4)-fold lower than the TDI. Considering the stability data provided for the clinical batches in the eCTD Module 3.2.P.8.3, the highest level of (b) (4) is within specification and the specified limit appears reasonable.

(b) (4)

The Applicant notes that (b) (4) (b) (4) .

As a note, the Applicant mentions that data from a single-dose toxicokinetic study in rats using (b) (4) [study# PH-42303] indicated that the (b) (4) (b) (4) was not measured). Considering the theoretical cumulative shelf-life specification limits for (b) (4)%, the total (b) (4) exposure would result in a (b) (4)mg daily dose, which is similar to the TDI of (b) (4) mg/day derived for (b) (4)

Conclusion for (b) (4)
The Applicant's justifications for the proposed specifications for (b) (4) and (b) (4) are considered acceptable. It is likely that the (b) (4) will break down in vivo, and it is reasonable to expect (b) (4) to be less toxic relative to the saturated (b) (4). Applying the NOAEL for (b) (4) to (b) (4) and (b) (4) is therefore considered acceptable. Based on the stability data provided for the clinical batches in Module 3.2.P.8.3, the highest level of (b) (4) is within specification and the specified limit appears reasonable.

Any unspecified degradation product
The limit is set at (b) (4)% for both release and shelf-life ((b) (4) and is considered acceptable.

Sum of all degradation products
The limit is set at (b) (4)% for release and (b) (4)% for shelf-life. Based on the stability data provided for the clinical batches in Module 3.2.P.8.3, the highest level of total degradation products is (b) (4)% at 36 months for batch 4308531, and thus the limit appears reasonable.

(b) (4)
The risk assessments for (b) (4) in the drug substance (Module 3.2.S.3.2 – risk assessment on (b) (4) and the drug product (Module 3.2.P.5.5 – risk assessment on (b) (4) were evaluated by the CMC team and noted to be adequate. No further evaluation was necessary from the Pharm/Tox perspective.

Residual Solvents
Residual solvents in the drug substance (b) (4) are controlled per ICH Q3C, as described in the eCTD Module 3.2.S.3.2 (Impurities – Residual solvents) (b) (4)

Elemental impurities
All the elemental impurities, considering the administration route, are controlled as per ICH Q3D as described in the eCTD Module 3.2.P.5.5 (Risk of elemental impurities).

Reviewer's comment (additional):

1) ***Based on the stability data provided for the clinical batches in Module 3.2.P.8.3, the two highest levels of (b) (4) detected were (b) (4)% in batch 4308531 at 36 months (at 30°C/75% relative humidity {RH}) and (b) (4)% in Batch A000029463-01 at 3 month (30 °C/75% RH) . Taking the batch results into account, along with the PDE/TDI determination, the shelf-life specification of (b) (4)% appears reasonable.***
2) ***Based on the stability data provided for the clinical batches in Module 3.2.P.8.3, the highest level of (b) (4) detected was (b) (4)% in batch 4308531 at 36 months (at 30 °C/75% RH). Taking the batch results into account, along with the PDE/TDI determination, the shelf-life specification of (b) (4)% appears reasonable.***
3) ***The release specification sets are (b) (4)% and (b) (4)% for (b) (4) and (b) (4) respectively. The highest levels of (b) (4) and (b) (4) detected in the clinical batches were (b) (4)% and (b) (4)% , respectively at 36 months for batch 4308531 [Module 3.2.P.8.3]. Thus, the levels of the impurities at expiry do not exceed the control specifications set at release.***

Overall Assessment and Summary (Drug Product):
The Drug Product release and shelf-life specifications are acceptable from the Pharm/Tox perspective.

2.6 Proposed Clinical Population and Dosing Regimen

The recommended dose of elinzanetant is 120 mg per day (two 60 mg soft gel capsules) taken once daily at bedtime in the general population of individuals with moderate to severe VMS associated with menopause.

2.7 Regulatory Background

The molecule was initially discovered by GlaxoSmithKline (GSK) under the code name GSK1144814. The drug product was subsequently acquired by NeRRE Therapeutics and KaNDy Therapeutics Ltd and repurposed for the current indication (moderate to severe VMS associated with menopause) under the code name NT-814 and submitted under IND 129492. On September 8, 2020, Bayer HealthCare Pharmaceuticals Inc. (Bayer) took over the sponsorship of IND 129492. Bayer has renamed the compound as BAY 3427080 or elinzanetant.

Notable regulatory activities and submission/reviews related to Pharm/Tox are summarized in the table below:

Type of Submission	**Notes on Pharm/Tox activities**	**Review/ communication in DARRTS**
IND 129492 opening	30-day safety review	1/30/2017
Activities under the IND	New clinical protocol reviewed	3/18/2019
	Rat FEED, rat EFD and rabbit EFD studies reviewed	8/2/2019
	Rat Carcinogenicity SPA (special protocol assessment) reviewed. [13- and 26-week rat repeat dose study including male fertility and genetic toxicology studies]	10/19/2020
EOP 2 meeting	EOP 2 meeting package reviewed.	5/7/2021
Activities under the IND	Nonclinical questions regarding their nonclinical program and Phase 3 clinical protocol Nonclinical development plan not adequate; Memo identifying nonclinical deficiencies (metabolite coverage) filed	5/12/2021
	Follow-up nonclinical advice given to sponsor and memo identifying nonclinical deficiencies filed in DARRTS	6/24/2021
	Nonclinical studies to support Phase 3 were fully reviewed and considered adequate	8/25/2022
	Tg-rasH2 mouse 6-month SPA carcinogenicity protocol submitted by sponsor. ECAC meeting held on 12/6/2022. ECAC advice sent to sponsor on 12/8-/2022	12/15/2022
	Follow-up letter with additional advice sent to sponsor on metabolites	
	Tg-rasH2 mouse SPA carcinogenicity review filed in DARRTS	12/13/2022
	Tg-rasH2 final protocol submitted; FDA stat consult requested	
	Sponsor request to terminate rat carcinogenicity study early ECAC consulted and advice letter sent on 3/6/2023	3/1/2023
	Draft Stat review completed by Dr. Karl Lin 4/3/2023 (FDA statistical reviewer) Review filed to DARRTS on 01/06/2023. Advice letter sent to sponsor with minor suggestions	1/19/2024

Reference ID: 5623053

Type of Submission	Notes on Pharm/Tox activities	Review/ communication in DARRTS
Type B pre-NDA meeting under IND 129492	The nonclinical program, including the ongoing pre-/post-natal development, carcinogenicity, and abuse potential studies, intended to support NDA submission determined to be complete. The in vitro studies pertaining to drug metabolism and drug-drug interaction deemed reasonable. The adequacy of data to support an NDA filing and approval will be a review issue.	2/26/2024
NDA 219469 opening	NDA opened. Final reports of carcinogenicity studies and rat PPND study submitted.	7/26/2024
Activities under the NDA	Request for information from Applicant on the CNS findings of convulsions and tremors in the rat repeat-dose study [study ID# R-13628 9RH17GJ)] and carcinogenicity study [study ID#B003186 (T105128-7)]	10/7/2024
	Response to information on the CNS findings from Applicant submitted on 11/13/2024 (SDN 12; eCTD 0012)	11/13/2024
	Carcinogenicity studies- statistical review filed	12/12/2024
	eCAC meeting minutes filed	12/20/2024
	Carcinogenicity studies- Pharmacology Toxicology review filed	2/04/2025

3 Studies Submitted

See tables below under section 3.1 and 3.2.

- Studies that were either not submitted previously or submitted but not reviewed fully under IND 129492 and are included and fully reviewed under this NDA review cycle.
- All other studies have been previously submitted under IND 129492 and fully reviewed. These studies are briefly summarized in the tables.

As a note, the original study reports have been renumbered by the current Applicant, Bayer. At the time they were reviewed under the IND 129492, study reports had different numbers/IDs; however, it was verified during review that they are the same studies as those listed under the NDA.

3.1 Studies Reviewed

Primary PD Studies					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
Determination of the affinity of GSK 1144814 for NK1/3 receptors across species	IND 129492 eCTD 002	No	In vitro	R-13857	GlaxoSmithKline, UK
Determination of the affinity of GSK 1144814 at native NK 1,3 receptors across species	IND 129492 eCTD 002	No	In vitro	R-13886	GlaxoSmithKline, UK
Effect of GSK 1144814 on saturation binding of [3H]-substance P at hNK 1 receptors expressed in CHO cells	IND 129492 eCTD 002	No	In vitro	R-13699	GlaxoSmithKline, UK
Investigation of the effect of DMSO on the pKi value of GSK 1144814	IND 129492 eCTD 002	No	In vitro	R-13881	GlaxoSmithKline, UK

Primary PD Studies					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
at human recombinant NK 1 and NK3 receptors					
GSK 1144814: Tachykinin Receptors Binding Assays	IND 129492 eCTD 002	No	In vitro	R-13884	GlaxoSmithKline, USA
Functional assessment of GSK 1144814B at cloned NK 1 and NK3 receptors across species using the inositol phosphate scintillation proximity assay	IND 129492 eCTD 002	No	In vitro	R-13859	GlaxoSmithKline, UK
Functional characterization of GSK 1144814 at hNK 1, hNK.3 and gpNKl receptors using label-free CellKey™ technology and inositol phosphate accumulation assays	IND 129492 eCTD 002	No	In vitro	R-13879	GlaxoSmithKline, UK
The effect of GSK 1144814 on NKB-induced neuronal activity in the medial habenula of the guinea pig	IND 129492 eCTD 002	No	In vitro	R-13877	GlaxoSmithKline, UK
In Vitro Pharmacology Study of Several Compounds	IND 129492 eCTD 0048	No	In vitro	R- 13858	(b) (4)
Ex vivo NK1 and NK.3 Receptor Occupancy by GSK 1144814 in Gerbil Forebrain	IND 129492 eCTD 002	No	Ex-vivo	R-13860	GlaxoSmithKline, UK
Evaluation of receptor occupancy of NK1 and NK3 receptors by GSK 1144814B in gerbil brain	IND 129492 eCTD 002	No	Ex-vivo	R-13883	GlaxoSmithKline, UK
Tachykinin NK1 and NK3 Receptor Occupancy by Ex-vivo autoradiography in the guinea pig- GSK 1144814A	IND 129492 eCTD 002	No	Ex-vivo	R-13878	GlaxoSmithKline, UK
Effect of Haloperidol on NK 1 and NK3 Receptor Occupancy of GSK1144814B by Ex-vivo Autoradiography in the Guinea Pig	IND 129492 eCTD 002	No	Ex-vivo	R-13880	GlaxoSmithKline, UK
Evaluation of the affinity of GSK1144814B binding to NK.1 receptors in human putamen	IND 129492 eCTD 002	No	Ex-vivo	R-13876	GlaxoSmithKline, UK
The Effect of GSK1144814B upon NK1 agonist (GR 73632)-Induced Gerbil Foot Tapping Behaviour	IND 129492 eCTD 002	No	In-vivo	R-13856	GlaxoSmithKline, UK
Temporal Profile of GSK 1144814B upon GR73632: induced gerbil foot tapping and ex vivo receptor occupancy	IND 129492 eCTD 002	No	In-vivo	R-13862	GlaxoSmithKline, UK
The Effect of GSK 1144814B upon NK3 receptor agonist (Senktide)-Induced Guinea Pig Wet Dog Shake Behaviour	IND 129492 eCTD 002	No	In-vivo	R-13863	GlaxoSmithKline, UK
GSK 1144814B in the Guinea Pig Forebrain Using in vivo Microdialysis Profiling Services Project Report	IND 129492 eCTD 002	No	In-vivo	R-13861	GlaxoSmithKline, UK
GSK 1144814B in the pharmacologically-induced Dopamine Increases in the Guinea Pig Nucleus Accumbens Using In Vivo Microdialysis	IND 129492 eCTD 002	No	In-vivo	R-13882	GlaxoSmithKline, UK
Brain NK1 receptor occupancy following single intravenous doses of GSK 1144814 measured with [^{11}C]GR-205171 PET in the baboon	IND 129492 eCTD 002	No	In-vivo	R-13885	(b) (4)

*There is no documentation of these studies being fully reviewed; however, summaries of some of these studies have been noted in previous reviews under the IND.

Secondary PD Studies					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
In Vitro Pharmacology: Delta Package - Study of GSK1144814B and (b) (4)	IND 129492 eCTD 002	No	In vitro	R-13669	(b) (4)
Secondary Pharmacology Report for GSK1144814A	IND 129492 eCTD 0032	No	In vitro	R-13674	GlaxoSmithKline, UK
(b) (4) Data Report for Pharmacology Services (Radioligand Binding Assays) on Compound CHH094-2021#	IND 129492 eCTD 0112	No	In vitro	R-14343	(b) (4)
(b) (4) Data Report for Pharmacology Services (Individual Functional Assay) on Compound CHH094-2021# # BAY 3427080	IND 129492 eCTD 0112	No	In vitro	R-14344	
(b) (4) Data Report for Pharmacology Services (Individual Radioligand and Enzyme Assays) on Compound CHH094-2021	(could not be located under module 4.2.1.2 of IND 129492)	No	In vitro	R-14381	
(b) (4) Data Report for Pharmacology Services (Radioligand Binding Assay) on Compound CHH080-2021	IND 129492 eCTD 0062	No	In vitro	R-14015	
(b) (4) Data Report for Pharmacology Services (Radioligand Binding Assays) on Compound CHH081-2021	IND 129492 eCTD 0062	No	In vitro	R-14016	
(b) (4) Data Report for Pharmacology Services (Bayer SafetyScreen) on Compound CHH080-2021	IND 129492 eCTD 0062	No	In vitro	R-14017	
(b) (4) Data Report for Pharmacology Services (Bayer SafetyScreen) on Compound CHH081-2021	IND 129492 eCTD 0062	No	In vitro	R-14018	
(b) (4) Data Report for Pharmacology Services (Bayer SafetyScreen) on Compound CHH082-2021	IND 129492 eCTD 0062	No	In vitro	R-14019	
(b) (4) Data Report for Pharmacology Services (Radioligand Binding Assay) on Compound CHH082-2021	IND 129492 eCTD 0062	No	In vitro	R-14020	
In Vitro Pharmacology: Dopamine Transporter Uptake Assay Study of CHH094-2021	IND 129492 eCTD 0130	No	In vitro	B002819	
(b) (4) Study Report for Pharmacology Services (Functional Dopamine Assays) on Compound CHH094-2021	IND 129492 eCTD 0130	No	In vitro	B002836	

Secondary PD Studies					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
Not fully reviewed:					
Pharmacological characterisation of GSK1144814 in the marmoset human threat test	IND 129492 eCTD 002. In module 4.2.1.1	No	In-vivo	R-13680	GlaxoSmithKline, Italy
The effect of the dual NK1/3 receptor antagonist GSK1144814C in a test of working memory using the standard delayed matching to sample (DMTS) task in aged (20 years +) Rhesus macaque monkeys	IND 129492 eCTD 002. In module 4.2.1.1	No	In-vivo	R-13671	(b) (4)
The effect of the dual NK1/3 receptor antagonist GSK1144814C in a test of attentive processing using the distractor delayed matching to sample (DMTS) task in young Rhesus macaque monkeys	IND 129492 eCTD 002. In module 4.2.1.1	No	In-vivo	R-13672	
Effect of GSK1144814 on amphetamine induced rearing in the guinea pig with NK1/NK3 receptor occupancy by autoradiography (b) (4)	IND 129492 eCTD 002. In module 4.2.1.1	No	In-vivo	R-13673	GlaxoSmithKline, UK
Assessment of Potential Cocaine Treatment Medications in Monkeys	IND 129492 eCTD 002. In module 4.2.1.1	No	In-vivo	R-13700	(b) (4)

* There is no documentation of these studies being fully reviewed; however, summaries of some of these studies have been noted in previous reviews under the IND.

Safety Pharmacology Studies: Parent Drug					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
Effect of GSK1144814C on hERG Tail Current Recorded from Stably Transfected HEK-293 Cells	IND 129492 eCTD 0002	No	In vitro	R-13675	(b) (4)
Cell Based Electrophysiological Evaluation of GSK1144814B as an Inhibitor of KCNH2 (hERG)	IND 129492 eCTD 0002	No	In vitro	R-13679	GlaxoSmithKline, USA
GSK1144814C: Acute Effects on Cardiovascular Function Following Oral Administration in the Conscious Cynomolgus Monkey (Safety Pharmacology Study)	IND 129492 eCTD 0002	No	Monkey (oral)	R-13670	GlaxoSmithKline, USA
GSK1144814C: Acute Neurobehavioral Effects Following Oral Administration in the Conscious CD™ Rat (Safety Pharmacology Study)	IND 129492 eCTD 0002	No	Rat (oral)	R-13668	(b) (4)
GSK1144814C: Acute Effects on Respiratory Function Following Oral Administration in the Conscious CD™ (SD) Rat (Safety Pharmacology Study)	IND 129492 eCTD 0002	No	Rat (oral)	R-13676	GlaxoSmithKline, USA

* There is no documentation of these studies being fully reviewed.

Safety Pharmacology Studies: Metabolites					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
Effects of BAY 3462932 (M27) on human cardiac ion channels in recombinant cell lines	IND 129492 eCTD 0062	No*	In vitro	PH-42243	Bayer AG, Germany
Effects of BAY 3462933 (M30/M34) on human cardiac ion channels in recombinant cell lines	IND 129492 eCTD 0062	No*	In vitro	PH-42244	Bayer AG, Germany
Effects of BAY 3462934 (M18/M21) on human cardiac ion channels in recombinant cell lines	IND 129492 eCTD 0062	No*	In vitro	PH-42245	Bayer AG, Germany

* There is no documentation of these studies being fully reviewed.

Pharmacokinetics

PK Studies: Absorption					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
NT-814: Pharmacokinetic Study by Oral Gavage Administration to Male CByB6F-Tg (HRAS)2Jic Wild-Type Mice.	IND 129492 eCTD 0128	No	Mouse (oral)	R-13630	(b) (4)
Summary of the Preclinical Pharmacokinetic and Drug Metabolism Studies Performed with GSK1144814 During Lead Optimisation.	IND 129492 eCTD 0002 in module 4.2.2.4	No	Rat, dog, marmoset, monkey (oral + IV)	R-13621	GlaxoSmithKline, UK
M27: Pharmacokinetic Study by Intravenous (Slow Bolus) Administration to Female Sprague-Dawley Rats	IND 129492 eCTD 0128	No	Rat (IV)	R-13622	(b) (4)
NT-814: Pharmacokinetic Study by Oral Gavage Administration to Rabbits	IND 129492 eCTD 0128	No	Rabbit (oral)	R-13620	
Comparative Oral PK Study with Two Formulations of NT-814 Free Base in Female Cynomolgus Monkeys	IND 129492 eCTD 0032	No	Monkey (oral)	R-13618	

* There is no documentation of these studies being fully reviewed, however summaries of some of these studies have been noted in previous reviews under the IND.

PK Studies: Distribution					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
BAY 3427080: In Vitro Investigations on Binding to Plasma Proteins in Different Species, to Purified Human Plasma Proteins, to Human Liver Microsomes, and on Determination of Blood/Plasma Partitioning	IND 129492 eCTD 0048	No	In vitro	PH-42081	Bayer, Germany
Elinzanetant: Supplementary In Vitro Investigations on Binding to Plasma Proteins in Different Species, to Cell Culture Medium and to Human Liver Microsomes of the Metabolites BAY 3462932 (M27), BAY 3462933 (M30/34) and BAY 3462934 (M18/21)	IND 129492 eCTD 0062	No	In vitro	PH-42138	Bayer, Germany

PK Studies: Distribution					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
Elinzanetant: Supplementary In Vitro Investigations on Binding towards Human Serum Albumin by Addition of Sodium Oleate and Itraconazole/ Hydroxyitraconazole	Could not be located in module 4.2.2.3 of IND 129492	No	In vitro	B002590	Bayer, Germany
Quantitative whole-body autoradiography following a single oral or a single intravenous administration of [14C]GSK1144814 tosylate to male Lister Hooded pigmented rats at target dose levels of 10 and 1 mg free base/kg, respectively	IND 129492 eCTD 0002	No	Rat (oral)	R-13624	(b) (4)
BAY 3427080: Quantitative and Qualitative Whole-Body Autoradiography in Timed Pregnant Female Albino Sprague Dawley Rats After Single Oral Administration of [14C]BAY 3427080	IND 129492 eCTD 0128	No	Rat (oral)	R-14360	
BAY 3427080: Quantitative and Qualitative Whole-Body Autoradiography in Male and Female Albino Sprague Dawley Rats and Female Pigmented Long-Evans Rats After Single Oral or Intravenous Bolus Dose of [14C]BAY 3427080	IND 129492 eCTD 0128	No	Rat (oral)	R-14368	

* There is no documentation of these studies being fully reviewed; however, summaries of some of these studies have been noted in previous reviews under the IND.

PK Studies: Metabolism					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
An In Vitro Investigation of the Metabolism of' 14C-GSK1144814 in Mouse, Rat, Rabbit, Dog, Cynomologus monkey and Human Hepatocytes.	IND 129492 eCTD 0002	No	In-vitro	R-13660	GlaxoSmithKline, Italy
An In Vitro Investigation of the Potential for Metabolic Activation Following Incubation of [14C]-GSK1144814 with Human and Rat Liver Microsomes	IND 129492 eCTD 0002	No	In-vitro	R-13654	GlaxoSmithKline, Italy
Metabolism of GSK1144814 in Male Sprague-Dawley Rats following a Single Oral Administration of [14C]GSK1144814 Tosylate at a Dose Level of 10 mg free base/kg.	IND 129492 eCTD 0002	No	Rat (oral)	R-13716	GlaxoSmithKline, Italy
Metabolism of GSK1144814 in a Male Isolated Perfused Rat Liver following Administration of [14C]GSK1144814 tosylate salt at 3 mg free base/kg body weight.	IND 129492 eCTD 0002	No	Rat (In-situ)	R-13655	GlaxoSmithKline, Italy
Metabolism of GSK1144814 in Male Cynomolgus Monkey Following a Single Oral Administration of [14C]GSK1144814 Tosylate at a Dose Level of 5 mg Free Base/kg.	IND 129492 eCTD 0002	No	Monkey (oral)	R-13714	GlaxoSmithKline, Italy

PK Studies: Metabolism					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
NT-814: Major Human Metabolites Structural Characterisation and Preliminary Estimation of Toxicological Species Exposures Relative to Human Exposures using Plasma Samples following Repeat Oral Dosing	IND 129492 eCTD 0032	No	Rat, monkey, human (oral)	R- 13650	GlaxoSmithKline, Italy
Preliminary Characterisation of Metabolites of GSK1144814 in Human Plasma and Urine after a Single and Repeat Oral Administration to Healthy Human Volunteers.	IND 129492 eCTD 0002	No	Human (oral)	R-13659	GlaxoSmithKline, Italy
NT-814: Definitive Structural Elucidation of Potential Major Human Circulating Metabolites M18/M21, M27, M30/M34	IND 129492 eCTD 0128	No	Human (oral)	R-13651	(b) (4)
Elinzanetant: Biotransformation in Man	IND 129492 eCTD 0078	No	Human (oral)	PH-42275	Bayer, Germany; (b) (4)
Determination of BAY3427080, BAY 3629436, BAY3629494 and BAY3629435 in human plasma samples from the clinical study 22050 by LC-MS/MS	Could not be located in module 4.2.2.4 under IND 129492	No	Human (oral)	B003239	

*There is no documentation of these studies being fully reviewed. However, summaries, of some of these studies have been noted in previous reviews under the IND.

PK Studies: Excretion					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
Elimination of drug-related material following a single oral administration of [14C] GSK1144814 tosylate to male Sprague Dawley rats at a target dose level of 10 mg free base/kg.	IND 129492 eCTD 0002	No	Rat (oral)	R-13623	(b) (4)
Elimination of Drug-Related Material Following a Single Oral Administration of [14C] GSK1144814 Tosylate to Male Cynomolgus Monkeys at a Target Dose Level of 5 mg free base/kg.	IND 129492 eCTD 0002	No	Monkey (oral)	R-13625	
BAY 3427080: Determination of Lacteal Excretion and Plasma pharmacokinetics in Postpartum Female Albino Sprague Dawley Rats Following a Single Oral Administration of [^{14}C]BAY 3427080	Could not be located in module 4.2.2.5 under IND 129492	No	Rat (oral)	B003245	

*There is no documentation of these studies being fully reviewed. However, summaries of some of these studies have been noted in previous reviews under the IND.

Toxicology

General Toxicology

Single-Dose Toxicity Studies					
Study Title	**Previously Submitted**	**Previously Reviewed***	**Test System**	**Study No.**	**Testing Facility**
GSK1144814A; Single Oral Dose Toxicokinetic Study in Male Crl:CD (SD) Rats	IND 129492 eCTD 0002	No	Rat (oral)	R-13645	GlaxoSmithKline, UK
GSK1144814B: Single-Dose Escalation (Maximum Tolerated Dose) Oral Toxicity Study in Cynomolgus Monkeys (GlaxoSmithKline Study No. D06424)	IND 129492 eCTD 0002	No	Cyno. Monkey (oral)	R-13575	GlaxoSmithKline, UK
GSK1144814B, Single-Dose Escalation (Maximum Tolerated Dose) Study by Oral Gavage Administration to Marmosets	IND 129492 eCTD 0002	No	Marmoset (oral)	R-13574	(b) (4)
Toxicokinetics Study in Cynomolgus Monkeys	IND 129492 eCTD 0081 (located in 4.2.3.7.3)	No	Cyno. Monkey (IV)	PH-42750	Bayer, Germany

*There is no documentation of these studies being reviewed.

Repeat-Dose Toxicity Studies					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
GSK1144814B: 7-Day Oral Candidate Selection Toxicity Study in Rats	IND 129492 eCTD 0002	Yes*	Rat (oral)	R-13585	GlaxoSmithKline, USA
GSK1144814C: 7-Day Oral Dose Range Toxicity Study in CD™ Rats (GlaxoSmithKline Study No R61009)	IND 129492 eCTD 0002	Yes*	Rat (oral)	R-13586	GSK , Italy
NT-814: Dose-Range-Finding Toxicity Study Followed by a 14-day Preliminary Toxicity Study in the Sprague Dawley Rat	IND 129492 eCTD 0128	No	Rat (oral, feeding)	R-13592	(b) (4)
A 2-Week Oral Gavage Toxicity and Toxicokinetic Study with NT-814 Administered Twice Daily in Rats	IND 129492 eCTD 0128	No	Rat (oral)	R-14212	
GSK1144814C: 4-Week Oral Toxicity Study in Sprague Dawley Rats (GSK Study Number R27990)	IND 129492 eCTD 0002	Yes*	Rat (oral)	R-13595	GlaxoSmithKline, UK
GSK1144814A: A 13-week Oral Gavage Toxicity Study in the Rat	IND 129492 eCTD 0002	Yes*	Rat (oral)	R-13596	(b) (4)
NT-814: 13-week Oral (Gavage) Toxicity Study in Rats with a 4-week Recovery Period	IND 129492 eCTD 0032	Yes**	Rat (oral)	R-13628 (as amended)	
NT-814: Toxicity and Male Fertility Study by Twice Daily Oral Gavage Administration to Sprague Dawley Rats for 26 Weeks	IND 129492 eCTD 0048,0055	Yes**,#	Rat (oral)	R-13894	
GSK1144814B: 4-day Oral Dose Range Toxicity Study in Cynomolgus Monkeys (GlaxoSmithKline Study No. D06377)	IND 129492 eCTD 0002	No$	Monkey (oral)	R-13580	GlaxoSmithKline, USA
GSK1144814C: 7-Day Oral Dose Range Toxicity Study in Cynomolgus Monkeys (GlaxoSmithKline Study No. D07179)	IND 129492 eCTD 0002	Yes*	Monkey (oral)	R-13627	GlaxoSmithKline, USA
GSK1144814A: 7-Day Oral Tolerability and Toxicokinetics Study in Female Cynomolgus Monkeys (GSK Study No. D08272)	IND 129492 eCTD 0002	No$	Monkey (oral)	R-13640	GlaxoSmithKline, UK

Repeat-Dose Toxicity Studies					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
NT-814: Maximum Tolerated Dose Study in the Cynomolgus Monkey by Oral (Gavage) Route	Could not be located in module 4.2.3.2 under IND 129492	No[$]	Monkey (oral)	R-13638	(b) (4)
GSK1144814C: 4-Week Oral Toxicity Study in Cynomolgus Monkeys	IND 129492 eCTD 0002	Yes*	Monkey (oral)	R-13639	GlaxoSmithKline, USA
GSK1144814A: A 13-week Oral Gavage Toxicity Study in the Cynomolgus Monkey	IND 129492 eCTD 0002	Yes*	Monkey (oral)	R-13629	(b) (4)
Final Report and 1st Amendment + 2nd Amendment NT-814: 13-week Toxicity Study in Cynomolgus Monkey by Oral (Gavage) Route	IND 129492 eCTD 0032	No[$]	Monkey (oral)	R-13612	
NT-814: Toxicity Study by Oral (Gavage) Administration to Cynomolgus Monkey for 39 Weeks	IND 129492 eCTD 0048,0055	Yes#	Monkey (oral)	R-13895	

[$] There is no documentation of these studies being reviewed.
* PT reviews under IND 129492 in DARRTS dated 01/30/2017.
** PT review under IND 129492 in DARRTS dated 10/19/2020 under the rat SPA (Carci) review.
# PT review under IND 129492 in DARRTS dated 08/25/2022 under the phase 3 protocol review.

Genotoxicity

Genotoxicity Studies: Parent Drug					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
GSK1144814C: Bacterial Mutation Assay (Ames Test) with Salmonella typhimurium and Escherichia coli	IND 129492 eCTD 002	Yes*	In vitro	R-13577	(b) (4)
GSK1144814C: In Vitro Mutation Assay with L5178Y Mouse Lymphoma Cells at the TK Locus	IND 129492 eCTD 002	Yes*	In vitro	R-13579	
GSK1144814C: Oral Bone Marrow Micronucleus Assay in Rats	IND 129492 eCTD 002	Yes*	Rat (oral)	R-13576	

Genotoxicity Studies: Metabolites					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
M27: Bacterial Reverse Mutation Assay	IND 129492 eCTD 0048	Yes**	In vitro	R-13888	(b) (4)
M27: In Vitro Human Lymphocyte Micronucleus Assay	IND 129492 eCTD 0048	Yes**	In vitro	R-13874	
M30/34: Bacterial Reverse Mutation Assay	IND 129492 eCTD 0048	Yes**	In vitro	R-13867	
M30/34: In Vitro Human Lymphocyte Micronucleus Assay	IND 129492 eCTD 0048	Yes**	In vitro	R-13866	
M18/21 Salmonella/Microsome Test	IND 129492 eCTD 0048	Yes**	In vitro	PH-42069	Bayer, Germany
M19/21 In Vitro Micronucleus Test With Chinese Hamster V79 Cells, Flow Cytometric Method	IND 129492 eCTD 0048	Yes**	In vitro	PH-42100	Bayer, Germany

* PT review under IND 129492 in DARRTS dated 10/19/2020 under the rat SPA (Carci) review
** PT reviews under IND 129492 in DARRTS dated 8/25/2022 under the phase 3 protocol review.

Carcinogenicity

Carcinogenicity Studies					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
A 2-Phase Toxicity and Toxicokinetic Study of NT-814 (BAY3427080) When Administered via Twice Daily Oral Gavage to RasH2 Mice in an Escalating Dose Design for Up to 21 Days (Phase I) or Twice Daily for 7 Days (Phase II)	IND 129492 eCTD 0078	Yes*	Transgenic mouse (oral)	R-14290	(b) (4)
A 3-Week Twice Daily Oral Gavage Toxicity and Toxicokinetic Study with NT-814 in RasH2 Mice	IND 129492 eCTD 0078	Yes*	Transgenic mouse (oral)	R-14213	
A 4-Week Toxicity and Toxicokinetic Study of BAY 3427080 When Administered Twice Daily via Oral Gavage to RasH2 Mice [Final Report Amendment]	IND 129492 eCTD 0078	Yes*	Transgenic mouse (oral)	R-14305	
A 4-Week Toxicity and Toxicokinetic Study of BAY 3427080 When Administered Twice Daily via Oral Gavage to RasH2 Mice	IND 129492 eCTD 0097	Yes*	Transgenic mouse (oral)	R-14411	Bayer, Germany
A 26-Week Carcinogenicity and Toxicokinetic Study of BAY 3427080 (NT-814) When Administered Twice Daily via Oral Gavage to Transgenic Mice	No	No	Transgenic mouse (oral)	B003184	(b) (4)
A 104-Week Twice Daily Oral Gavage Toxicokinetic and Carcinogenicity Study with NT-814 (BAY3427080) in Sprague Dawley Rats	No	No	Rat (oral)	B003186	

* PT under IND 129492 in DARRTS dated 12/13/2022 under mouse SPA (carci) review

Reproductive and Developmental Toxicity

Fertility and Early Embryonic Developmental Studies (Segment I)					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
GSK1144814: Oral Female Fertility and Early Embryonic Development Study in Rats (GSK Study No. G08291)	IND 129492 eCTD 0002	Yes*	Rabbit	R-13611	GSK, UK

Embryo-Fetal Developmental Studies (Segment II)					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
GSK1144814A: Oral Embryo Fetal Development Study in Rabbits (GlaxoSmithKline Study No. G09062)	IND 129492 eCTD 0002	Yes*	Rabbit	R-13597	GSK, UK
GSK1144814: Oral Dose Range Study in Female Rabbits	IND 129492 eCTD 0002	Yes*	Rabbit	R-13608	GSK, UK
GSK1144814A: Oral Embryo-Fetal Development Study in Rats (GlaxoSmithKline Study No. G08290)	IND 129492 eCTD 0002	Yes*	Rat	R-13610	GSK, UK
Oral Gavage Study with BAY 3427080 (NT814) in Pregnant Female Rabbits, Including Toxicokinetics	IND 129492 eCTD 0128	No	Rabbit	B002328	(b) (4)

* PT reviews under IND 129492 in DARRTS dated 08/02/2019

Pre- and postnatal Developmental Studies (Segment III)					
Study Title	**Previously Submitted**	**Previously Reviewed**	**Test System**	**Study No.**	**Testing Facility**
BAY 3427080: Oral Gavage Range-Finding Study of Pre- and Postnatal Development in the Rat (GLP)	No	No	Rat (oral)	B003162	(b) (4)
BAY 3427080: An Oral Gavage Study of Prenatal and Postnatal Development, Including Maternal Function in the Rat (GLP)	No	No	Rat (oral)	B003187	

Others

Study Title	Previously Submitted	Previously Reviewed	Test System	Study No.	Testing Facility
Mechanistic					
NT-814: Investigation of Muscle Disposition in Male Rats Following Oral Gavage Administration for 14 Days	IND 129492 eCTD 0128	No	Rat (oral)	R-13644	(b) (4)
Dependence (these studies are reviewed by CSS staff)					
Assessment of the Subjective Effects of Elinzanetant in Male Cynomolgus Monkeys in a Drug Discrimination Model	No	No	Cyno monkey (oral)	B003002	(b) (4)
Abuse Liability of Elinzanetant Administered Intravenously: Assessment of the Reinforcing Potential in Cynomolgus Monkeys Maintained to Self-Administer Cocaine	No	No	Cyno monkey (oral)	B003288	
Physical Dependence Liability of Elinzanetant in Male Cynomolgus Monkeys and an Assessment of Discontinuation Syndrome After Repeated Dose Treatments for 30 Days	No	No	Cyno monkey (oral)	B003013	
Metabolite: Repeat dose toxicity study					
M27: Toxicity Study by Daily 4 Week Intravenous Infusion and 4 Week Subcutaneous Administration to Sprague Dawley Rats	IND 129492 eCTD 0062	No	Rat (oral)	R-13999	(b) (4)
M27: Toxicity Study by Daily Oral Administration to Sprague Dawley Rats for 26 weeks	IND 129492 eCTD 0049	Yes*	Rat (oral)	R-13953	
Impurities					
4-Week Repeat Dose Systemic Toxicity Study in Wistar Rats with Once Daily Oral Administration by Gavage	IND 129492 eCTD 0062	No	Rat (oral)	PH-42298	Bayer, Germany
Single Dose Toxicokinetic Study in Wistar Rats with One Oral Administration by Gavage	IND 129492 eCTD 0062	No	Rat (oral)	PH-42303	Bayer, Germany
(b) (4) Bacterial Reverse Mutation Test	IND 129492 eCTD 0062	No	In-vitro	R-14064	(b) (4)
Final Report Salmonella/Microsome Test Preincubation Method	Could not be located in module 4.2.3.7.6 under IND 129492	No	In-vitro	B002884	Bayer, Germany

Study Title	Previously Submitted	Previously Reviewed	Test System	Study No.	Testing Facility
Final Report Salmonella/Microsome Test Preincubation Method	Could not be located under module 4.2.3.7.6 under IND 129492	No	In-vitro	B002889	Bayer, Germany
Final Report Salmonella/Microsome Test Preincubation Method	Could not be located under module 4.2.3.7.6 under IND 129492	No	In-vitro	B003093	Bayer, Germany
Phototoxicity					
NT-814: In Vitro Balb/c 3T3 Neutral Red Uptake Phototoxicity Assay	IND 129492 eCTD 0032	No	In-vitro	R-13578	(b) (4)
Environmental Assessment Nonclinical Studies are not listed here. Refer to module 4.2.3.7.7					

* PT reviews under IND 129492 in DARRTS dated 8/25/2022

3.2 Studies Not Reviewed

The analytical methods and validation reports (46 studies under NDA 219469) were not reviewed in detail during the NDA cycle.

3.3 Previous Reviews Referenced

Review	Reviewer (s)	Date in DARRTS	Notes
Under IND 129429			
PT review	Dr. Frederic Moulin	01/30/2017	30-day safety review (Monkey 7-day dose ranging, 4-week tox, 13-week tox studies reviewed)
PT memo	Dr. Frederic Moulin	03/18/2019	Phase 2b clinical protocol review
PT review	Dr. Frederic Moulin	08/02/2019	Phase 1 clinical protocol review (Reprotox: FEED female rat EFD rat and rabbit studies reviewed)
PT review	Dr. Frederic Moulin	10/19/2020	2-year rat carcinogenicity SPA Executive CAC Protocol Minutes for 2-year rat study attached
PT memo	Dr. Frederic Moulin	05/07/2021	EOP2 meeting review (major human metabolites identified)
PT memo	Dr. Andrea Benedict	05/12/2021	Phase 3 SPA-2 (Clinical): Memo for nonclinical deficiencies to be addressed prior to phase 3.
PT memo	Dr. Andrea Benedict	06/24/2021	Phase 3 SPA-2 (Clinical): Memo for nonclinical deficiencies (follow up advice)
PT review	Dr. Andrea Benedict	08/25/2022	Phase 3 clinical protocol review Nonclinical studies reviewed to support Phase 3 trials [26-week rat, 39-week monkey, M27 26-week rat, genetic toxicology for metabolites reviewed]

Review	Reviewer (s)	Date in DARRTS	Notes
Under IND 129429			
PT review	Dr. Leslie McKinney	12/13/2022	6-month transgenic (TgRAS) mouse carcinogenicity study SPA [dose ranging finding studies in wildtype and transgenic mice reviewed] Executive CAC Protocol Minutes for mice study attached
PT memo	Dr. Leslie McKinney	03/01/2023	Memo on 2-year rat carcinogenicity study termination, discussion on metabolite exposures in TgRAS mouse study
PT review	Dr. Edna Albuquerque, Dr. Pratistha Tamrakar, Dr. Sarah Lee	02/04/2025	Full review on 2-year rat and 6-month TgRAS mouse carcinogenicity studies with ECAC meeting minutes

4 Pharmacology

4.1 Primary Pharmacology

Three forms of elinzanetant [free base (BAY 3427080), hydrochloride (HCl) salt (BAY 3453656), and tosylate salt (BAY 3453651)] have been used in nonclinical studies.

The following associated synonyms are noted in some tables below and provided here for ease of reference.

- GSK1144814 or GSK1144814A: elinzanetant free base
- GSK1144814B: elinzanetant HCl
- GSK1144814C: tosylate salt

However, all doses and concentrations in the tables are expressed in terms of free base.

Mechanism of action

Primary PD Studies		
Study No.	**Study Aim**	**Findings**
In-Vitro Receptor Binding Assay Studies		
R-13857	Determination of the affinity of GSK 1144814 for NK1R/NK3R across species (gerbil, rat, guinea pig, baboon, or human) using radioligand assay	• GSK1144814B (HCl salt) displayed very high affinity for the human cloned NK1R (pKi = 10.15 ± 0.06), the baboon cloned NK1R (pKi = 9.91 ± 0.10) and gerbil and guinea pig striatal NK1Rs (pKi = 10.2 ± 0.03 and 9.91 ± 0.02, respectively). • GSK1144814B displayed a lower affinity for rat striatal NK1Rs (pKi = 8.40 ± 0.05) compared to NK1Rs of other species. • GSK1144814B displayed a lower affinity for the human cloned NK3R (pKi = 8.03 ± 0.03) as well as for gerbil and guinea pig cortical NK3Rs (pKi = 7.84 ± 0.14 and 7.48 ± 0.06, respectively) compared to NK1Rs in the same species.

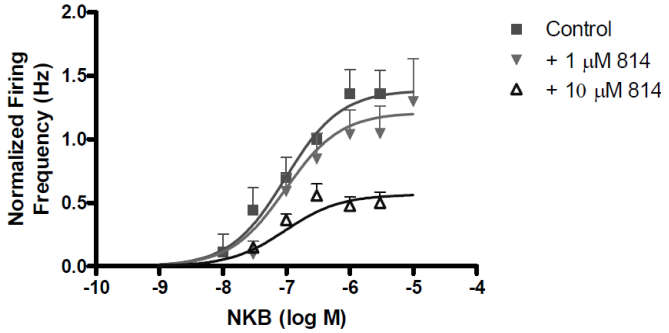
<table>
<tr><th colspan="3">Primary PD Studies</th></tr>
<tr><th>Study No.</th><th>Study Aim</th><th>Findings</th></tr>
<tr><td></td><td></td><td>Table 6: Binding affinity of elinzanetant [HCl salt] and GR-205171A [NK1R antagonist] at NK1R and NK3R across species.
<table><tr><th>Receptor/species</th><th colspan="2">pK_i (mean ± SEM (n ≥ 3))</th></tr><tr><th></th><th>GR-205171A[a]</th><th>Hydrochloride salt of elinzanetant</th></tr><tr><td>NK-1</td><td></td><td></td></tr><tr><td>Human</td><td>10.56 ± 0.16</td><td>10.15 ± 0.06</td></tr><tr><td>Baboon</td><td>10.97 ± 0.05</td><td>9.91 ± 0.10</td></tr><tr><td>Gerbil</td><td>10.8 ± 0.06[b]</td><td>10.2 ± 0.03</td></tr><tr><td>Guinea pig</td><td>10.9 ± 0.14[b]</td><td>9.91 ± 0.02</td></tr><tr><td>Rat</td><td>9.75 ± 0.13</td><td>8.40 ± 0.05</td></tr><tr><td>NK-3</td><td></td><td></td></tr><tr><td>Human</td><td>-</td><td>8.03 ± 0.03</td></tr><tr><td>Gerbil</td><td>-</td><td>7.84 ± 0.14</td></tr><tr><td>Guinea pig</td><td>-</td><td>7.48 ± 0.06</td></tr></table>a NK-1 receptor antagonist tool compound for comparison (vofopitant dihydrochloride)
b pK_i value derived from saturation analysis
Source: Module 2.6.2 (Pharmacology written summary)</td></tr>
<tr><td>R-13886</td><td>Determination of the affinity of GSK 1144814 at native NK1R/NK3R across species (gerbil, guinea pig and human striatal NK1Rs) using radioligand assay</td><td>• GSK1144814 (free form) displayed high affinity for gerbil, guinea pig and human striatal NK1Rs (pKi = 8.90 ± 0.06, 8.89 ± 0.01 and 8.71 ± 0.08, respectively)
• Lower affinity for gerbil and guinea pig cortical NK3Rs (pKi = 8.22 ± 0.04 and 7.83 ± 0.02, respectively)

Table 7: Binding affinity of elinzanetant and GR-205171A [NK1R antagonist] at NK1Rs and NK3Rs across species.
<table><tr><th>Receptor/species</th><th colspan="3">pK_i (mean ± SEM (n ≥ 3))</th></tr><tr><th></th><th>GR-205171A[a]</th><th>Elinzanetant</th><th>Hydrochloride salt of elinzanetant</th></tr><tr><td>NK-1</td><td></td><td></td><td></td></tr><tr><td>Human</td><td>10.70 ± 0.10</td><td>8.71 ± 0.08</td><td>-</td></tr><tr><td>Gerbil</td><td>10.81 ± 0.06</td><td>8.95 ± 0.09</td><td>8.85 ± 0.08</td></tr><tr><td>Guinea pig</td><td>11.06 ± 0.02</td><td>8.89 ± 0.01</td><td>-</td></tr><tr><td>NK-3</td><td></td><td></td><td></td></tr><tr><td>Gerbil</td><td>≤ 6.00</td><td>8.22 ± 0.04</td><td>-</td></tr><tr><td>Guinea pig</td><td>≤ 6.00</td><td>7.83 ± 0.02</td><td>-</td></tr></table>a NK-1 receptor antagonist tool compound for comparison (vofopitant dihydrochloride)
Source: Module 2.6.2 (Pharmacology written summary)</td></tr>
<tr><td>R-13699</td><td>Saturation binding studies at human NK1R (hNK1R) stably expressed in Chinese Hamster Ovary (CHO) cells</td><td>• Elinzanetant displays non-competitive antagonism at hNK1.
• Statistically significant decrease of the maximal binding (B_{max}) of [^{3}H]-substance P [NK1R agonist] (P<0.05) in the presence of unlabeled GSK1144814 was seen at 6 nM and 10 nM elinzanetant, but there was no statistically significant variation of the Kd for NK1R.</td></tr>
<tr><td>R-13881</td><td>Determination of the effect of the use of final DMSO concentrations <0.01% or 1% on the measured affinity of GSK 1144814 for human recombinant NK1R and NK3R.</td><td>• Total and specific binding levels were not significantly altered at the higher 1% DMSO concentration.
• GSK1144814 has high affinity for human recombinant NK1R and NK3R, and the affinity for NK1R is approximately 5- to 7-fold higher than that for NK3R.</td></tr>
</table>

<table>
<tr><th colspan="3">Primary PD Studies</th></tr>
<tr><th>Study No.</th><th>Study Aim</th><th>Findings</th></tr>
<tr><td>R-13884</td><td>Receptor binding competition assay using free base form and HCl form of GSK1144814</td><td>• Strong affinity for NK1R and NK3R, with mean pKi values at 9.3 and 8.8, respectively.
• No significant difference in potencies between the two salt forms of GSK1144814.
• Affinity for NK2R was much lower with a mean pKi = 6.0.</td></tr>
<tr><td colspan="3">In-Vitro Functional assessments</td></tr>
<tr><td>R-13859</td><td>Antagonist activity of GSK1144814B at the human cloned NK1R and at human, marmoset and rat cloned NK3Rs has been assessed using an inositol phosphate scintillation proximity assay.</td><td>Elinzanetant exhibited:
• Potent, non-surmountable antagonist profiles at the human cloned NK1R (pKB = 9.02 ± 0.07) and NK3R (pKB = 8.20 ± 0.07)
• Potent non-surmountable antagonism at the marmoset NK3R (pKB = 8.74 ± 0.17)
• Surmountable antagonist profile at the rat NK3R with a reduced potency (pA2 = 6.77 ± 0.06) compared to that at the human NK3R.

Table 8: Summary of pKB values for elinzanetant (HCL salt) at the human cloned NK1R and human, marmoset and rat cloned NK3R.
<table><tr><th>Species</th><th colspan="2">pK_B or pA_2 (mean ± SEM)</th></tr><tr><th></th><th>NK-1</th><th>NK-3</th></tr><tr><td>Human</td><td>9.02 ± 0.07</td><td>8.17 ± 0.07</td></tr><tr><td>Marmoset</td><td>-</td><td>8.74 ± 0.17</td></tr><tr><td>Rat</td><td>-</td><td>6.77 ± 0.06</td></tr></table>NK: neurokinin; pA_2: potency of a competitive reversible antagonist; pK_B: -log of K_B with K_B is the binding constant, i.e., a unit for functional antagonism, SEM: standard error of the mean.

Source: Module 2.6.2 (Pharmacology written summary)</td></tr>
<tr><td>R-13879</td><td>Functional activity of GSK1144814 HCl and free base at endogenous human NK1R and at human and guinea pig NK3R.</td><td>Elinzanetant exhibited:
• Non-surmountable human NK1R antagonist profile with an apparent pKB of 9.1 ± 0.13 (calculated using an operational model for non-competitive antagonism)
• Non-surmountable antagonist profile at both human and guinea pig NK3Rs.</td></tr>
</table>

Primary PD Studies		
Study No.	**Study Aim**	**Findings**
R-13877	To determine if GSK1144814 was an antagonist at NK3Rs in the guinea pig its effects on neurokinin B (NKB)-induced cell firing in the medial habenula (mHb)	• Elinzanetant (1 & 10 µM) produced a decrease in the maximum response to the NK3R agonist neurokinin B (NKB). This finding is consistent with elinzanetant-induced unsurmountable inhibition of NK3Rs. • A significant reduction in the maximum NKB-induced response from 1.43 to 0.54 was observed in the presence of 10 µM elinzanetant. Figure 6: Effect of elinzanetant on NKB-induced neuronal firing in the guinea pig medial habenula  Data are expressed as mean ± SEM (n = 6 - 11 per group). Source: Figure extracted from study report R-13877 ***Reviewer's comments:*** ***1. The habenula is synaptically connected to brain regions such as the amygdala, which plays a central role in seizures, and the hippocampus, which is essential for cognitive processing (Norden et al. 2002).[5]*** ***2. The finding that elinzanetant inhibits neuronal excitability suggests that the seizures noted in some repeat-dose toxicity studies of elinzanetant-treated rats are unrelated to elinzanetant-induced NK3R inhibition.*** ***3. Elinzanetant-induced inhibition of NK3Rs in the habenula (and other brain regions involved in cognitive processing) could contribute to cognitive deficits noted in elinzanetant-treated human subjects.***

[5] Norden AD, Blumenfeld H. The role of subcortical structures in human epilepsy. Epilepsy Behav. 2002 Jun;3(3):219-231.

<table>
<tr><th colspan="3">Primary PD Studies</th></tr>
<tr><th>Study No.</th><th>Study Aim</th><th>Findings</th></tr>
<tr><td>R- 13858</td><td>NK1R, NK3R binding and functional assays for the primary metabolites of elinzanetant (M18/21, M27, and M30/34), and the minor metabolite (b) (4) (b) (4) M22 at human NK1R (expressed in U373 cells) and NK3R (ectopically expressed in CHO cells)</td><td><u>M27:</u>
Ki (nM) of 1.1 (pKi of 8.96) and KB (nM) of 0.13 (pKB of 9.89) for human NK1R.
Ki (nM) of 11 (pKi of 7.96) and KB (nM) of 3.0 (pKB of 8.52) for human NK3R.
<u>M18/21:</u>
Ki (nM) of 0.24 (pKi of 9.62) and KB (nM) of 0.16 (pKB of 9.80) for human NK1R.
Ki (nM) of 13 (pKi of 7.89) and KB (nM) of 2.3 (pKB of 8.64) for human NK3R.
<u>M30/34:</u>
Ki (nM) of 1.7 (pKi of 8.77) and KB (nM) of 0.38 (pKB of 9.42) for human NK1R.
Ki (nM) of 5.0 (pKi of 8.30) and KB (nM) of 11 (pKB of 7.96) for human NK3R.
<u>M22:</u>
Ki (nM) of 1.1 (pKi of 8.96) and KB (nM) of 0.13 (pKB of 9.89) for human NK1R.
Ki (nM) of 4.2 (pKi of 8.38) and KB (nM) of 1.7 (pKB of 8.77) for human NK3R.</td></tr>
<tr><td>Summary of studies R-13857, R-13859, R- 13858, R-13884, R-13886 , R-13879</td><td>Binding activity studies at the human NK1R and NK3R for elinzanetant, its primary metabolites (M18/21, M27, and M30/34), and the minor metabolite (b) (4) (b) (4) M22</td><td>Results from binding studies show that elinzanetant, its primary metabolites (M18/21, M27, and M30/34), and the minor metabolite (b) (4) M22 have high affinity and activity at the human NK1 and NK3Rs.

Table 9: Binding affinity and functional antagonism of elinzanetant and its metabolites at human NK1R and NK3R.
<table>
<tr><th>Compound</th><th>Binding assay [pK_i]</th><th>Functional assay [pK_B]</th></tr>
<tr><td>Elinzanetant</td><td></td><td></td></tr>
<tr><td>NK-1R</td><td>8.71 – 10.15</td><td>9.02 – 9.1</td></tr>
<tr><td>NK-3R</td><td>8.03 - 8.8</td><td>8.17 – 8.5</td></tr>
<tr><td>Metabolite M18/21</td><td></td><td></td></tr>
<tr><td>NK-1R</td><td>9.62</td><td>9.80</td></tr>
<tr><td>NK-3R</td><td>7.89</td><td>8.64</td></tr>
<tr><td>Metabolite M22§</td><td></td><td></td></tr>
<tr><td>NK-1R</td><td>8.96</td><td>9.89</td></tr>
<tr><td>NK-3R</td><td>8.38</td><td>8.77</td></tr>
<tr><td>Metabolite M27</td><td></td><td></td></tr>
<tr><td>NK-1R</td><td>8.96</td><td>9.89</td></tr>
<tr><td>NK-3R</td><td>7.96</td><td>8.52</td></tr>
<tr><td>Metabolite M30/34</td><td></td><td></td></tr>
<tr><td>NK-1R</td><td>8.77</td><td>9.42</td></tr>
<tr><td>NK-3R</td><td>8.30</td><td>7.96</td></tr>
</table>
pK_B: -log of K_B, pK_i -log of K_i; NK: neurokinin; R: receptor.
(b) (4)</td></tr>
</table>

Primary PD Studies

Study No.	Study Aim	Findings
		Table 10: Binding and cellular agonist or antagonist effect of metabolites of elinzanetant, namely M27, M18/21, M30/34, and M22 to human (h) NK1R and human (h) NK3R.

Assay/metabolite	IC_{50} (nM)	K_i (nM)	K_B (nM)	EC_{50} (nM)	nH
Metabolite M18/21					
NK-1(*h*) (agonist radioligand)	0.55	0.24	-	-	1
NK-1(*h*) (antagonist effect)	1.1	-	0.16	-	-
NK-3(*h*) (antagonist effect)	26	-	2.3	-	-
NK-3(*h*) (antagonist radioligand)	23	13	-	-	1
Metabolite M22					
NK-1(*h*) (agonist radioligand)	2.4	1.1	-	-	1.8
NK-1(*h*) (antagonist effect)	0.92	-	0.13	-	-
NK-3(*h*) (antagonist effect)	19	-	1.7	-	-
NK-3(*h*) (antagonist radioligand)	7.7	4.2	-	-	0.8
Metabolite M27					
NK-1(*h*) (agonist radioligand)	2.6	1.1	-	-	1.4
NK-1(*h*) (antagonist effect)	0.88	-	0.13	-	-
NK-3(*h*) (antagonist effect)	33	-	3.0	-	-
NK-3(*h*) (antagonist radioligand)	20	11	-	-	1
Metabolite M30/34					
NK-1(*h*) (agonist radioligand)	3.9	1.7	-	-	1.2
NK-1(*h*) (antagonist effect)	2.6	-	0.38	-	-
NK-3(*h*) (antagonist effect)	120	-	11	-	-
NK-3(*h*) (antagonist radioligand)	9.3	5.0	-	-	1.3

EC_{50}: effective concentration at 50% inhibition; *(h)*: human; IC_{50}: concentration required for 50 % inhibition; K_B: binding constant; K_i: inhibition constant; nH: slope factor; NK: neurokinin.

Source : Tables extracted Module 2.6.2 (Pharmacology written summary)

Ex-vivo studies

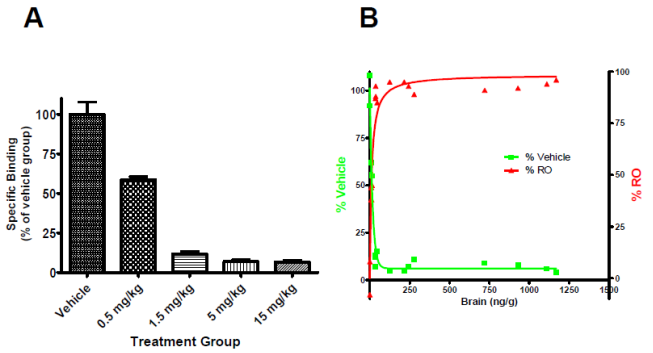
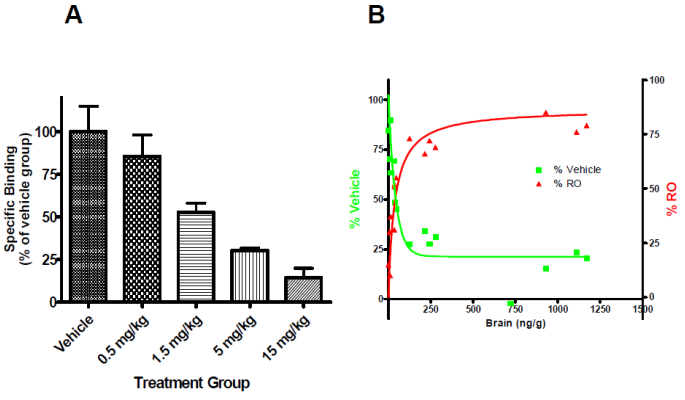
Receptor occupancy- autoradiography studies

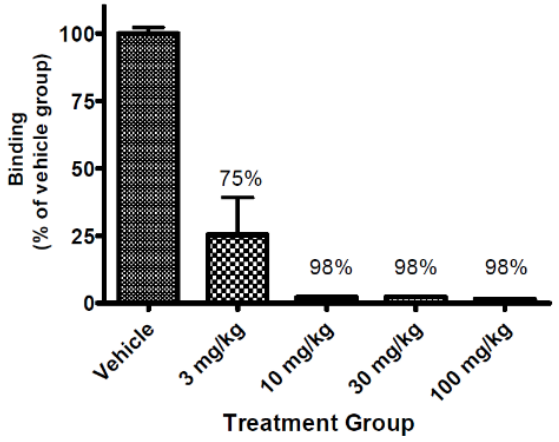
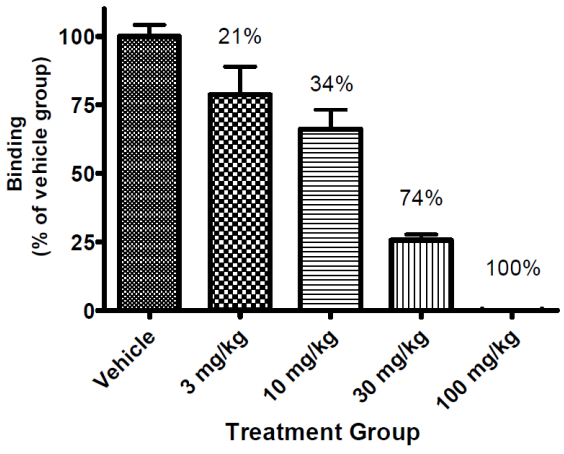
R-13860	To determine NK1 and NK3R occupancy in gerbil dorsal striatum and cingulate cortex.	• GSK1144814B penetrates the gerbil CNS following single oral dosing (1, 3, 10, and 30 mg/kg) and occupies both NK1R and NK3R. • NK1R occupancy by GSK1144814B was greater than NK3R occupancy. • Daily dosing (4-5 days) did not result in tissue accumulation or increased NK1R/NK3R occupancy. • There was no evidence of elinzanetant accumulation in brain or blood after single oral dosing. Table 11: NK1R and NK3R occupancy in gerbil striatum and cerebral cortex at 1 mg/kg oral dose.

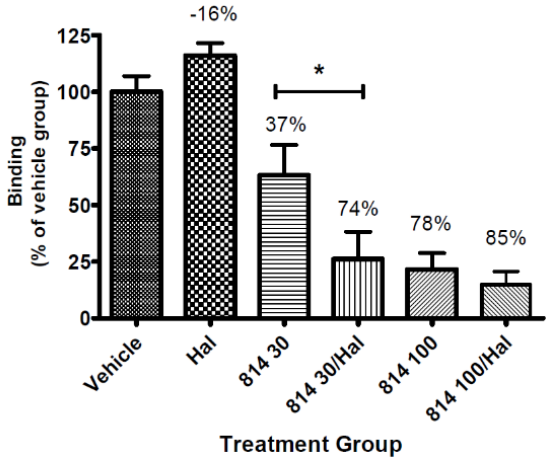
GSK1144814B (1.0 mg/kg, p.o.)	% NK_1 receptor occupancy	% NK_3 receptor occupancy (10 min incubation)	% NK_3 receptor occupancy (90 min incubation)	Blood Concentration (ng/mL) [range]	Total Brain Concentration (ng/g) [range]
Vehicle (single)	0 ± 3.7	0 ± 2.8	0 ± 6.9	-	-
GSK1144814B (single)	72.5 ± 10.3	31.4 ± 5.0	31.3 ± 8.4	<12 [<2 – 18]	<12 [<3 – 17]
vehicle (5 day)	0 ± 3.6	0 ± 5.2	0 ± 7.2	-	-
GSK1144814B (5 day)	67.6 ± 2.8	-3.1 ± 3.3	-10.2 ± 7.1	12 [6 – 23]	15 [8 – 23]
GSK1144814B (4 day + 1 day vehicle)	85.4 ± 2.6	11.0 ± 6.9	14.0 ± 6.4	<2 [<2]	<3 [<3]

Data are expressed as mean ± SEM (n=5 per group)

Source: Table from study report R-13860

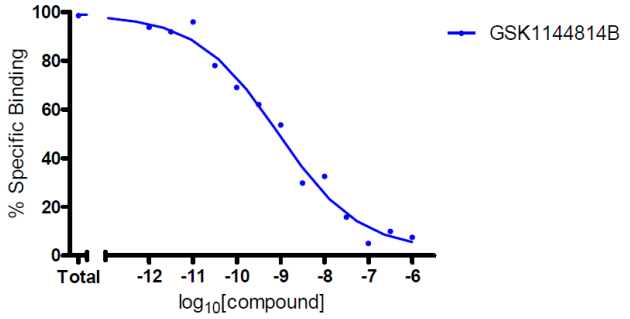
Primary PD Studies		
Study No.	**Study Aim**	**Findings**
R-13883	To determine NK1R occupancy in gerbil striatal (caudate putamen) and NK3R occupancy in cingulate cortex using radiolabeled NK1R antagonist, [^{3}H]GR205171 and radiolabeled NK3R agonist, [^{3}H]-senktide.	• GSK1144814B occupied striatal NK1R and cerebral cortical NK3R in a dose- and concentration-dependent manner. • IC_{50} values for GSK1144814 to displace NK1R binding of [^{3}H]GR205171 were 14 ng/g brain and 5-13 ng/mL blood (equivalent to free concentrations of <0.1 ng/g in brain and <0.1 ng/mL in blood). • IC_{50} values for GSK1144814 to displace the NK3R ligand senktide were not reported due to insufficient characterization of the dose-response curve. Figure 7: Ex-vivo NK1R occupancy by elinzanetant in gerbil striatum.  (A) Data represent mean + s.e.m. Specific binding of [^{3}H] GR205171 assayed following administration of 0.5-15mg/kg GSK1144814B relative to the vehicle-treated group (n=4 animals / treatment group) (B) *Ex vivo* NK_1 receptor occupancy, expressed both relative to the vehicle- treated group and as % receptor occupancy by GSK1144814B in gerbil striatum vs total brain exposure of GSK1144814B. Figure 8: Ex-vivo NK3R occupancy by elinzanetant in gerbil striatum.  (A) Data represent mean + s.e.m specific binding of [^{3}H]senktide assayed following administration of 0.5-15mg/kgGSK1144814B expressed relative to the vehicle-treated group (n=4 animals / treatment group) (B) *Ex vivo* NK_3 receptor occupancy,expressed both relative to the vehicle-treated group and % receptor occupancy) by GSK1144814B in gerbil striatum vs total brain exposure of GSK1144814B. Source: Figures extracted from study report R-13883.

R-13878	To determine the occupancy of NK1R and NK3R in guinea pig brain (striatum and frontal cerebral cortex) using autoradiography	• GSK1144814A (free base) occupied striatal NK1R and cerebral cortical NK3R in a dose- and concentration-dependent manner. • IC_{50} values for elinzanetant to displace [^{3}H]-GR205171 binding from NK1R were not reported due to insufficient characterization of the dose-response curve. • IC_{50} values for elinzanetant to displace [^{3}H]-senktide binding from NK3Rs were 83 ng/g brain and 58 ng/mL blood (equivalent to unbound concentrations of 0.04 ng/g brain and 0.4 ng/mL blood). Figure 9: Ex-vivo [^{3}H]-GR205171 binding at NK1Rs in guinea pig striatum.  Data represent mean ± s.e.m. (n=4 animals except for 100mg/kg group where n=3) expressed as % of vehicle binding of [^{3}H]-GR205171. Numbers above data bars are % RO (receptor occupancy) of GSK1144814A. Figure 10: Ex-vivo [^{3}H]-senktide binding at NK3Rs in guinea pig frontal cortex.  Data represent mean ± s.e.m. (n=4 animals except for 100mg/kg group where n=3) expressed as % of vehicle binding of [^{3}H]-Senktide. Numbers above data bars are % RO (receptor occupancy) of GSK1144814A. Source: Figures extracted from study report R-13878.

Primary PD Studies		
Study No.	**Study Aim**	**Findings**
R-13880	To determine the effect of haloperidol (D2 antagonist) on elinzanetant exposure and receptor occupancy (by ex-vivo autoradiography) in guinea pig brain.	• Treatment of guinea pigs with haloperidol (Hal) had no significant effect on NK1R occupancy by elinzanetant, and mean NK1R occupancy was >97% at all doses tested (30 mg/kg and 100 mg/kg). • Mean NK3R occupancy by elinzanetant at 30 and 100 mg/kg was 37% and 78% in vehicle-treated guinea pigs, respectively, and 74% and 85% in Hal-treated guinea pigs, respectively. The apparently higher NK3R occupancy in guinea pigs treated with Hal plus the lower dose of elinzanetant correlated with higher exposure of the Hal-treated animals to elinzanetant. • The data suggest that NK1R/NK3R occupancy by elinzanetant was not affected by the dopamine D2 receptor antagonist Hal. Figure 11: Ex-vivo [^{3}H]-senktide binding at NK3Rs in guinea pig frontal cerebral cortex.  Note# 814 = elinzantent; Hal= haloperidol Source: Study report R-13880

<table>
<tr><th colspan="3">Primary PD Studies</th></tr>
<tr><th>Study No.</th><th>Study Aim</th><th>Findings</th></tr>
<tr><td>R-13876</td><td>To assess elinzanetant binding to NK1R in human putamen.</td><td>GSK1144814B (HCl form) occupied NK1Rs in the human putamen in a concentration-dependent manner with a pKi of 9.44.

Figure 12: Evaluation of NK1R occupancy by elinzanetant in human putamen.

The non-specific binding values were subtracted from the total binding values to produce specific binding and expressed as % specific binding with respect to total. The data was analysed by one-site competition (variable slope) to directly estimate pKi which was determined to be 9.44.

Source: Study report R-13876</td></tr>
<tr><th colspan="3">In-vivo studies</th></tr>
<tr><td>R-13856</td><td>To determine the ability of GSK1144814B to reverse NK1R agonist (GR73632)-induced foot tapping behavior in male gerbils.</td><td>Oral GSK1144814B significantly inhibited GR73632-induced foot tapping behavior at all doses tested (ID_{50} = 1.36 mg/kg) in male gerbils.

Table 12: Effect of elinzanetant on GR72623-Induced Foot Tapping in the Mongolian Gerbil.

<table>
<tr><th>Treatment</th><th>Time spent foot tapping mean ± sem</th><th>Blood Concentration (ng/mL) [range]</th><th>Total Brain Concentration (ng/g) [range]</th></tr>
<tr><td>Vehicle</td><td>225.6 ± 12.5</td><td>-</td><td>-</td></tr>
<tr><td>GSK1144814B (1 mg/kg)</td><td>162.0 ± 29.0 *</td><td>6.4 [4 - 12]</td><td><15</td></tr>
<tr><td>GSK1144814B (3 mg/kg)</td><td>43.7 ± 19.7 **</td><td>22 [9 – 40]</td><td>35 [16 – 55]</td></tr>
<tr><td>GSK1144814B (10 mg/kg)</td><td>0.8 ± 0.9 **</td><td>87 [67 – 123]</td><td>126 [75 – 171]</td></tr>
</table>
*=p<0.05, **=p<0.01; Dunn's planned comparisons;
Source: Study report R-13856</td></tr>
</table>

<table>
<tr><th colspan="3">Primary PD Studies</th></tr>
<tr><th>Study No.</th><th>Study Aim</th><th>Findings</th></tr>
<tr><td>R-13862</td><td>To determine reversal of foot tapping induced by the NK1R agonist GR73632 in male gerbils.</td><td>

GSK1144814B significantly inhibited GR73632-induced foot tapping behavior [maintained up to 72 h post dose].
Cerebral cortical NK3R occupancy by GSK1144814B was shown to decline from ~90% to 39% by 24 h following dosing with no occupancy detectable by 48 h after administration.
GSK1144814B exhibits more prolonged efficacy in the gerbil foot-tapping paradigm than GR205171A.

Table 13: Temporal profile of the effects of elinzanetant (HCl form) on GR73632-induced foot tapping in the mongolian gerbil.
<table>
<tr><th>Treatment</th><th>Time post dose</th><th>Time spent foot tapping (s)</th><th>% Inhibition of Foot Tapping</th></tr>
<tr><td>Vehicle</td><td>1 hour</td><td>231 ± 20</td><td>-</td></tr>
<tr><td>Vehicle</td><td>24 hour</td><td>255 ± 9</td><td>-</td></tr>
<tr><td>Vehicle</td><td>48 hour</td><td>223 ± 23</td><td>-</td></tr>
<tr><td>Vehicle</td><td>72 hour</td><td>282 ± 5</td><td>-</td></tr>
<tr><td>GSK1144814B (10 mg/kg)</td><td>1 hour</td><td>0 ± 0</td><td>100 ± 0</td></tr>
<tr><td>GSK1144814B (10 mg/kg)</td><td>24 hours</td><td>0 ± 0</td><td>100 ± 0</td></tr>
<tr><td>GSK1144814B (10 mg/kg)</td><td>48 hours</td><td>23 ± 9</td><td>90 ± 4</td></tr>
<tr><td>GSK1144814B (10 mg/kg)</td><td>72 hours</td><td>194 ± 30</td><td>31 ± 10</td></tr>
<tr><td>GR205171A (1 mg/kg)</td><td>1 hour</td><td>0 ± 0</td><td>100 ± 0</td></tr>
<tr><td>GR205171A (1 mg/kg)</td><td>24 hours</td><td>264 ± 7</td><td>- 4 ± 3</td></tr>
<tr><td>GR205171A (1 mg/kg)</td><td>48 hours</td><td>232 ± 30</td><td>- 17 ± 13</td></tr>
<tr><td>GR205171A (1 mg/kg)</td><td>72 hours</td><td>273 ± 8</td><td>3 ± 3</td></tr>
</table>
Data shown is mean ± sem. n=7-10 per treatment group

Source: Table from study report R-13862
</td></tr>
</table>

<table>
<tr><th colspan="3">Primary PD Studies</th></tr>
<tr><th>Study No.</th><th>Study Aim</th><th>Findings</th></tr>
<tr><td>R-13863</td><td>To determine the in-vivo effect of GSK1144814B on senktide (potent NK3R agonist)-induced wet-dog shake behavior in guinea pigs.</td><td>GSK1144814B significantly reversed senktide-induced wet-dog shake behavior following 8.5 and 25.5 mg/kg doses indicating central NK3R antagonist activity.

Table 14: Effect of elinzanetant (HCl form) to reduce senktide-induced wet-dog shake behavior.
<table><tr><th>Treatment</th><th>Wet Dog Shakes (± sem)</th><th>Blood Concentration (ng/mL) [range]</th><th>Total Brain Concentration (ng/g) [range]</th></tr><tr><td>Vehicle (n=11)</td><td>43.7 ± 2.0</td><td>-</td><td>-</td></tr><tr><td>GSK172981A 30 mg/kg (n=10)</td><td>18.1 ± 3.0***</td><td>643 [368 – 1061]</td><td>737 [300 – 1228]</td></tr><tr><td>GSK1144814B 2.6 mg/kg (n=12)</td><td>37.2 ± 2.3</td><td>17 [<5 – 20]</td><td>12 [<3 – 19]</td></tr><tr><td>GSK1144814B 8.5 mg/kg (n=9)</td><td>31.7 ± 2.0*</td><td>27 [10 – 71]</td><td>28 [9 – 53]</td></tr><tr><td>GSK1144814B 25.5 mg/kg (n=12)</td><td>30.0 ± 3.9**</td><td>91 [34 – 192]</td><td>92 [25 – 161]</td></tr></table>* = p<0.05;
** = p<0.01, *** = p<0.001 vs. vehicle; Repeated measures GLM, followed by planned comparisons.

Source: Table from study report R-13863</td></tr>
<tr><td>R-13861</td><td>In vivo microdialysis study to investigate the effects of GSK1144814B (3, 10, 30 mg/kg, i.p.) on extracellular levels of dopamine (DA), noradrenaline (NA) and serotonin (5-HT) in the prefrontal cortex (PFC) and dorsal hippocampus (DH) of moving guinea pigs.</td><td>• GSK1144814B modulates noradrenergic (NA) and serotonergic (5-HT) levels in the guinea pig forebrain.
• GSK1144814B produced significant increases in NA levels in the prefrontal cortex (PFC) at 10 mg/kg ($P < 0.05$) and 30 mg/kg ($P < 0.001$) and in the dorsal hippocampus (DH) at 3 mg/kg ($P < 0.01$) and 30 mg/kg ($P < 0.001$).
• Administration of GSK1144814B at 10 mg/kg produced a significant increase ($P < 0.001$) of extracellular levels of 5-HT in the DH.</td></tr>
<tr><td>R-13882</td><td>To investigate effects on the amphetamine and haloperidol-induced dopamine (DA) efflux in the guinea pig nucleus accumbens (NAcc).</td><td>• The effect of elinzanetant on levels of dopamine (DA) in the nucleus accumbens (NAcc) of the guinea pig was assessed following pre-treatment of GSK1144814B (10, 30 or 100 mg/kg, i.p.) and administration of haloperidol (0.5 mg/kg, i.p.) or amphetamine (0.5 mg/kg, i.p.).
• At 30 mg/kg, GSK11144814B alone had no effects on basal extracellular levels of DA in the absence of amphetamine or haloperidol.
• Pre-treatment with GSK11144814B up to 100 mg/kg did not affect the amphetamine- or haloperidol-induced increases in DA efflux.

Note#: Based on this study, the Applicant concluded that elinzanetant does not modulate basal or stimulated dopaminergic function.</td></tr>
</table>

Primary PD Studies		
Study No.	**Study Aim**	**Findings**
R-13885	Positron emission tomography (PET) study to determine the in-vivo NK1R occupancy following single IV dose in baboon.	• GSK-1144814 (free base) was administered as an IV infusion to baboons over 60 minutes, at doses between 0.01 and 2 mg/kg (n = 2). • Receptor occupancy was dose dependent with estimates of ED_{50} (administered dose leading to 50% occupancy of the NK1R) of 0.21 mg/kg and EC_{50} (plasma concentration associated with 50% occupancy of the NK1R) of 9.93 ng/ml. [also refer to studies under distribution]

4.2 Secondary Pharmacology

Secondary PD Studies		
Study No	**Study Aim**	**Key Findings**
In-vitro Studies of Parent Compound		
R-13669	(b) (4) screen for a wide range of target classes of in-vitro receptors, ion channels, transporters, enzymes.	At a concentration of 1 µM, elinzanetant (HCl salt) was >100-fold more selective for the human NK3R and human NK1R versus 88 other non-tachykinin human receptors, enzymes, and transporters.
R-13674	Selectivity profile investigation	Concentrations of 25 – 100 µM (free base form) were assessed for activity in 44 molecular target assays. No significant findings were noted. Only inactive or weakly active signals [IC_{50} >10µM] were detected in a number of assays.
R-14343	Selectivity screen	Concentrations up to 30 µM (free base form) were tested. IC_{50} =22.5 µM was noted for the estrogen receptor α (ERα), while a lower value [IC_{50} = 0.64 µM] was noted for PR-B.
R-14344	Selectivity screen	At concentrations up to 30 µM (free base form), no relevant findings for estrogen receptor coactivator or progesterone receptor coactivator in the functional assay.
R-14381	Selectivity screen	No significant results for monoamine oxidase MAO-A, dopamine D1, and opiate δ1 (OP1, DOP) up to 10 µM (free base form). IC_{50} values could not be calculated.
B002819	To determine effects of elinzanetant on dopamine transporter uptake assay in rat striatum synaptosomes	IC_{50}: 3.6 µM
B002836	Functional dopamine assay (agonist and antagonist screen) in cAMP Hunter cell lines	rDRD1 IC_{50}: 11.37 µM rDRD2L EC_{50}: 12.34 µM rDRD2S EC_{50}: 7.43 µM rDRD (isoforms): rat dopamine receptors D1, D2L and D2S

<table>
<tr><th colspan="3">Secondary PD Studies</th></tr>
<tr><th>Study No</th><th>Study Aim</th><th>Key Findings</th></tr>
<tr><td colspan="3">In-vitro Studies of Metabolites</td></tr>
<tr><td>R-14015</td><td rowspan="2">Selectivity screen for metabolite <u>M27</u> (referred as SCG-2529 or CHH080-2021 in the study report)</td><td>IC_{50}= 1.34 µM for inhibition of radioligand binding to PR-B.</td></tr>
<tr><td>R-14017</td><td>M27@10 µM: 84% inhibition of radioligand binding to PR-B.</td></tr>
<tr><td>R-14016</td><td rowspan="2">Selectivity screen for metabolite <u>M30/M34</u></td><td>IC_{50}: 16.5 µM for ERα
IC_{50}: 1.20 µM for PR-B</td></tr>
<tr><td>R-14018</td><td>@10 µM, the metabolites inhibited radioligand binding to:
Adrenergic α2C receptors = 55%
Estrogen ERα = 63%
$GABA_A$ receptor-chloride channels, TBOB ([^{3}H]t-butyl bicyclo-orthobenzoate) = 55%
Glucocorticoid receptors = 68%
PR-B = 83%
Transporter, Norepinephrine (NET) = 64%</td></tr>
<tr><td>R-14019</td><td rowspan="2">Selectivity screens for metabolite <u>M18/M21</u></td><td>M18/M21@10 µM: 80% inhibition of radioligand binding to PR-B</td></tr>
<tr><td>R-14020</td><td>IC_{50}: 1.69 µM for PR-B</td></tr>
<tr><td>Summary of studies R-14015, R-14016, R-14017, R-14018, R-14019, R-14020</td><td></td><td>Table 15: Results of radioligand binding/functional assays of elinzanetant metabolites.
<table>
<tr><th></th><th>Test concentration</th><th>M27</th><th>M30/34</th><th>M18/21</th></tr>
<tr><td>IC_{50} in µM</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Progesterone PR-B</td><td>≤30 µM</td><td>1.34 µM</td><td>1.20 µM</td><td>1.69 µM</td></tr>
<tr><td>Estrogen ER</td><td>≤30 µM</td><td>-</td><td>16.5 µM</td><td>-</td></tr>
<tr><td>%Inhibition</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Progesterone PR-B</td><td>10 µM</td><td>84%</td><td>83%</td><td>80%</td></tr>
<tr><td>Estrogen ER</td><td>10 µM</td><td>-</td><td>63%</td><td>-</td></tr>
<tr><td>Adrenergic α2C</td><td>10 µM</td><td>-</td><td>55%</td><td>-</td></tr>
<tr><td>$GABA_A$, Chloride Channel, TBOB</td><td>10 µM</td><td>-</td><td>55%</td><td>-</td></tr>
<tr><td>Glucocorticoid</td><td>10 µM</td><td>-</td><td>68%</td><td>-</td></tr>
<tr><td>Transporter, Norepinephrine (NET)</td><td>10 µM</td><td>-</td><td>64%</td><td>-</td></tr>
</table>
Source: Module 2.6.2 (Pharmacology written summary)

<u>Reviewer's comment</u>: The data demonstrate a potential for elinzanetant metabolites to inhibit PR-B. As discussed later in this review, inhibition of these receptors may be an important determinant of the uterine carcinogenic signals detected in rats treated orally with elinzanetant doses ≥60 mg/kg/day for 104 weeks. It could also contribute to the convulsions observed in a repeat-dose toxicity study in Harlan Sprague-Dawley (SD:Hsd) rats treated with elinzanetant doses ≥20 mg/kg/day for 13 weeks and in the carcinogenicity study in female SD:Hsd rats treated with elinzanetant doses ≥60 mg/kg/day for 104 weeks.</td></tr>
</table>

Secondary PD Studies		
Study No	**Study Aim**	**Key Findings**
In-vivo studies: The following studies were conducted to demonstrate that the anxiolytic and antipsychotic profile and working memory improvement is not relevant to the current proposed indication. A brief summary of these studies is provided below.		
R-13680	Marmoset human threat test	Study noted anxiolytic-like profile at 10 and 30 mg/kg. Elinzanetant HCl form was used.
R-13671	Working memory study in aged Rhesus monkeys	Study noted distractor delayed matching to sample (DMTS) Task: trend towards increase in accuracy at doses ranging between 1.27 and 38 mg/kg. Elinzanetant tosylate form was used.
R-13672	Attentive processing study in rhesus monkeys	
R-13673	Amphetamine-induced rearing with RO by autoradiography (PK: blood and brain) in guinea pig to study antipsychotic potential	Elinzanetant (9.5, 29, and 95 mg/kg i.p.) produced a dose-related inhibition of amphetamine-induced rearing and thus considered to have antipsychotic potential and can modulate dopaminergic function. Elinzanetant HCl form was used.
R-13700	Cocaine drug discrimination and self-administration study in monkeys.	Oral doses of up to 56 mg/kg elinzanetant produced no marked or statistically significant effects against cocaine administration. Elinzanetant tosylate form was used.

4.3 Safety Pharmacology

Safety Pharmacology Studies	
Study No. & Design	**Study Findings**
In-Vivo and In-Vitro Studies on the Parent Compound	
R-13668 / 20080011PGRB (GLP) Central Nervous System (CNS), Crl: CD (SD) rats, male, oral gavage, single dose @ 0, 5, 25, 100 mg/kg elinzanetant (GSK1144814 tosylate salt) Endpoints: General activity, behavior, and body temperature	Clinical signs: • 25 mg/kg increased defecation and urination at 4 and 24 h, respectively. • 100 mg/kg increased response to finger approach and rearing at 24 h • No seizures, tremors, or twitches. • No effect on body temperature. NOAEL = 100 mg/kg/day (23X), based on $C_{max,\ unbound}$ = 98 µg/L for male rats (on Day 1; Study No. R-13595), when compared to human unbound fraction $C_{max,\ unbound}$ = 4.3 µg/L at 120 mg QD, obtained from Study No B002427. Note: R-13595: 4-week study uses CRL SD rats with the tosylate salt and has TK data for Day 1 and 28.

Reference ID: 5623053

R-13675 (GLP) Amendment 1 Cardiovascular System (CVS), in vitro hERG assay (1.91 µM, 1.27 µg/mL, limit of solubility in 0.3 % v/v DMSO:bath solution) Endpoint: % of hERG current blockade compared to vehicle	• No inhibition of hERG tail current up to the maximum soluble concentration of elinzanetant (1.91 µM, 1.27 µg/mL). MOE (0.89X; 295X), based on total C_{max} = 1423 µg/L and unbound fraction $C_{max, unbound}$ = 4.3 µg/L at MRHD of 120 mg QD, obtained from Study No. B002427.
R-13679 (non-GLP) CVS, in vitro hERG assay (0.0228 – 50 µM) Endpoint: pIC_{50} of hERG current blockade	IC_{50} = 31 µM (20,728 µg/L). MOE (14.6X; 4,820X), based on total C_{max} = 1423 µg/L and $C_{max, unbound}$ = 4.3 µg/L at MRHD of 120 mg QD, obtained from Study No. B002427.
R-13670 (GLP) CVS, monkey, male, oral gavage @ 0, 6, 20, 60 mg/kg, single dose, random dose level (4x4 crossover design), 7-day washout between dosing Endpoints: General activity, body temperature, blood pressure, heart rate and ECG. Tosylate salt (BAY 3453651)	Observations: • 60 mg/kg: increase in heart rate (12 bpm/ +15%), decrease in body temperature (0.63°C) • 20 mg/kg decrease in body temperature (0.32°C) • No effect on arterial pressure or ECG parameters. NOAEL = 20 mg/kg/day (4X) based on $C_{max, unbound}$ = 18 µg/L for male monkeys (on Day 1) obtained from the 4-week monkey study (Study No. R-13639, when compared to human unbound fraction $C_{max, unbound}$ = 4.3 µg/L at the MRHD of 120 mg QD, obtained from Study No. B002427.
R-13676 (GLP) Respiratory, Crl: CD (SD) rats, male, oral gavage @ 0, 5, 25, 100 mg/kg, single dose, random dose level (4x4 crossover design), 7-day washout between dosing elinzanetant (tosylate salt, BAY 3453651) Endpoints: Tidal volume, minute volume, rate of respiration, airway resistance, and body temperature	• No change in tidal volume, respiratory rate, minute volume, pulmonary resistance, or body temperature NOAEL = 100 mg/kg/day (23X), based on $C_{max, unbound}$ = 98 µg/L for male rats (on Day 1; Study No. R-13595), when compared to human unbound fraction $C_{max, unbound}$ = 4.3 µg/L at the MRHD of 120 mg QD, obtained from Study No B002427. Note: R-13595: 4-week study uses CRL SD rats with the tosylate salt and has TK data for Day 1 and 28.
In-vitro Safety Pharmacology on Metabolites	
PH-42243 / T105350-04 In-vitro assay on human cardiac ion channels in recombinant cell lines with BAY 3462932 (M27).	• No inhibitory effect on the hERG potassium channel, hNav1.5 sodium channel, thCav1.2 L-type calcium channel, hKvLQT1 potassium channel, hKv4.3 potassium channel, and hKir2.1 potassium channel with M27, M30/34 or M18/21.
PH-42244 /T105351-5	

In-vitro assay on human cardiac ion channels in recombinant cell lines with BAY 3462932 (M30/34)	
PH-42245 /T105352-6 In-vitro assay on human cardiac ion channels in recombinant cell lines with BAY 3462932 (M18/21)	

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

PK Studies: Absorption	
Study No & Design	**Study Findings**
R-13630 wild-type RasH2 mouse, oral gavage @ 10 mg/kg, single dose	• Elinzanetant was absorbed rapidly in wild-type RasH2 mouse. M27 (metabolite) and appeared in plasma over a comparable duration, with median T_{max} values of 0.5 h for both the parent and metabolite. • Exposure to the parent compound appeared sufficient (mean C_{max} = 225 ng/mL and AUC_{0-24} = 2,530 ng.h/mL) whereas exposure to metabolite M27 was low (mean C_{max} = 9.18 ng/mL and AUC_{0-24} = 14.4 ng.h/mL). • Mean half-life ($t_{1/2}$) value of parent was 8.2 h, and that of metabolite could not be calculated.
R-13621 Rat, oral gavage @ 3 mg/kg and IV (infusion) @ 1 mg/kg (elinzanetant) Dog, IV (bolus) @ 1 mg/kg and oral @ 3 mg/kg Marmoset, IV (bolus)@ 3 mg/kg and oral@ 10 mg/kg Monkey, IV (infusion) @ 3 mg/kg and oral @ 6 mg/kg	Key findings: • Rat: clearance was low; plasma elimination terminal half-life of the unchanged compound was long with 6.3 h and 7.8 h in male and female rats. • Dog: clearance was high in female Beagle dogs (1.8 L/(h·kg)), with short terminal half-life ($t_{1/2}$ = 1.7 h). • Marmoset: clearance was noted to be moderate to high ($t_{1/2}$ = 13 h). • Monkey: short terminal half-life ($t_{1/2}$ = 1.8 h). • Vss (volume of distribution at steady state) was high in all species ranging from 3.0 L/kg to 11.0 L/kg. • Low to moderate bioavailability [dog = 19%, monkey = 19%, marmoset = 34%, rat = 47% (female), >77% (male)]. • GSK1144814 was brain penetrant in the mouse, rat, and monkey with brain:blood ratios of 0.5:1, 0.1:1 to 0.5:1, and 0.6:1 respectively [also refer to distribution summary]. • Plasma protein binding was very high across all preclinical species tested (99.5 to 99.9%) and higher in human (>99.9%). Binding to brain tissue was also very high across all species tested (≥99.95%).
R-13622 Rat, IV (slow bolus) @ 0.03, 0.1 and 0.3 mg/kg (M27), single dose	• M27 was well tolerated. • Exposures to M27 [mean C_{max} and AUC_{0-t} values] increased non-linearly with increasing doses, and exposure increases were greater than dose proportional. • Mean Vss values increased with the increase in dose and ranged from 1460 to 1780 mL/kg and were greater than the total body of

PK Studies: Absorption

Study No & Design | **Study Findings**

water in rats (668 mL/kg), indicating that M27 is highly distributed in tissues.

Table 16: PK of M27 in rats post intravenous administration

Species		Rat	Rat	Rat
Sex		Female	Female	Female
Dose	[mg/kg]	0.03	0.1	0.3
AUC	[µg·h/L]	11.7	67.4	242
AUC_{norm}	[kg·h/L]	0.390	0.674	0.807
CL_{blood}	[L/(h·kg)]	2.60	1.55	1.25
V_{ss}	[L/kg]	1.46	1.52	1.87
$t_{1/2}$	[h]	0.403	0.797	1.26

Source: Module 2.6.4 Pharmacokinetic written summary

Summary of studies R-13630, R-13620 and R-13621

Summary of PK in different species after oral administration.

Table 17: PK of elinzanetant after oral administration to mice, rats, rabbits, dogs, and monkeys.

Species		Mouse	Rat	Rat	Rabbit	Dog	Marmoset monkey	Cynomolgus monkey
Sex		Male	Male	Female	Female	Male	Male	Male
Dose	[mg/kg]	10	3	3	140 (70 BID)	3	10	6
AUC	[µg·h/L]	2910	1918	3181	n.r.[b]	331	1595	1006
AUC_{norm}	[kg·h/L]	0.291	0.64	1.06	n.r.[b]	0.11	0.16	0.17
C_{max}	[µg/L]	225	190	436	964	145	281	275
$C_{max,norm}$	[kg/L]	0.0225	0.063	0.14	0.00689[c]	0.048	0.028	0.046
t_{max}	[h]	0.50	2.0	1.0	9.48	1.0	0.75	0.5
$t_{1/2}$	[h]	8.20	5.9	7.5	n.r.[b]	2.7	13	6.7
F[a]	[%]	n.a.[d]	47	77	n.a.[d]	19	34	19

a = related to the mean AUC 1 mg/kg iv of rat (AUC_{norm}, mean = 1.36 kg·h/L, male and AUC_{norm}, mean = 0.94 kg·h/L, female), the AUC_{norm} 1 mg/kg iv of dog; the AUC_{norm} 3 mg/kg iv of Marmoset monkey, or the AUC_{norm} 3 mg/kg iv of Cynomolgus monkey
b = not reported, lack of adequate sampling during the elimination phase
c = C_{max}/D [1/L]
d = not applicable

Source: Module 2.6.4 Pharmacokinetic written summary

R-13620
Rabbit, oral @ 70 mg/kg BID, 8 h apart [140 mg/kg/day]

Note: death of one animal attributed to gavage error.

- Plasma concentrations of elinzanetant and M27 were variable but the dose was generally well tolerated.

TK (elinzanetant):

- Mean T_{max} = 9 h, C_{max} = 964 ng/mL, and AUC_{0-24} = 11600 ng*h/mL

TK (M27):

- Mean T_{max} = 9.3 h, C_{max} = 735 ng/mL, and AUC_{0-24} = 8880 ng*h/mL

R-13618

Monkey, oral @ 25 mg (soft gel capsule) @ 50 mg (hard-gelatin capsule) in a crossover study design

PK of two formulations of elinzanetant was investigated in monkeys.

- Oral exposure was higher based on mean C_{max} and mean $AUC_{(0-tlast)}$ and less variable for the soft gel capsule formulation as compared with that for the hard gelatin capsule formulation.

PK Studies: Absorption	
Study No & Design	**Study Findings**
	Table 18: PK of elinzanetant soft gel versus hard gel capsule.

Species		Cynomolgus monkey	
Sex		Female	
Formulation		Soft gel capsule	Hard gelatine capsule
Dose	[mg/animal]	25	50
AUC (0-t_{last})	[µg·h/L]	4372	2263
AUC(0-t_{last})/D	[h/L]	0.175	0.04
C_{max}	[µg/L]	1643	584
C_{max} /D	[1/L]	0.0656	0.117
t_{max}	[h]	2.00	3.67
$t_{1/2}$	[h]	3.77	2.30

Source: Module 2.6.4 Pharmacokinetic written summary

Distribution

PK Studies: Distribution	
Study No & Design	**Study Findings**
PH-42081 In vitro, protein binding assay [Transil®] with elinzanetant	• Plasma protein binding of elinzanetant was high in human, female SD rat, and female Cynomolgus monkey and moderate in female and male CD-1 mouse, male SD rat, female New Zealand rabbit, and female beagle dog. • The fu (fraction unbound) ranged between 0.272% in male human plasma and 4.66% in female New Zealand rabbit plasma. • Elinzanetant distributes more into plasma than the blood cells resulting in a Cb/Cp [blood-to-plasma concentration ratio] range of 0.574 to 0.663 in human blood and 0.6-0.7 in the animal species. • No concentration dependency seen in human blood and plasma. Table 19: Elinzanetant binding to plasma proteins of selected species (in vitro) and to in vitro matrices as well as blood to plasma concentration ratio (Cb/Cp).

Species / Matrix	Concentration [µg-eq/L]	f_u[a] [%]	C_b/C_p
Human (m)	711 - 6739	0.272	0.574
Human (f)	706 - 6268	0.332	0.663
CD-1 mouse (m)	982 - 10735	2.30	0.6[b]
CD-1 mouse (f)	1005 - 10891	2.65	n.d.
Sprague Dawley rat (m)	989 - 10679	1.91	0.6[b]
Sprague Dawley rat (f)	976- 10734	0.843	n.d
NZW rabbit (f)	1031 - 10981	4.66	n.d.
Cynomolgus monkey (m)	966 - 10318	2.96	0.7[b]
Cynomolgus monkey (f)	977 - 10566	0.434	n.d.

a= fraction of free (unbound) drug in plasma; b= at a concentration of 10000 µg/L

Source: Module 2.6.4 Pharmacokinetic written summary

R-13621 Rat, oral gavage @ 3 mg/kg and IV (infusion) @ 1 mg/kg (elinzanetant) Dog, IV (bolus) @ 1mg/kg and oral @ 3 mg/kg Marmoset, IV (bolus)@ 3 mg/kg and oral@ 10 mg/kg	**Rat:** • IV coadministration of elinzanetant with elacridar (GF120918A) – a non-specific inhibitor of P-glycoprotein efflux transporters – caused a 5-fold increase in the elinzanetant brain:blood ratio, suggesting that efflux transporters regulate elinzanetant entry in the rat brain. • Following administration of elinzanetant via oral route, brain concentrations at 0.5 and 1 h were below the limit of quantification (<3 ng/g brain) which may be an indication of slow distribution into the brain given that C_{max} in blood was 0.5 h (equivalent to 90 ng/mL). Brain C_{max} was equivalent to 7 ng/g and the brain to blood $AUC_{(0-7)}$ ratio was **0.1:1.** **Monkey:** • After IV infusion (1 h), the brain concentration of elinzanetant was 0.059 µg/L and lower than that in the blood at 0.098 µg/L, resulting in a mean

PK Studies: Distribution	
Study No & Design	**Study Findings**
Monkey, IV (infusion) @ 3 mg/kg and oral @ 6 mg/kg	brain:blood ratio of 0.6:1. In addition, elinzanetant was not quantifiable in the cerebral spinal fluid sample. • A dose-dependent receptor occupancy with estimates of ED_{50} (administered dose leading to 50% occupancy of the NK1R) of 0.21 mg/kg and EC_{50} (plasma concentration associated with 50% occupancy of the NK1R) of 9.93 ng/mL was seen in the brain by PET (Positron Emission Tomography) using an NK1R ligand in an in-vivo study in male baboons [study R-13885]. Note# Key findings for distribution noted here. Also refer to same study described under 'absorption'.
PH-42138 In-vitro, protein binding assay [Transil®] with BAY 3462932 (M27), BAY 3462933 (M30/34) and BAY 3462934 (M18/21)	**M27**: • Plasma protein binding of M27 was high in male and female human, female Cynomolgus monkey, and female beagle dog and resulted in a low fu (fraction unbound) of less than 1%. • Plasma protein binding was moderate in female and male CD-1 mouse, in male and female SD rat rabbit, and in male Cynomolgus monkey. • The fu´s ranged between 0.0679% in male human plasma and 3.35% in New Zealand rabbit plasma. **M30/34**: • Protein binding of M30/34 was high in all species and resulted in a low fu of less than 1% except of female CD-1 mouse, rabbit, and male Cynomolgus monkey, which was moderate. • The fu's ranged between 0.475% (male human) and 3.44% in (rabbit). **M18/21** • M18/21 plasma protein binding was high in male and female human and in female beagle dog and resulted in a low fu of less than 1%. • fu was moderate in male and female CD-1 mouse, male and female SD rat, and female Cynomolgus monkey. Low protein binding (~10%) was observed for rabbit and male Cynomolgus monkey. Note# Refer to Table 20 below.

Table 20: Plasma protein binding in vitro for elinzanetant and metabolites.

Test compound:	[¹⁴C]Elinzanetant	M27	M18/21	M30/34				
Batch no.:	PII 150-1-02 A	EB1182-73-P1	EB1740-14-P1	EB1182-86-P1	Method:	Transil®		
Test system:	Plasma; *in vitro* incubation matrix				Assay:	LSC; LC-MS/MS		
Analyte:	**Elinzanetant**		**M27**		**M30/34**		**M18/21**	
Species / Test system	**Conc. [µg/L]**	**Fraction unbound [%]**	**Conc. [µg/L]**	**Fraction unbound [%]**	**Conc. [µg/L]**	**Fraction unbound [%]**	**Conc. [µg/L]**	**Fraction unbound [%]**
Human (m)	711 - 6739	0.272	298 to 18204	0.0679	181 to 17514	0.475	467 to 1841 19768	0.181 0.322
Man (f)	706 - 6268	0.332	201 to 19374	0.0689	169 to 14843	0.514	371 to1786 19502	0.140 0.302
CD-1 mouse (m)	982 - 10735	2.30	247 to 17229	1.23	196 to 1537	0.699	355 to 25667	2.99
CD-1 mouse (f)	1005 - 10891	2.65	208 to 18762	2.00	171 to 16886	1.17	202 to 21786	2.84
SD rat (m)	989 - 10679	1.91	265 to 19000	1.44	242 to 14024	0.661	346 to 26371	2.37
SD rat (f)	976- 10734	0.843	201 to 19143	1.25	165 to 11879	0.510	385 to 26257	2.51
NZW rabbit (f)[a]	1031 - 10981	4.66	219 to 18286	3.35	1674 to 17114	3.44	340 to 15417	10.4
Cynomolgus monkey (m)	966 - 10318	2.96	193 to 16321	2.34	1611 to 17543	2.28	300 to 17375	10.2
Cynomolgus monkey (f)	977 - 10566	0.434	185 to 16229	0.537	169 to 13683	0.872	291 to 18300	6.69

Source: Pharmacokinetic tabulated summary [truncated table summarizing studies PH-42081 and PH-42138

PK Studies: Distribution	
Study No & Design	**Study Findings**
B002590 In vitro, Transil®	• Protein binding towards the major binding partner HSA (Human Serum Albumin) of elinzanetant was studied by addition of Sodium Oleate (SO)-free fatty acid and Itraconazole/Hydroxyitraconazole. • Results showed that protein binding of elinzanetant was reduced by increasing SO concentrations.
R-13624; GLP In vivo, male partially pigmented (Lister Hooded) rats, single oral or a single IV (slow bolus over approximately 30 seconds) administration of [^{14}C]GSK1144814 tosylate @ 10 mg/kg and 1 mg/kg, respectively	Oral dose: • Administered radioactivity was rapidly distributed to all tested tissues by 2 h. • Radioactivity concentration at 2 h: brown fat > liver > adrenal cortex > exorbital & intraorbital lacrimal glands > pancreas > bulbo-urethral gland > mucous gland > renal cortex > abdominal fat > myocardium • Radioactivity decreased in most tissues at 8 h but increased in abdominal fat > Harderian gland > pigmented skin > bone marrow > nonpigmented skin > meninges > testis > seminal vesicles. • Radioactivity was quantifiable in half of tissues at 35 days post-dosing: brown fat > uveal tract (choroids, ciliary body and iris)/retina > spleen > thyroid > adrenal cortex. • Radioactivity (~10% of peak) was still detectable in retina/uveal tract at 35 days suggesting elinzanetant has long-term association with melanin containing tissues. IV dose: • Radioactivity was widely distributed at 5 min post dose: adrenal cortex/medulla > myocardium > liver > pancreas > renal cortex/medulla > bulbo-urethral gland > tongue > small >intestine mucosa. • Radioactivity decreased in most tissues at 8 h but increased in abdominal fat > Harderian gland > pigmented skin > epididymis > pineal > pituitary gland. • Lens of the eye had its highest concentration at post-dosing day 1. • Radioactivity was quantifiable in 25% of tissues at post-dosing day 35: brown fat > renal cortex > adrenal cortex > uveal tract/retina > spleen. • Radioactivity (~5% of peak) was still detectable in retina/uveal tract at post-dosing day 35 suggesting a long-term association of drug-related material with melanin in the eyes. ***Reviewer's comment: The Applicant notes that radioactivity in the uveal tract/retina at post-dosing day 35 indicate long-term association of drug-related material with melanin. In an in-vitro study, elinzanetant produced a positive phototoxicity signal (see Section 10 Special Toxicology Studies). Considering the highest level of elinzanetant accumulation in the eyes and pigmented skin of rats and the IC_{50} for elinzanetant to induce in-vitro phototoxicity, a safety margin of ~11 was estimated. Caution is warranted when interpreting this margin, because the degree of elinzanetant accumulation in melanin-rich human tissue is unknown. The potential for elinzanetant to cause photosensitivity in humans cannot be ruled out and is further discussed in Section 11 Integrated Summary and Safety Evaluation and the full review of the phototoxicity study in the Appendix section at the end of this review. In addition, photosensitivity adverse events were***

Reference ID: 5623053

PK Studies: Distribution	
Study No & Design	**Study Findings**
	noted in 5 patients who received elinzanetant during the clinical studies.
R-14360; non-GLP In vivo, oral @ 2 mg/kg in pregnant (day 19) Sprague Dawley rats	• Main objective of the study was to investigate the tissue distribution, and penetration of radioactivity across the placental barrier. • Radioactivity widely distributed from blood to most peripheral organs, tissues, and less in the tissues of fetuses. • As in the non-pregnant rats (i.e., male lister hooded rats), the maternal tissues with the highest concentrations were brown adipose, adrenal gland (average of adrenal cortex and medulla), liver, white adipose, and harderian gland in addition to the mammary gland at 48-h post-dosing, while the lowest concentrations were found in brain and bone. • The fetal blood $AUC_{0\text{-last}}$ was 12% of the maternal blood $AUC_{0\text{-last}}$. Fetal and associated tissue concentrations were generally much lower than maternal blood, except for amnion, placenta, and brain. $AUC_{0\text{-last}}$ ratio of placenta/maternal blood was 1.3, fetus average/amniotic fluid was 18.3, and fetal brain/maternal brain was 2.4.
R-14368 In vivo, albino Sprague Dawley rats (non-pigmented): oral @ 2 mg/kg [Male(M) and Female(F)] IV @1 mg/kg (F) and in pigmented Long-Evans rats, oral @ 2 mg/kg (female)	Albino/non-pigmented (SD rat): • Mostly similar distribution in male and female rats. • At 5 h post-dosing, the highest concentrations were found in adipose white, liver, brown adipose, and mammary gland region. • At 8 h post-dosing, lowest concentrations were found in eye wall, brain, and bone. • Greater amounts of radioactivity were found in the reproductive organs of females (1.715 µg-equiv/g in ovary and 0.692 µg-equiv/g in uterus) relative to males (0.143 µg-equiv/g in testis) at 5 h post-dosing. • Blood to plasma ratios determined for each time point ranged from 0.58 to 0.79 suggesting greater portioning to plasma. Pigmented rat (Long Evans rat): • Concentrations of radioactivity in the tissues and blood was similar to that in non-pigmented rat. • Concentration of radioactivity at 35-days post-dosing remained elevated in the eye uvea (0.019 µg-equiv/g) but was below detection in pigmented skin. Findings in the eye are similar to that in study R-13624.

Metabolism

PK Studies: Metabolism	
Study Title & Design	**Study findings**
R-13660 In-vitro (hepatocytes suspensions of male CD1 mouse, male SD rat, rabbit, Beagle dog, male Cynomolgus monkey, and human) @ 5 µM	• Comparable in-vitro metabolism was observed in human hepatocytes and hepatocytes of male rat, female rabbit, and male cynomolgus monkey. Metabolism was extensive in male dog and female rat, while male mouse metabolized poorly. • Main route of metabolism was **oxidation** followed by de-alkylation, N-demethylation, O-glucuronidation and N,O-de-ethylation. • No human-specific metabolites were observed in hepatocytes.

PK Studies: Metabolism	
Study Title & Design	**Study findings**
	Table 21: Elinzanetant metabolites detected in hepatocytes after 4 h incubation of 5 µM [^{14}C] elinzanetant [% radioactivity]. **Species** / **Analyte**: Human Male [%] · Human Female [%] · Mouse Male [%] · Rat Male [%] · Rat Female [%] · Rabbit Female [%] · Dog Male [%] · Cynomolgus monkey Male [%] Elinzanetant: 67 · 74 · 87 · 60 · 94 · 70 · 4.2 · 61 M14: 2.2 · BQL[f] · BQL[f] · 5.4[d] · 1.9 · BQL[f] · 2.3 · n.d[g] M18/M21/M20[a,b,e]: 3.6 · 1.6 · n.d.[g] · 5.7 · n.d[g] · 1.6 · 12.4 · 2.3 M27: 3.1 · 2.2 · 3.2 · 4.5 · n.d[g] · 15.6 · 4.3 · 4.9 M28: 1.7 · BQL[f] · BQL[f] · BQL[f] · n.d[g] · 3.8 · 7.2 · 1.3 M30/M34[a,c]: 4.3 · 3.4 · BQL[f] · 1.6 · n.d[g] · 2.5 · 4.0 · 8.6 M32: 3.2 · 2.5 · BQL[f] · 3.1 · n.d[g] · 1.4 · 5.0 · 4.2 M39[e]: 4.9 · 4.2 · 2.8 · 4.7 · 1.1 · 7.8 · 11.5 · 7.3 a = co-eluting metabolites b = M18/M21 represent interconverting metabolites c = M30/M34 represent interconverting metabolites d = co-elution with M16 e = traces also observed in control f = below quantification limit g = not detected Source: Module 2.6.4 Pharmacokinetic written summary
R-13654 In-vitro, metabolism-dependent non-extractable levels of radioactivity following incubations of [^{14}C]-GSK1144814 (tosylate salt) with human and rat liver microsomes @1, 5, 10 and 30 µM	• Formation of non-extractable radioactivity was significantly lower in human (3X) compared to rat liver microsomes. • Metabolism-dependent non-extractable radioactivity ranged from 11.7 to 108 pmol free base/mg protein in human liver microsomes, whereas it ranged from 22.5 to 381 pmol free base/mg protein in rat liver microsomes.
R-13716 Rat single oral dose of [^{14}C] Elinzanetant (tosylate salt) @ 10 mg/kg	Note# Major and selected metabolites noted below. For complete table refer to table 5-8 in Module 2.6.5 Pharmacokinetic tabulated summary. Plasma: • Unchanged elinzanetant (parent) represented approximately 43%, 13% and 4% of radioactivity (@ 2, 8, and 24 h post-dosing). • M30, M31 (two oxidized derivatives) and M39 (dehydrogenated metabolite) accounted for up to 8%, 5%, and 10% of radioactivity (@ 2 or 8 h post-dosing). • M18/21 was present at ~2% • M27 at ~3.0% Liver (8 h postdose): • Elinzanetant (parent) at ~8% • M16 (N,O-deethylated) at 5% • M30 (oxidized derivative) at 5% Brain (2 h postdose): • Elinzanetant (parent) at 41% • M39 at 11% Bile: • M14 (O-glucuronidation) at 24% Feces: major route of elimination [94.2%]

PK Studies: Metabolism	
Study Title & Design	**Study findings**
	• Elinzanetant 12% • M16 (N,O-deethylated) and M27 (oxidized) 7%
R-13655 ; non-GLP Rat (M), metabolic profiling isolated perfused rat liver post administration of 3 mg/kg	Bile: • Major metabolite was M14 (O-glucuronidated parent compound), and it was followed by co-eluting M9/M11/M49, M9 (formed by parent compound oxidation the followed by glucuronidation), M11 (oxidized M16), and M49 (oxidized and glucuronidated parent compound). • Additionally, M10/M50/M54 (oxidized / N-dealkylated and methyl hydroxylated (tentative) / oxidized and dehydrogenated) and oxidized metabolite M17 were present along with minor levels of two glutathione conjugates M41 and M43. • Unchanged elinzanetant not quantified. Liver: • Parent compound was notable, followed by metabolites generated by dehydrogenation (M39), oxidation (M30), and other metabolic reactions (e.g., M32/M33/M34, M29, M53, and M28).
R-13714 ; non-GLP Monkey, single oral dose of [^{14}C]Elinzanetant (Tosylate salt) @ 5 mg/kg	Predominant routes of metabolism were oxidative metabolism and N,O-dealkylation of the morpholine ring. Plasma: • Unchanged elinzanetant represented approximately 41%, 6%, and 5% of radioactivity @ 2, 8, and 24 h post-dose, respectively. • M14 (O-glucuronide of elinzanetant) was detected at 2 h only (~11%) • M32 (oxidation), M33 (N-demethylation), M34(oxidation), and M75 (oxidation) co-eluted to a level of ~5%. • M30 and M31 (oxidation) and dehydrogenated M39 (@ 2h): 5-6% Feces: major route of elimination [85.6%] • Parent compound [~9%) • M80 (oxidized) and co-eluting M13 (oxidized)/M50 (N-dealkylated, hydroxylated) = all ~7% each For complete table refer to table 5-11 in Module 2.6.5 Pharmacokinetic tabulated summary
R- 13650 Rat, monkey and human, (exploratory metabolite monitoring in plasma) Male rat @ 120 mg/kg/day at day 91+ Female rat @ 50 mg/kg/day at day 91 [study R13628] Monkey @ 80 mg/kg/day at day 91 [study R-13612]	Human circulating metabolites **M27, M30/M34, M18/21, M22** were observed in both rat and cynomolgus monkey plasma. The table below illustrates how metabolite exposures in rats and monkeys treated with different doses of elinzanetant compare to those in women at 7-day post-dosing with the maximum tolerated dose (MTD) of 160 mg/day [study no. 814-1-02 / 21678 ; R-13551)] Note# Refer to Table 22 below The structures of human metabolites were identified in study R-13659 (VD2010/00088/00 study). % of observed drug-related material (%oDRM) from this study is also noted in Table 22 below.

Table 22: In vivo metabolism, exploratory metabolite monitoring, and species comparison.

ID	%oDRM[a]	Rat Day 91/Human Dosing Day 7		Cynomolgus Monkey Day 91 / Human Dosing Day 7
		Male (120 mg/kg)[b]	Female (50 mg/kg)[b]	Male and Female (80 mg/kg)[c]
Elinzanetant P	38	>equivalent	>equivalent	~equivalent
M18+M21 (Metabolites interconvert) Oxidation	7	~equivalent	<equivalent	<equivalent
M22 Oxidation	8	~equivalent	<equivalent	~equivalent
M27 Oxidation	12	~equivalent	<equivalent	<equivalent
M30+M34 (Metabolites interconvert) Oxidation	14	~equivalent	~equivalent	~equivalent
M31 Oxidation	5[d]	>equivalent	>equivalent	>equivalent
M75 Oxidation	5[d]	~equivalent	>equivalent	>equivalent

a = % of observed drug related material (oDRM) reported in M4.2.2.4 R-13659 after repeated dose of 90 mg to male subjects
b = MTD dose
c = NOAEL dose
d = as total for M31+M75
~ equivalent: 0.5 ≤ preclinical species/human exposure ≤3.0
> equivalent: preclinical species/human exposure >3.0
< equivalent: preclinical species/human exposure <0.5

Source: Pharmacokinetic tabulated summary

PK Studies: Metabolism	
Study No & Design	**Study Findings**
R-13659 In-vivo, exploratory metabolite monitoring in human plasma and urine Oral dose: @ 200, 230 and 250 mg (single dose) @160 and 90 mg (repeat dose) [clinical studies# R-13556, R-13557 and R-13551]	Plasma: • Single dose: M27 (10%), M18/21 (6%), and M30/34 (18%) were observed. • Repeat dose: M22 (8%) was quantifiable only after repeat dose and not observed after single administration. There were no other significant differences compared to single-dose administration. Urine: • M11 (N,O-deethylated and oxidized derivative) was the major metabolite in urine. • Elinzanetant not quantifiable in urine. M30/34 was identified as major metabolite. However, all three metabolites, M27, M30/34, and M18/20 were further investigated in toxicology studies as they exhibit similar pharmacological activity as elinzanetant.
R-13651 Structural elucidation of metabolites [M18/M21, M27, and M30/M34] from plasma samples from health females who received a single oral dose of 160 mg in clinical study 814-1-02.	• Definitive chemical structures of the metabolites were confirmed by comparing the correspondence of LC/MS spectrometric data from pooled human plasma samples with those from corresponding metabolite reference standards. • Refer to Figure 14 and Table 23, which depict the main metabolic pathways and metabolite structures combining the results from study PH-42275.

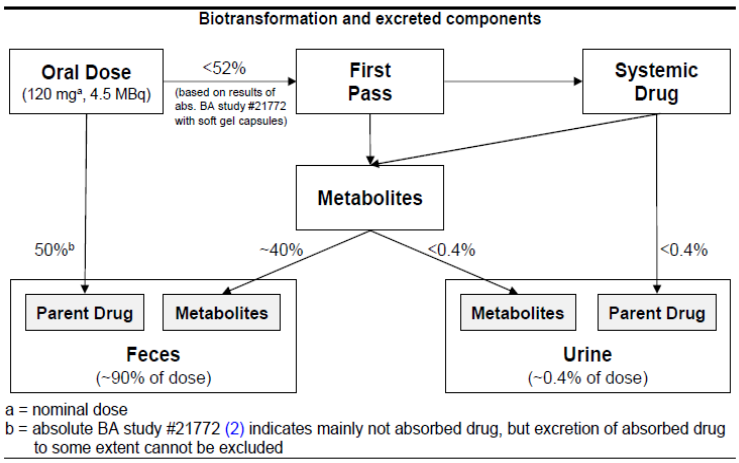
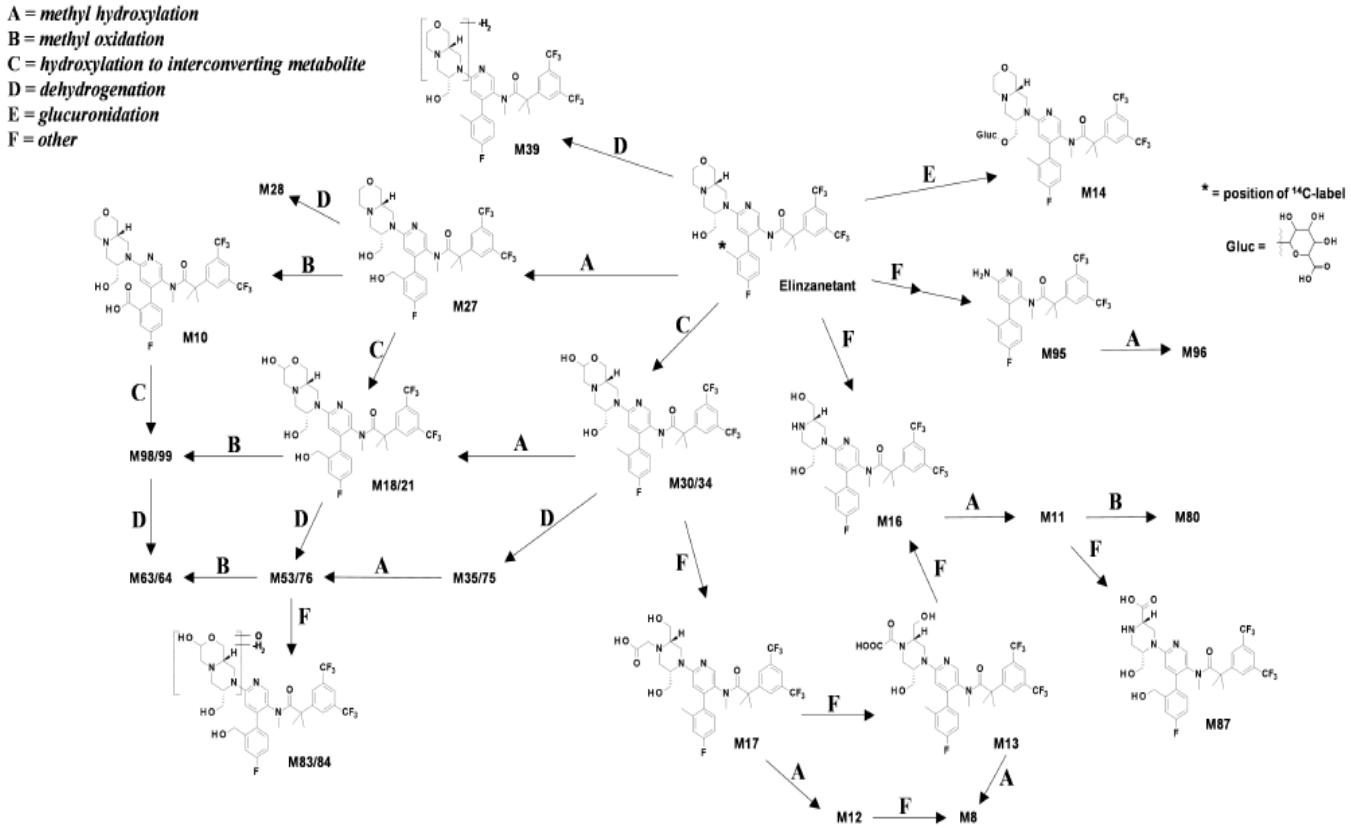
PK Studies: Metabolism	
Study No & Design	**Study Findings**
PH-42275 Metabolite profiling in plasma and excreta from human Male healthy participants (clinical study 21664/ R-13993) oral @120 mg oral suspension	Biotransformation and disposition of [^{14}C] elinzanetant in humans by analysis of plasma, urine, and feces. Percentages of total radioactivity $AUC_{(0\text{-}144h)}$ of notable metabolites are listed below. Plasma: • Elinzanetant = 39.1% • M30/M34 = 13.7%, • M27 = 7.6% (including traces of M28) • M18/M21 = 4.9% • All other metabolites (M11, M14, M16, M28, M39, M35/M75, M53/M76, M95, M96) covered in sum 14.3% of total radioactivity $AUC_{(0\text{-}144h)}$ (each less than 3.5%) Feces: • 89.9% of total administered dose • Elinzanetant = 50.5% [variable between subjects (range: 19.9-67.3% of dose)]. The variability is noted to possibly be originating from non-absorbed drug and/or unchanged excretion of absorbed drug. • ~40% cleared via oxidative biotransformation: ○ M80 > M17 > M13, M8+M87, M27, M18/M21, M12 > M30/M34, M11, M98/M99 > M63/M64: each 1-6% of dose ○ M10, M16, M53/M76, M83/M84, M96, M39: each <0.7% of dose Urine: • Negligible amount (<0.5% of dose). Figure 13: Elinzanetant biotransformation and excreted components.  Source: Figure from Study Report PH-42275
B003239 Chiral conversion in human plasma samples [clinical study PH-42579]. Oral @ 120 mg (single dose, multiple dose; 2X2 crossover study) in healthy subjects	No conversion of elinzanetant (S,S enantiomer; BAY 3427080) to possible stereoisomers [(S,R: BAY 3629435), (R,R: BAY 3629494), and (R,S: BAY 3629436)] was observed in any of the analyzed human plasma samples.

Figure 14 and Table 23 below depict the main metabolic pathways and structure of potential major human metabolites, respectively, described by the applicant.

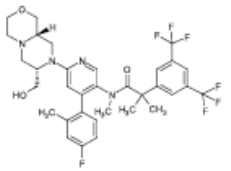
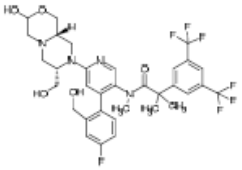
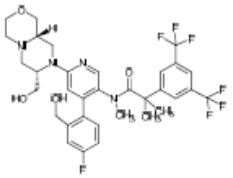
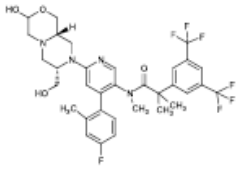
Figure 14: Main metabolic pathways of elinzanetant from in-vitro and in-vivo studies.



Note# M18/M21, M30/34, M35/75, M53/76, M63/64, M83/84 and M98/99 represent interconverting metabolites

Source: Pharmacokinetic tabulated summary

Table 23: Structures of potential major human metabolites following repeat oral administrations of NT-814 (elinzanetant) to healthy female volunteers (160 mg).

Peak ID Biotransformation	Definitive Structure
P NT-814	
M18 & M21[b] Di-hydroxylation named as Metabolite M18/M21	
M27 Mono-hydroxylation named as Metabolite M27	
M30 &M34[b] Mono-hydroxylation named as Metabolite M30/M34	

[b]= Metabolites interconvert
Source: Truncated table from study report R-13651

Excretion

PK Studies: Excretion	
Study Title & Design	**Study findings**
R-13623 Rat (oral) @ 10 mg/kg In intact rats and bile duct cannulated rats	In intact rats: • Major route of elimination was found to be via the feces (94.2%) within 168 h post-dosing. • Urinary elimination was minor (0.9%). • 76.5% of the dose was recovered within 24 h of dosing, remaining dose was eliminated relatively slowly [total recovery: 96.6%]. In bile duct-cannulated rats: • Major route of elimination was via the bile (61.1%). • Fecal and urinary excretion accounted for means of 29.5% and 0.9% of the dose respectively. • Considering the radioactivity recovered in bile, urine, and the residual carcass (minus the gastrointestinal tract), at least 66.1% of the dose was absorbed by these animals. Also refer to study R-13716 summarized above.

PK Studies: Excretion	
Study Title & Design	**Study findings**
R-13625 Monkey (oral), [^{14}C] GSK1144814 tosylate @ 5 mg/kg	• Elimination was primarily via feces (85.6% of the dose was eliminated at 168 h after dosing). • Urinary elimination was very minor (0.1%). • Similar to rats, 79.4% of the dose was recovered within 72 h of dosing; small amounts of radioactivity continued to be recovered in the feces up to the final collection period, indicating that a portion of the dose was being eliminated relatively slowly. Blood/Plasma • Mean plasma concentrations of total radioactivity were 859, 202, 173, and 35.6 ng equivalents of GSK1144814 free base/g at 2, 8, 24, and 96 h post-dose, respectively. • The corresponding mean blood:plasma ratios were 0.64, 0.69, 0.73 and 0.77, respectively [radioactivity seen predominately in plasma] Also see study R-13714 summarized above.
B003245; non-GLP Rat (oral) @ 2 mg/kg (single dose)	• Radioactivity was secreted into the milk of lactating SD rats to a moderate extent (6.1% of dose within 48 h post-administration). • Highest mean milk to plasma ratio was 3.969 at 32 h post-dosing. • The milk/plasma ratio at C_{max} of both matrices was 2.1 at 8 h post-dosing.

In-vitro Pharmacokinetic Drug Interaction Studies

Effects of elinzanetant and metabolites on cytochrome P450 isoforms (CYP)

- Data from human liver microsomes with selective CYP inhibitors and from recombinant human CYP enzymes indicated that CYP3A4 is the primary CYP isoform involved in the oxidative metabolism of elinzanetant [study R-13657, PH42629]. Inhibition of CYP2E1 could not be determined [R-13658].
- Induction potential of elinzanetant and its metabolites M27, M30/34, and M18/21 towards human CYP isoforms was assessed at both mRNA and enzyme activity level, as summarized in Table 24 and Table 25 [Summary from study R-13656 and B003095].

Table 24: Induction potential of elinzanetant and its metabolites towards human CYP isoforms at the mRNA level.

CYP	Result for elinzanetant
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 21-fold
2B6	Concentration-dependent induction up to 9-fold
2C19	Concentration-dependent induction up to 4.5-fold
CYP	**Result for M27**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 21-fold
2B6	Concentration-dependent induction up to 17-fold
2C19	Concentration-dependent induction up to 8-fold
CYP	**Result for M30/34**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 16-fold
2B6	Concentration-dependent induction up to 8-fold
2C19	Concentration-dependent induction up to 3-fold
CYP	**Result for M18/21**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 16-fold
2B6	Concentration-dependent induction up to 12-fold
2C19	Concentration-dependent induction up to 4-fold

Source: Module 2.6.4 Pharmacokinetic written summary

Table 25: Induction potential of elinzanetant and its metabolites – M27, M30/34 and M18/21 – towards human CYP isoforms at the enzyme activity level.

CYP	Result for elinzanetant
1A2	No induction up to 90 000 µg/L
3A4	No induction up to 90 000 µg/L
2B6	Concentration-dependent induction up to 3-fold
2C19	Concentration-dependent induction up to 5-fold
CYP	**Result for M27**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 3-fold
2B6	Concentration-dependent induction up to 5-fold
2C19	Concentration-dependent induction up to 9-fold
CYP	**Result for M30/34**
1A2	No induction up to 90 000 µg/L
3A4	No induction up to 90 000 µg/L
2B6	Concentration-dependent induction up to 4-fold
2C19	Concentration-dependent induction up to 4-fold
CYP	**Result for M18/21**
1A2	No induction up to 90 000 µg/L
3A4	Concentration-dependent induction up to 4-fold
2B6	Concentration-dependent induction up to 5-fold
2C19	Concentration-dependent induction up to 6-fold

Source: Module 2.6.4 Pharmacokinetic written summary

- In-vitro evaluation of the potential for BAY 3427080 (elinzanetant) and its metabolites M30/M34, M18/M21, and M27 to act as direct-acting inhibitors of human CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 2J2 and 3A4 showed no direct-acting inhibitory potency up to the highest test concentration (IC_{50} > 5 µM) except inhibitory potency on CYP3A4 (midazolam 1'-hydroxylation):

BAY 3427080 (IC_{50} = 0.77 µM), M30/M34 (IC_{50} = 0.98 µM), M18/M21 (IC_{50} = 1.1 µM) and M27 (IC_{50} = 1.2 µM).

- There was no relevant metabolism-dependent (time-dependent) inhibitory potency of elinzanetant on biotransformation reactions catalyzed by these cytochrome P450 isoforms, except for a slight increase in the inhibitory potency of elinzanetant and its metabolites on CYP3A4 after preincubation in the presence of NADPH [PH-42451].
    - CYP3A4 inactivation kinetic parameters were as follows [Study B003014]:
        - Elinzanetant (BAY 3427080): K_I = 2.14 µM, k_{inact} = 0.0134 min^{-1}
        - M27 (BAY 3462932): K_I = 1.66 µM, k_{inact} = 0.0150 min^{-1}
        - M30/34 (BAY 3462933): K_I = 2.39 µM, k_{inact} = 0.0166 min^{-1}
        - M18/21 (BAY 3462934): K_I = 3.37 µM, k_{inact} = 0.0218 min^{-1}
- The metabolic stability of GSK1144814 in the presence of aldehyde oxidase was determined by incubation of cynomolgus monkey and human cytosol with an elinzanetant concentration of 0.5 µM with isovanillin (a known inhibitor of aldehyde oxidase). The data suggested that elinzanetant was not a substrate for aldehyde oxidase [R-13621].

Effects of Elinzanetant and Its Metabolites on Transporters

The interaction of elinzanetant with various transporters was investigated in in-vitro studies.

Elinzanetant as a transporter substrate:

- Elinzanetant is classified as a substrate of P-glycoprotein (P-gp), a transporter that removes substances from cells. IV coadministration of elinzanetant with elacridar (GF120918A) [a non-specific inhibitor of P-gp efflux transporters] to rats increased by ~5X the elinzanetant brain:blood ratio and by ~2.5X the systemic exposure to elinzanetant [study R-13621].
- Elinzanetant is not a substrate of the bidirectional transporter breast cancer resistance protein (BCRP), the uptake transporters hOATP1A2 and hOATP2B1, and the MRP4 efflux transporters.
- Elinzanetant is not a substrate of the OATP1B1, OATP1B3, OATP1A2 and OATP2B1 uptake transporters.

Elinzanetant and its metabolites as transporter inhibitors:

- Elinzanetant inhibited MATE1-, BSEP-, and OCT1-mediated metformin transport as well as OAT3-, OATP1B1-, OATP1B3-mediated transport. Elinzanetant is an an inhibitor of BCRP with an IC_{50} value of 7.4 µM [study R-13631, R-13686, B002205, R-13635].
- OATP1B1 was inhibited by elinzanetant with an IC_{50} value of 0.7 µM [study R-13633].
- Elinzanetant inhibited the transport of digoxin via human P-gp in vitro with an IC_{50} of 14 ± 6 µM (corresponding to 9.6 µg/mL as free base) [study R-13634].

- BAY 3427080 (elinzanetant), BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 3462934 inhibited OATP1B1 with IC_{50} values of 0.69 µM, 0.59 µM, 0.38 µM, and 1.21 µM, respectively [study B002050].
- BAY 3427080 (elinzanetant), BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 3462934 (M18/21) inhibited OATP1B3 with IC_{50} values of 0.25 µM, 0.21 µM, 0.19 µM, and 0.27 µM, respectively [study B002050].
- Elinzanetant, BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 3462934 (M18/21) inhibited human P-gp with IC_{50} values of 0.22 µM, 1.51 µM, 0.09 µM, and 2.94 µM, respectively [study B002191].
- Elinzanetant and the metabolites inhibited BCRP, with IC_{50} values of 0.08 µM (elinzanetant), 0.48 µM (M27) , 0.17 µM (M30/34), and 1.38 µM (M18/21) [study B002163].
- Using nonspecific binding of elinzanetant to OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K, the Applicant predicted no in-vivo drug-drug interaction [study R-14407].
- BAY 3427080 (elinzanetant), M27, M30/34, and M22 directly inhibited UGT1A1 in the uridine diphosphate glucuronosyltransferases (UGTs) with IC_{50} values of 2.6 µM, 0.46 µM, 1.8 µM, and 2.6 µM, respectively [B002074].
- Elinzanetant, BAY 3469432 (M27), BAY 3469433 (M30/34), and BAY 3469434 (M18/21) were classified as inhibitors of BSEP (human bile salt export pump) with IC_{50} values of 2.13 µM, 5.91 µM, 9.20 µM, and 16.7 µM, respectively [B002085].

Reviewer's comment. It is noted that elinzanetant and its metabolites are inhibitors of BSEP (human bile salt export pump).

5.2 Toxicokinetics

See Section 6.2 Repeat-Dose Toxicity for TK data obtained from the repeat-dose toxicity studies conducted in rats and monkeys.

6 General Toxicology

6.1 Single-Dose Toxicity

Rat, Monkey and Marmoset

Single-Dose Toxicity Studies: non-pivotal	
Study No. & Design	**Study findings**
R-13645 (non-GLP) Rat (M), oral gavage @ 100 mg/kg elinzanetant (free base form)	• 100 mg/kg dose was well tolerated. • AUC_{0-t} = 64.4 µg.h/mL and C_{max} = 4.65 µg/mL • T_{max} = 2 h

Single-Dose Toxicity Studies: non-pivotal	
Study No. & Design	**Study findings**
R-13575 Cynomolgus monkey (M+F), oral gavage @ 30, 100, 300, 1000 mg/kg (escalating elinzanetant doses, HCl form) on Days 1, 5, 8, 12	• No mortality • Clinical signs: loose, watery feces @ ≥100 mg/kg, emesis @ 1000 mg/kg • TK @ 1000 mg/kg: ○ $AUC_{(0-24)}$ = 173 (F), 85.5 (M) µg.h/mL ○ C_{max} = 8.41 (F), 6.06 (M) µg/mL ○ T_{max} = 8 h (M +F) Concentrations at 24 h following the 1000 mg/kg dose still appeared to be increasing, indicating sustained plasma concentration and very long half-life. • Oral MTD and limit dose (LD) >1000 mg/kg.
R-13574 Marmoset (M+F), oral gavage @ 10, 30, 100, 300, 1000 mg/kg (escalating elinzanetant doses, HCL form) on Days 1, 4, 8, 11, 15	• No mortality, no clinical signs. • TK @ 1000 mg/kg: ○ $AUC_{(0-24)}$ = 30.8 (F), 49.2 (M) µg.h/mL ○ C_{max} = 3.26 (F), 5.52 (M) µg/mL ○ T_{max} = 4 h (M +F) • Oral MTD and limit dose (LD) >1000 mg/kg.
PH-42750 Cynomolgus monkey (F), IV @ 6.5 mg/kg (elinzanetant free base form in Tween 80/soybean oil 85/15 (v)v)]/PBS as vehicle)	• No mortality • Severely reduced food intake in 2 animals during the first (morning) and second feeding (overnight). • TK @ 6.5 mg/kg: ○ AUC_{0-24} =14.8 µg.h/mL ○ C_{max} = 16.1 µg/mL • LD (IV) >6.5 mg/kg in female monkey Note# Bioanalytical quantification of metabolites included in the study report. Refer to full study report for details.

6.2 Repeat-Dose Toxicity

Rat

Repeat-Dose Toxicity Studies: Non-Pivotal	
Study No. & Design	**Study findings**
R-13585* (non-GLP, candidate selection, Dose Range-Finding [DRF] study) Rat (M), oral gavage 7 days @ 0, 30, 100, 300 mg/kg/day elinzanetant (HCl form) Dosing: once daily NOAEL= 30 mg/kg/day	• Mortality: 1 rat @ 300 mg/kg on day 7 • Clinical signs: hunched posture, rough coat, and red staining of muzzle @ 300 mg/kg. • Body weight: decreased body weight gain @ ≥100 mg/kg/day (~0.95 X). • Clinical chemistry: changes in white blood cell parameters • Organ weight: Increase (1.3 X) in liver weights in males ≥100 mg/kg/day, no histological correlates. • Microscopic findings: minimal degeneration of the mucosal epithelium of the glandular stomach and minimal vacuolation of the renal tubular epithelium in males @ ≥100 mg/kg/day • TK: The mean C_{max} values increased proportionally with dose to 100 mg/kg/day then increased less than proportionally to 300 mg/kg/day. The mean AUC_{0-24} values increased

Reference ID: 5623053

<table>
<tr><th colspan="2">Repeat-Dose Toxicity Studies: Non-Pivotal</th></tr>
<tr><th>Study No. & Design</th><th>Study findings</th></tr>
<tr><td></td><td>proportionally with dose to 100 mg/kg/day (both days) and to 300 mg/kg/day on Day 7.

Table 26: PK parameters of elinzanetant following 7-day oral dosing in rats.
<table><tr><th rowspan="2">Pharmacokinetic Parameters</th><th colspan="6">Males</th></tr><tr><th colspan="2">30 mg/kg</th><th colspan="2">100 mg/kg</th><th colspan="2">300 mg/kg</th></tr><tr><th>Day 1</th><th>Day 7</th><th>Day 1</th><th>Day 7</th><th>Day 1</th><th>Day 7</th></tr><tr><td>AUC_{0-24} (µg.h/mL)</td><td>46.9</td><td>44.7</td><td>126</td><td>179</td><td>270</td><td>396</td></tr><tr><td>C_{max} (µg/mL)</td><td>3.49</td><td>3.63</td><td>8.64</td><td>11.3</td><td>13.3</td><td>17.8</td></tr><tr><td>T_{max} (h)</td><td>2</td><td>2</td><td>4</td><td>4</td><td>8</td><td>8</td></tr></table>Results are reported as mean (AUC0-t and Cmax) or median (Tmax)
Source: Excerpted from review by Dr. Frederic Moulin*</td></tr>
<tr><td>R-13586* (non-GLP, candidate selection, DRF)

Rat (M+F), oral gavage
7 days
@ 0, 30, 100, 300 mg/kg/day elinzanetant (tosylate form)

Dosing: once daily

NOAEL= 30 mg/kg/day</td><td>• Mortality (early termination): 1 rat @ 300 mg/kg/day on day 7.
• Clinical signs: Higher severity in males: hunched posture, red discharge from nose and eye, vocalization, cold to touch, prostration and decreased activity @ 300 mg/kg.
• Body weight: Decreased body weight gain @ ≥100 mg/kg with corresponding decrease in food consumption.
• Clinical chemistry: Increases in hematocrit, hemoglobin, and red blood cell counts, increases in neutrophils, monocytes and basophils in M+F and decreases in albumin, total protein and calcium in F, increases in glucose/decreases in cholesterol in M+F and a decrease in triglycerides in M, decrease in electrolytes @ 300 mg/kg.
• Organ weight: Increase in liver weights @ ≥100 mg/kg, with corresponding increases in ALT and AST @ 300 mg/kg that were more notable in F (11X and 25X, respectively) than M (2.9X and 4X, respectively).
• Microscopic findings:
○ GI: Mucosa degeneration/regeneration of the mucosa, isthmus regenerative hypertrophy/hyperplasia of the isthmus epithelium @ 300 mg/kg/day; Minimal multifocal degeneration/regeneration in the stomach in F @100 mg/kg/day.
○ Lungs: Inflammation @ 300 mg/kg/day.
○ Liver: Hepatocellular necrosis and lobular hepatocellular hypertrophy @ 100 and 300 mg/kg/day.
○ Testes: Luminal dilation @ 300 mg/kg/day.
○ Ovaries: Follicular degeneration @ 300 mg/kg/day.
○ Kidneys: Tubular vacuolation, exfoliation, dilation @ 300 mg/kg/day.
○ Thymus: Atrophy / lymphocytolysis @ 300 mg/kg/day.
○ Adrenals: Cortical hemorrhage/congestion and hypertrophy @ 300 mg/kg/day, cortical hypertrophy @ 100 mg/kg/day; only minimal changes @ 30 mg/kg/day.</td></tr>
</table>

Repeat-Dose Toxicity Studies: Non-Pivotal

Study No. & Design	Study findings
	• TK: Table 27: PK parameters of elinzanetant following 7-day oral dosing in rats. **Males** **Pharmacokinetic Parameters** / **30 mg/kg** (Day 1, Day 7) / **100 mg/kg** (Day 1, Day 7) / **300 mg/kg** (Day 1, Day 7) AUC_{0-24} (µg.h/mL): 29.4, 37.1, 122, 150, 181, 195 C_{max} (µg/mL): 2.99, 3.44, 8.66, 9.49, 10.6, 8.58 T_{max} (h): 2, 2, 2, 4, 2, 10 Results are reported as mean (AUC0-t and Cmax) or median (Tmax) **Females** **Pharmacokinetic Parameters** / **30 mg/kg** (Day 1, Day 7) / **100 mg/kg** (Day 1, Day 7) / **300 mg/kg** (Day 1, Day 7) AUC_{0-24} (µg.h/mL): 58.4, 99.4, 145, 223, 300, 288 C_{max} (µg/mL): 4.22, 5.80, 7.52, 10.7, 14, 14.7 T_{max} (h): 2, 2, 4, 8, 12, 24 Results are reported as mean (AUC_{0-24} and C_{max}) or median (T_{max}) Source: Excerpted from review by Dr. Frederic Moulin*

R-13592[$] (non-GLP, DRF)
 	
Rat (M+F), oral gavage
14 days
 	
Dosing: BID (6 h apart)
 	
Adaptive treatment based on clinical signs:
 	
Group 1 (2M+2F): Ascending dose
Days 1-3: 200 mg/kg/day (100 mg/kg BID)
Days 5-7: 350 mg/kg/day (175 mg/kg BID)
Days 9-11: M: 500 mg/kg/day (250 mg/kg BID); F: 250 mg/kg/day (125 mg/kg BID)
Days 13-15: M: 750 mg/kg/day (375 mg/kg BID)
 	
Group 2 (4M+4F): Constant dose
Days 1-4: M: 600 mg/kg/day (300 mg/kg BID); F: 225 mg/kg/day (112.5 mg/kg BID)
Days 5-15: M: 500 mg/kg/day (250 mg/kg BID); F: 290 mg/kg/day (95 mg/kg BID)
 	
Group 3 (2M+2F): Ascending dose
Days 1-7: M: 300 mg/kg/day (150 mg/kg BID); F: 100 mg/kg/day (50 mg/kg BID)
 	
Days 7-14: M: 350 mg/kg/day
	Group 1:
	• Mortality: @350 mg/kg/day, F were sacrificed for animal welfare reasons
	• Clinical signs: @250 and 350 mg/kg/day in F.
	• Body weight and food consumption: Body weight decreased with food consumption decrease @ 250 and 350 mg/kg/day (F) and body weight decrease @ 750 mg/kg/day (M).
	
	Group 2:
	• Mortality: All animals were sacrificed for animal welfare reasons after 6 days of treatment.
	• Clinical signs: Piloerection, hunched posture and partially closed eyelids, abnormal gait, un-coordination, abnormal red color in the cecum, and severely distended and enlarged colon (F).
	• Body weight: Decreased during the treatment period.
	
	Group 3:
	• Mortality: 1F euthanized for welfare reasons on day 13.
	• Clinical signs:
	  ○ No test item-related effects were recorded after 7 days of treatment @ 100 mg/kg/day (F) and 300 mg/kg/day (M).
	  ○ Test-item-related clinical signs (hunched posture, piloerection, abnormal gait) were recorded at 150 mg/kg/day (F) and 350 mg/kg/day (M) from day 5 of treatment onwards. The dose of 300 mg/kg/day was established as the MTD for males.
	• Body weight and food consumption: An evident decrease in food consumption and body weight was observed after 7 days of treatment at 150 mg/kg/day (F) and 350 mg/kg/day (M).

Repeat-Dose Toxicity Studies: Non-Pivotal

Study No. & Design	Study findings
(175 mg/kg BID); F: 150 mg/kg/day (75 mg/kg BID). NOAEL= not determined	• Macroscopic findings: No test-item-related macroscopic findings.
R-14212[$] (non-GLP) Rat (F), oral gavage 2 weeks @ 0, 60, 80 mg/kg/day [0, 30, 40 mg/kg BID] (free base form) Dosing: BID (6 h apart) Rat strain: Hsd:Sprague Dawley (SD), breeder: Envigo RMS, Inc., Indianapolis, Indiana USA NOAEL= 60 mg/kg/day	Clinical signs: • @ 80 mg/kg/day (40 mg/kg BID): Piloerection at day 13 and thin appearance associated with body weight loss and low body tone and hunched posture (day 14) in 1F. TK: Table 28: PK parameters of elinzanetant and metabolic ratios in rats (Envigo, Indiana USA)

Female Day 14

Dose [mg/kg/day]	60		80	
Time [h]	gMean [µg/L]	gSD	gMean [µg/L]	gSD
0	4800	1.15	10300	2.05
3	7400	1.19	8180	1.33
6	6490	1.07	11400	1.36
9	10300	1.40	9810	1.45
12	12800	1.17	17700	1.14
24	7240	1.33	8020	1.38

Parameter	Unit		
$AUC_{(0-24h)}$	µg*h/L	216000	277000
$AUC_{(0-24h),norm}$	kg*h/L	3.60	3.46
t_{last}	h	24	24
C_{max}	µg/L	12800	17700
$C_{max,norm}$	kg/L	0.214	0.221
t_{max}	h	12	12
C_{last}	µg/L	7240	8020
$C(t_{int})/C_{max}$	%	56.6	45.3
RA-$AUC_{(0-24h)}$	%	271.7	277.0
RA-C_{max}	%	186.9	313.3
MR-$AUC_{(0-24h),norm}$ (BAY 3462932)	%	1.2	1.7
MR-$AUC_{(0-24h),norm}$ (BAY 3462933)	%	12.3	13.1
MR-$AUC_{(0-24h),norm}$ (BAY 3462934)	%	0.2	0.3
MR-$C_{max,norm}$ (BAY 3462932)	%	1.1	1.8
MR-$C_{max,norm}$ (BAY 3462933)	%	11.5	10.9
MR-$C_{max,norm}$ (BAY 3462934)	%	0.2	0.3

Source: Study report R-14212 (page 12).

***Reviewer's Comments*: Study conducted to ensure that tolerability and toxicokinetics were comparable between Sprague-Dawley rats from the European (Netherlands) and US breeder (Indianapolis, IN) of Envigo RMS, Inc. Applicant concluded that 80 mg/kg/day (40 mg/kg BID) could potentially exceed tolerability in Hsd:Sprague Dawley (SD) rats from US breeder. Elinzanetant exposures (AUC and C_{max}) in female rats was similar to those obtained in the rat carcinogenicity study [Study No. T105128-7; conducted in (b) (4) using same strain of SD rats; AUC_{0-24} = 252000 µg•h/L and C_{max} = 12500 µg/L].**

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The key findings from all **pivotal repeat-dose toxicity studies** are described in the table below. For calculation of nonclinical safety or exposure margins, the clinical exposure at the MRHD [$AUC_{0\text{-}24}$ = 8572 µg.h/L] from clinical study CPM50130 (report number B002427)] was used, unless otherwise noted.

Repeat-Dose Toxicity Studies: Pivotal

Study No. & Design	Study findings
R-13595* (GLP) Rat (M+F), oral gavage 4 weeks @ 0, 5, 25, 100 mg/kg/day (tosylate salt form) Dosing: once daily NOAEL= 25 mg/kg (F), 100 mg/kg/day (M) Safety margin = 10.0-fold (F), 10.5-fold (M) on AUC basis for MRHD Rats used= SD:Crl (Charles river, UK)	Mortality: 1F @ 100 mg/kg euthanized on day 12 due to severe clinical signs (piloerection, hunched posture, tiptoe gait, pale extremities, pinched flanks, and irregular/labored breathing). Clinical signs: Transient clinical signs noted in in all groups included chewing movements and tense appearance (increasing in incidence in animals dosed at 100 mg/kg), rubbing chin on the cage floor, and vocalizing. Clinical chemistry: Higher group mean plasma total bilirubin concentration was observed in M @100 mg/kg (1.48 X of control) and F at ≥25 mg/kg (1.78 to 1.54 X of control). Organ weight: • Liver: Increased in M (1.1 X control) and F (1.2 X control) @ 100 mg/kg, no corresponding microscopic changes. • Adrenals: Increased in males @100 mg/kg/day (1.2 X control). Microscopic findings: • 2F @ 100 mg/kg had abnormalities in the reproductive tract characterized by abnormal diestrus, mucification of the vaginal mucosa, atrophy of the uterus and persistent corpora lutea in the ovary. • Minimal adrenal cortical hypertrophy in M @ 100 mg/kg. TK: Systemic exposure was typically higher in F than M, with no relevant change in the absorption rate as dose increased. Table 29: PK parameters of elinzanetant following 4-week oral repeat dosing in SD rats (once daily dosing). **PK parameters** / **5 mg/kg/day** / **25 mg/kg/day** / **100 mg/kg/day** **Male values on day 1** $AUC_{(0\text{-}24)}$ [µg·h/mL] 6.98 25.9 73.7 C_{max} [µg/mL] 0.777 2.57 5.15 T_{max} [h] 2 2 4 **Male values on day 28** $AUC_{(0\text{-}24)}$ [µg·h/mL] 7.31 20.9 89.9 C_{max} [µg/mL] 0.741 2.75 6.36 T_{max} [h] 2 2 4 **Female values on day 1** $AUC_{(0\text{-}24)}$ [µg·h/mL] 12.4 51.0 99.5 C_{max} [µg/mL] 1.02 3.38 5.37 T_{max} [h] 2 2 4 **Female values on day 28** $AUC_{(0\text{-}24)}$ [µg·h/mL] 14.7 85.8 344 C_{max} [µg/mL] 1.09 5.07 18.9 T_{max} [h] 1 2 4 Source: Reviewer-generated table.

Repeat-Dose Toxicity Studies: Pivotal

Study No. & Design	Study findings
R-13596* Rat (M+F), oral gavage 13 weeks @ 0, 5, 25, 100 mg/kg/day (free base form: Batch Number: NE-021414-Batch-01-2008, purity 97.7%.) Dosing: once daily NOAEL= 100 mg/kg Safety margin = 6.6-fold (M), 15.7-fold (F) on AUC basis for MRHD Rats used= SD:Crl (obtained from Charles River, Canada) Conducting lab = (b) (4) (b) (4) in 2009	Mortality and Clinical Signs • No mortality • No clinical signs Clinical chemistry • Minimal decreases in lymphocyte counts (0.79 X to 0.86 X of control mean) for M and F @ 100 mg/kg, starting in F at Week 4 and for both sexes at Week 13 • Increase in bilirubin (2.5 X in M @ 100 mg/kg, 3.4 X in F @ 100 mg/kg), urea (5.1 X in F @ ≥25 mg/kg), creatinine (43.3 X @ ≥25 mg/kg) and glucose (6.5 X in M @ 100 mg/kg, 5.85 to 6.88 X @ ≥25 mg/kg) • Decreases in serum phosphorus (~2.5 X) and potassium (~5 X) @ 100 mg/kg in both M and F. Urine • Increases in glucose concentration per collection period (1.22 X to 1.28 X mean control) in Weeks 4 and 13, and minimal increases in urinary glucose (1.88 X mean control) for F @ 100 mg/kg by week 13. TK • No significant differences (<2-fold) in C_{max} and $AUC_{(0-24)}$ were observed between Week 4 and Week 13 • No notable difference in exposure (in terms of $AUC_{(0-24)}$) was observed between M and F at the lowest dose (5 mg/kg). However, systemic exposures were significantly higher (at least 2.4-fold) in F than in M at 25 and 100 mg/kg on both Week 4 and 13. Table 30: PK parameters of elinzanetant following 13-week repeat-dose toxicity in SD rats (once a day dosing). **PK parameters** | **5 mg/kg/day** | **25 mg/kg/day** | **100 mg/kg/day** **Male values on day 28** $AUC_{(0-24)}$ [µg·h/mL] | 4.57 | 7.73 | 30.7 C_{max} [µg/mL] | 0.51 | 0.867 | 2.49 T_{max} [h] | 2 | 2 | 2 **Male values on day 91** $AUC_{(0-24)}$ [µg·h/mL] | 5.8 | 12 | 56.7 C_{max} [µg/mL] | 0.586 | 1.19 | 4.72 T_{max} [h] | 2 | 2 | 2 **Female values on day 28** $AUC_{(0-24)}$ [µg·h/mL] | 8.05 | 27.5 | 116 C_{max} [µg/mL] | 0.626 | 1.8 | 6.57 T_{max} [h] | 1 | 1 | 2 **Female values on day 91** $AUC_{(0-24)}$ [µg·h/mL] | 7.06 | 32.2 | 135 C_{max} [µg/mL] | 0.677 | 2.41 | 8.28 T_{max} [h] | 1 | 1 | 2 Source: Review-generated table. ***Reviewer's note# No convulsions, tremors or CNS-related effects seen in this study.***

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Repeat-Dose Toxicity Studies: Pivotal	
Study No. & Design	**Study findings**
R-13628 ** (as amended) Rat (M+F), oral gavage 13 weeks with 4-week recovery M @ 0, 50, 120, 300 (175) mg/kg/day [0, 25, 60, 150 (87.5) mg/kg BID] (Note# dose in HD males was reduced after 9 days of dosing to 175 mg/kg/day because of marked intolerability and then discontinued altogether on the 11th day of dosing because of continued toxicity) F @ 0, 20, 50, 100 mg/kg/day [0, 10, 25, 50 mg/kg BID] (free base form: Lot 1144814A-B-01P, Purity 99.4%) Dosing: BID (6 h apart) Conducting lab = (b) (4) in 2018 Deviation from protocol: HD decreased from 300 mg/kg/day to 175 mg/kg/day Rats used: SD:Hsd obtained from Envigo RMS B.V.; Netherlands conducting lab: (b) (4) (b) (4) **NOAEL**= not determined **Multiple of exposure for involuntary muscle contractions** @ low dose of 20 mg/kg/day (F) and 50 mg/kg/day [Refer to reviewer's comment for labelling for MOE calculations] [note# taking AUC @ week 13] **Multiple of exposure for skeletal muscle findings:** M= 16-fold, F= 8-fold @ 300 mg/kg/day for males and 100 mg/kg/day for females.	Mortality: • @ 300 mg/kg/day (M): 5 died prematurely, 3 on day 9 and 2 on day 11; 6 were euthanized on day 9 or 11 due to clinical signs [dehydration, prostration or hunched back and body weight loss (between 3 and 14%)] • On day 12, all surviving 7 M from 300 mg/kg/day were euthanized, with the exception of the 3 TK animals which were necropsied after a 28-day treatment free recovery period (Day 40) • @ 100 mg/kg/day (F): 6 euthanized on day 11 to 68 after showing prostration, decreased activity, hunched back, pallor, moderate to severe dehydration and rapid breathing. • 1 F @ 20 mg/kg/day and 2 F @ 50 mg/kg/day euthanized on day 34 to 68 due to severe clinical signs [involuntary muscle contractions, spasms, rigidity, tremors, stiffness of the tail, salivation and in some animals, irritability, and aggressive behavior for a short period after dosing]. Gross Pathology in unscheduled deaths: • The histology showed muscle degeneration and necrosis in the tongue, the larynx, and the skeletal muscles of the leg. Myotoxicity was also considered the cause of death for these animals @ 100 mg/kg/day F and @ 300 mg/kg/day M. • Alterations in the large intestine consisting of distended colon or cecum and/or hard content in the colon was noted in 3 M @ 300 mg/kg/day and 2 F @ 100 mg/kg/day suggesting alteration of food transport in the GI tract and may correlate with the decrease in food consumption noted in the first two weeks of treatment. • Histologic lesion associated with these findings in M was the depletion of secretions from the acinar cells in the salivary glands, which would possibly be associated with dry mouth, a difficulty in swallowing food and corresponding appetite suppression. Clinical signs: • CNS: tremors, rigidity, spasms (generally lasting 1-2 minutes and occasionally up to 3 minutes), abnormal involuntary muscle contractions (generally lasting 1-30 seconds and occasionally up to 2 minutes) and stiff tails in 1 M each from 50 and 120 mg/kg/day. F @ all doses had spasms, involuntary contractions, and convulsions. • A few animals also appeared disoriented and showed irritability or aggressive behavior for a short period after dosing. Body weight: • 5% decrease in M @ 300 mg/kg/day during first 12 days. • Transient weight loss in F.

Repeat-Dose Toxicity Studies: Pivotal

Study No. & Design	Study findings
[note# taking AUC from day 1 since high-dose animals that had skeletal muscle findings did not survive to week 13]	Food consumption: • M @ 300mg/kg/day had marked decrease (approximately half of the food consumption compared to controls). • F @ 100 mg/kg/day decrease intake (10%) during first 15 days. Organ weight: • Heart (+23%), kidney (+28%), liver (+42%), lungs (+32%), and thymus (+110%) relative weights (compared to body weight) were elevated in the 7 M euthanized on day 12. • After recovery phase, significant increases in heart, kidney, liver and spleen weights (absolute and relative to body weight except for the spleen) were noted @ 120 mg/kg/day M. Histopathology: • Liver: Increased liver weight was accompanied by minimal hepatocellular atrophy. • Lung: Alveolar macrophage infiltrates. • Thymus: Minimal involution and atrophy. • GI: Lumen of the colon was slightly dilated in 2/7 animals and the mandibular and parotid salivary glands showed minimal depletion of the secretory granules in the acinar cells in 3/7 animals. • Skeletal muscle: Moderate or severe degeneration /necrosis in the skeletal muscle in all 100 mg/kg F and 300 mg/kg M (or group 4) that died prematurely. Table 31: Incidence of skeletal muscle degeneration in male and female rats euthanized due to overt toxicity induced by the highest test doses of elinzanetant.

Tissue/ Findings	Male Rats (300 mg/kg/day)	Female Rats (100 mg/kg/day)
	# of Affected Rats/Total # Rats	
Skeletal Muscle Degeneration/Myofiber	11/11	3/6
Larynx Degeneration/Necrosis, Muscle	9/11	1/6
Tongue Degeneration/Necrosis, Myofiber	11/11	1/6

Source: Reviewer-generated table using data from study report (page 54).

• 7 M @ 300 mg/kg/day that were prematurely sacrificed also had degeneration/necrosis in the skeletal muscle of the leg (3 in7), tongue (4 in 7) or larynx (2 in 7). Clinical chemistry: • M @ 300 mg/kg/day had increase in ALT, AST, CK plasma levels and decreased A/G ratio. • LDH, AST, and CK increases correlated with findings of necrosis and degeneration in skeletal muscles, suggesting

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Repeat-Dose Toxicity Studies: Pivotal

Study No. & Design	Study findings

that transaminase elevation was due to myotoxicity.
- However, no changes in above parameters in F.
- F @ ≥50 mg/kg/day had increase in plasma creatinine, calcium, inorganic phosphorus, and sodium.

Urinalysis:
- Urine volume was increased, and urine creatinine values were decreased in a dose dependent fashion in both sexes and these changes were statistically significant in the F @ 100 mg/kg/day at week 6 [150% increase in urine vol; 43% decrease in urine creatinine]. These effects disappeared at week 13, suggesting an adaptation of the nephron.

TK:
- 2.6 to 4.3-fold accumulation in systemic exposure was observed (based on C_{max} and AUC_{last}) seen in F @ all doses.

Table 32: PK parameters of elinzanetant following 13 weeks oral repeat dosing in SD rats (BID dosing).

PK parameters	50 mg/kg/day	120 mg/kg/day	300 mg/kg/day
Male values at day 1			
$AUC_{(0-24)}$ [µg·h/mL]	29.460	54.68	140.6
C_{max} [µg/mL]	2.31	3.9	8.14
T_{max} [h]	12	3	3
Male values at week 13			
$AUC_{(0-24)}$ [µg·h/mL]	36.07	78.14	NA
C_{max} [µg/mL]	2.81	5.32	NA
T_{max} [h]	9	12	NA
PK parameters	**20 mg/kg/day**	**50 mg/kg/day**	**100 mg/kg/day**
Female values at day 1			
$AUC_{(0-24)}$ [µg·h/mL]	20.36	37.25	69.63
C_{max} [µg/mL]	1.12	2.06	3.93
T_{max} [h]	3	12	3
Female values at week 13			
$AUC_{(0-24)}$ [µg·h/mL]	59.84	152.5	297.5
C_{max} [µg/mL]	2.93	7.95	16
T_{max} [h]	3	12	12

NA = not available (animals did not survive for TK analysis)
Source: Reviewer-generated table.

***Reviewer's comment**: The Applicant does not provide any mechanistic basis for the findings of skeletal muscle degeneration and necrosis, but nevertheless has included the findings in the proposed labeling in Section 13.2, along with the CNS findings observed in this study. A follow up mechanistic study [R-13644 [QL24QG]]$ failed to reproduce the skeletal muscle degeneration seen in this study. Refer to study summary under mechanistic studies.*

Repeat-Dose Toxicity Studies: Pivotal	
Study No. & Design	**Study findings**
	Reviewer's comment for labelling: In Section 13.2 of the label, under CNS subheading, the lowest doses that caused involuntary muscle contractions in male and female rats are noted as being equivalent to ≥4-fold the MRHD based on AUC exposures at the time of onset. The multiple of exposure was estimated using extrapolated $AUC_{(0-24)}$ values for male and female rats. $AUC_{(0-24)}$ data are available only for treatment days 1 and 91, whereas the safety signals were noted around treatment day 24 (tremors) and day 34 (convulsions) in females and around day 31 (rigidity/spasms) and day 34 (convulsions) in males. Linear regression of the available data for the LOAELs (20 mg/kg/day in female rats and 50 mg/kg/day in male rats) allowed the extrapolation of the AUCs for the days when convulsions were noted. Additional caveat in the study was that the monitoring was not done continuously and hence findings could have occurred prior to day 24.
R-13894 **, # Rat (M+F), oral gavage 26 weeks M @ 0, 50,120, 180 mg/kg/day [0, 25, 60, 90 mg/kg BID] F@ 0, 20, 50, 80 mg/kg/day [0, 10, 25, 40 mg/kg BID] (free base form; Lot 1144814A-B-01P, Purity 99.8%) Dosing: BID (6 h apart) Rats used= SD: Hsd (Envigo, UK) Conducting lab= (b) (4) in 2019 NOAEL= 120 mg/kg/day (M) [note# Applicant regards 180 as the NOAEL) and 80 mg/kg/day (F) Safety margin = 8.8-fold (M) and 36.3-fold (F) on AUC basis for MRHD	Mortality: 1 in control and 1 in 50 mg/kg/day males (difficulty breathing noted), not considered treatment related. Body weight: The final body weight was marginally (1-5%) lower in treatment groups than in the respective controls, without a clear dose-effect relationship. Hematology: @ 180 mg/kg/day in M and 80 mg/kg/day in F: Lower hematocrit and red cell distribution width in both sexes @ week 13 and 26, higher mean cell hemoglobin concentrations in both sexes at Week 13 only, low mean cell volume and low hemoglobin concentration in males only @ week 13 and 26. Clinical Chemistry: • Elevated ALT at week 26 in M @ 180 mg/kg/day (2-fold). AST increase in F @ 50, 80 mg/kg/day at week 26 (2-fold). • Bilirubin levels increased in treatment groups in M @ both week 13 and 26. • Cholesterol levels decreased in M @ 120 and 180 mg/kg/day @ week 13 and 26 (180 mg/kg/day only). • Alterations of plasma electrolyte concentrations and markers of glomerular filtration rate. Urinalysis: • Increase in protein and glucose concentration in the urine from @ 180 mg/kg/day in M and 80 mg/kg/day in F. • Urine volume of male rats dosed at 120 and 180 mg/kg/day was higher than controls. • Increased incidence of white blood cells in the urine of males [consistent with mild kidney damage]. Gross pathology:

Repeat-Dose Toxicity Studies: Pivotal	
Study No. & Design	**Study findings**
	• Depressions were noted in the kidneys of 2M @ 50 mg/kg/day, 4M from the 120 mg/kg/day group and 2M @ 180 mg/kg/day. • Pale areas were noted in the lungs of 1M @ 50 mg/kg/day, 3M @ 120 and 7M and 2F @ 180 and 80 mg/kg/day, respectively. Organ weight: • Dose-dependent increase in the relative weight of the adrenal gland, heart, kidney, and liver, and decrease in thymus weight in M. • Relative weight of the adrenal, heart, kidney, and liver were statistically elevated @ 80 mg/kg/day in F. Histopathology: Lung: Dose-related incidence of macrophage infiltrations in the alveoli was noted in both sexes, without increase in severity. Minimal infiltrates were noted in M and F @ 50 and 20 mg/kg/day, respectively (low-dose), and also @ higher dose groups. Kidney: tubular basophilia, hyaline casts and cortical scars were seen in males (no dose response), correlated with the increase relative kidney weights and kidney macroscopic observations. Additionally, the alterations of plasma electrolyte concentrations and markers of glomerular filtration rate suggest mild kidney toxicity. Adrenal: Minimal hypertrophy of the adrenal cortex noted in 5/12 males and 4/12 females @ the high dose in M and F. Thymus: Dose-related decrease in thymus weight in males was consistent with the dose-related increase in incidence and severity of the atrophy in the thymus in F (minimal severity, increased incidence with dose) and M (minimal to moderate severity, increased severity and incidence with dose). Liver: No histopathological findings in the liver. Mild dose-related effects on hepatic function in M included elevated ALT and AST activity, increased bilirubin levels, and reduced cholesterol levels. In the absence of histopathology, the effects were considered adaptive rather than adverse. TK: In males, no accumulation occurred but in females at all doses, a significant accumulation (2.4- to 3.0-fold) was observed after 26 weeks of dosing. At the comparable dose for males and females (50 mg/kg/day), exposure in females was notably higher than in males and this difference was more pronounced with repeated administration.

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Repeat-Dose Toxicity Studies: Pivotal

Study No. & Design	Study findings
	Table 33: PK parameters of elinzanetant following 26-week oral repeat dose in SD rats (BID dosing).

PK parameters	50 mg/kg/day	120 mg/kg/day	180 mg/kg/day
Male values at day 1			
$AUC_{(0-24)}$ [µg·h/mL]	22.5	73.1	121
C_{max} [µg/mL]	1.98	5.70	8.06
T_{max} [h]	12	12	12
Male values at week 26			
$AUC_{(0-24)}$ [µg·h/mL]	36.2	76.1	108
C_{max} [µg/mL]	2.61	4.64	6.83
T_{max} [h]	9	9	12
PK parameters	**20 mg/kg/day**	**50 mg/kg/day**	**80 mg/kg/day**
Female values at day 1			
$AUC_{(0-24)}$ [µg·h/mL]	23.0	73.8	102.0
C_{max} [µg/mL]	1.42	4.64	6.33
T_{max} [h]	12	12	12
Female values at week 26			
$AUC_{(0-24)}$ [µg·h/mL]	67.4	194	311
C_{max} [µg/mL]	3.37	114	150
T_{max} [h]	9	9	12

Source: Reviewer-generated table.

Note# Safety margins and multiples of exposures calculated based on clinical exposure at the MRHD of 120 mg/day [$AUC_{(0-24)}$ = 8572.0 µg.h/L; Clinical study number CPM50130 (report number B002427)].
$ Not previously reviewed under IND 129492.
* Nonclinical review under IND 129492 in DARRTS dated 01/30/2017.
** Nonclinical review under IND 129492 in DARRTS dated 10/19/2020 under rat SPA (carcinogenicity) review.
# Nonclinical review under IND 129492 in DARRTS dated 08/25/2022 (phase 3 protocol).

Repeat-Dose Toxicity Studies: Metabolites

Study No. & Design	Study findings
R-13999 (GLP) M27 metabolite Rat, IV infusion @ 0, 1, 2, 3 mg/kg for 4 weeks followed by 7-day washout, then subcutaneous (SC) injection @ 0, 3, 6, 10 mg/kg for 4 weeks Dosing: once daily NOAEL = 3 mg/kg/day (0.3 mg/mL, IV highest feasible dose) or 10 mg/kg/day (2 mg/mL, SC)	Clinical signs: Bruising at IV injection site, subcutaneous injection site eschar, not dose related. Body weight: Reductions in body weight compared to control in all treatment groups (IV), similar body weight gains with SC injection. Hematology: @ HD, shortening of partial thromboplastin in males (0.87 X) and females (0.96 X). Urinalysis: @ HD F: Increased urine volume/output. Clinical chemistry: • Increased ALT 1.69 X and AST 2.01 X @ all doses in M. • Increased bilirubin 2.2 X and 3.1 X @ MD & HD F. • Increased glucose @ HD both sexes. • Increased triglycerides @ HD M.

Repeat-Dose Toxicity Studies: Metabolites	
Study No. & Design	**Study findings**
	Histopathology: Injection-site reactions included inflammatory cell infiltrate and fibrosis; no treatment-related findings. Toxicokinetics: • Sex differences in M27 C_{max} and AUC_{0-24} values < 2-fold, tendency for increased AUC_{0-24} in females. • Generally, dose proportional TK. • No accumulation following IV or SC injection.
R-13953 T105056-7 # (GLP) M27 metabolite Rat (SD M+F), oral gavage 13 (Interim) or 26 weeks (main study) @ 0, 5, 10, 20 mg/kg/day Dosing: once daily Note# No mention of convulsions or tremor. NOAEL = 20 mg/kg/day Week 26 C_{max} (ng/mL) = 1740 (M) or 3490 (F) AUC_{0-24} (ng*h/mL) = 13700 (M) or 38300 (F) Safety margin = 5.4-fold (M) and 15-fold (F)** **= based on $AUC_{(0-24)}$ of 2496.3 ng.h/mL (M27), obtained from clinical study B002427	Mortality: Two F @ 20 mg/kg (one main study at day 83, one satellite on day 64) euthanized for welfare reasons not considered related to M27 treatment. Clinical Signs: No treatment-related changes in clinical signs. Body weight: Decreased body weight gain compared to control @ 10 and 20 mg/kg in F from week 13 to termination. Overall, body weight gain (Week 0-26) was unaffected by treatment. Hematology: Increased leucocyte subpopulation counts in treated groups @ 20 mg/kg F in Week 13/14 and 26, @ 20 mg/kg M in Week 13 and 26. Clinical Chemistry: Bilirubin concentration was increased in all treated female groups (up to 4x control at 20 mg/kg) at Week 13/14 and 26 and in the high-dose (20 mg/kg) male group (up to 2x control) at Week 13 and 26. There were no correlating findings of hemolysis, cholestasis, organ weight changes, macroscopic, or microscopic changes in the liver at 13 or 26 weeks. Histopathology: No treatment-related changes in histopathology. Note# @ 20 mg/kg/day: Slightly higher incidence and severity of myofiber regeneration, degeneration, and necrosis in the tongues of males and females administered 20 mg/kg/day for 13 weeks. In the study report, this finding was considered to be related to the sublingual blood sampling, rather than the test item, based on the location and characteristics of this finding (Heimann et al, 2009). However, this finding was also observed in a 13-week toxicity study in rats with the parent compound (Study R-13628) and cannot be ruled out as potentially treatment-related, particularly when also considering skeletal muscle toxicities observed in other studies. M27 Toxicokinetics: • Exposure increased generally dose proportionally, with a tendency to be greater than dose proportional in both sexes on Day 1 and in females during Weeks 13 and 26. • Accumulation occurred after multiple doses, highest @ 5 mg/kg/day and lowest @ 20 mg/kg/day in both sexes. • Sex differences were generally greater than 2-fold, with increased exposure observed in F compared to M.

Repeat-Dose Toxicity Studies: Metabolites	
Study No. & Design	**Study findings**
	TK of M27 metabolites: • M18/21: Exposure increased proportional to M27 dose, accumulation was observed after repeat dosing in females, sex differences <2-fold. • M30/34: Low levels generated in all dosing groups; higher exposure in F compared to M (~2-fold higher in F).

Nonclinical review under IND 129492 in DARRTS dated 08/25/2022 (phase 3 protocol)

Monkey

Repeat-Dose Toxicity Studies: Non-Pivotal	
Study No. & Design	**Study findings**
R-13580$ (non-GLP); DRF study Monkey (oral) 4 days @ 100, 300, and 1000 mg/kg (1 M + 1 F /group) elinzanetant (HCl salt) Dosing: once daily Reviewer's notes#: 1. There was no vehicle control group. 2. The lowest oral dose (100 mg/kg/day) can be considered as the MTD and the LD in this study because higher doses induced serious adverse events, including deaths.	Mortality: 1 F @ 300 mg/kg and all M and F @ 1000 mg/kg were euthanized in moribund condition following 3 or 4 daily doses. Clinical signs: Loose/watery and/or soft feces were noted @ 100 and 1000 mg/kg. Other signs include emesis, excessive salivation, inappetence, fecal abnormalities, and red nasal discharge. Clinical chemistry: Increased bilirubin concentrations (up to ~7 X) in M @ ≥100 and F @ 1000 mg/kg. Hematology: Decreased lymphocyte and eosinophil counts (≤1X) in M @ 100 and 1000 and F @ 100 mg/kg. Histopathology: Stomach, liver, thymus were noted as the main target organs. • Hepatocellular vacuolation and/or single-cell necrosis were noted at doses @ 300 mg/kg. • Gastric erosions, ulcers and glandular degeneration were noted at doses ≥300 mg/kg. • Thymic lymphoid necrosis ≥100 mg/kg. • Degeneration/regeneration of submucosal duodenal artery was noted @1000 mg/kg (M).

Repeat-Dose Toxicity Studies: Non-Pivotal

Study No. & Design	Study findings
	TK: Table 34: PK parameters of elinzanetant following 4-day treatment in monkeys.

Parameter	Day	Dose (mg/kg)		
		100	300	1000
Male		P07M-181	P07M-183	P07M-185
AUC_{0-24} (µg.h/mL)	1	19.1	113	255
	4	170	567	372[1]
C_{max} (µg/mL)	1	1.69	6.49	15.8
	4	12.5	38.9	60.4[1]
T_{max} (h)	1	24	24	24
	4	24	8	2[1]
Female		P07F-182	P07F-184	P07F-186[2]
AUC_{0-24} (µg.h/mL)	1	18.2	24.0[3]	6.79
	4	68.7	ND	257
C_{max} (µg/mL)	1	0.97	1.67[3]	0.95
	4	3.91	ND	19.7
T_{max} (h)	1	24	5[3]	2
	4	12	ND	5

ND = No data. Animal euthanized after the predose bleed on Day 4 due to declining clinical condition.
1. Animal euthanized after the 8-hour sample on Day 4 due to declining clinical condition; AUC calculated to 8 hours with C_{max} reported over this time period.
2. Multiple episodes of emesis were noted at approximately 0.5 and 2.5 hours postdose on Days 1 and 4, respectively. Because the amount of drug lost due to emesis could not be determined in this monkey, toxicokinetic parameters are reported without interpretation.
3. Emesis noted at approximately 1.5 hours postdose.

Source: Extracted from study report R-13580

R-13638[$;] Non-GLP, DRF/MTD study

Monkey (oral)
@ following doses:

DRF group:

Group #	Dose (mg/kg/day)	Treatment Days
1	80 (2 x 40)	1-4
	120 (2 x 60)	5-7
	160 (2 x 80)	8-9

Fixed dose group:

Group #	Dose (mg/kg/day)	Treatment Days
2	110 (2 x 55)	1-4
	Washout	5-9
	80 (2 x 40)	10-23

Washout - day 5 to 9

Key findings:

DRF phase: F @ ≥80 mg/kg/day had loose feces, with abdominal distension @ 160 mg/kg/day. M @ 160 mg/kg/day had vomiting along with loose feces.

Fixed dose phase: Similar GI findings of loose feces, decreased food consumption, decreased bodyweight. Increased liver weight in 1M and 1F @ 80 mg/kg/day with no correlating histopathology.

Based on the findings, 80 mg/kg/day (40 mg/kg, BID) was chosen as the high dose for the 13-week repeat-dose toxicity study.

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<table>
<tr><th colspan="2">Repeat-Dose Toxicity Studies: Non-Pivotal</th></tr>
<tr><th>Study No. & Design</th><th>Study findings</th></tr>
<tr><td>R-13640$; non-GLP

Monkey (oral, 3 F)
7 days @ 40 mg/kg/day (free base form)

Dosing: once daily

NOAEL = not determined</td><td>Key findings:

Clinical signs: Excessive salivation was observed in 1F on post-dosing Days 6 and 7. Soft feces was observed in 1F on Days 1 and 6. Reduced eating was observed in 1F on Days 2, 3 and 8.

Body weight: A slight decrease in body weight (0.97 X compared to Day 1 values) was observed in 2F on Day 7.

TK:
Table 35: PK parameters of elinzanetant following 7-day treatment in monkeys at 40 mg/kg/day.

<table>
<tr><th>Parameter[1]</th><th>Period</th><th>40 (mg/kg/day)</th></tr>
<tr><td rowspan="2">AUC_{0-24} (µg.h/mL)</td><td>Day 1</td><td>4.87
(3.26 to 6.26)</td></tr>
<tr><td>Day 7</td><td>7.59
(5.74 to 8.96)</td></tr>
<tr><td rowspan="2">C_{max} (µg/mL)</td><td>Day 1</td><td>0.314
(0.255 to 0.401)</td></tr>
<tr><td>Day 7</td><td>0.667
(0.415 to 1.12)</td></tr>
<tr><td rowspan="2">T_{max} (h)</td><td>Day 1</td><td>8
(4 to 24)</td></tr>
<tr><td>Day 7</td><td>8
(4 to 24)</td></tr>
</table>
1. Values presented as mean (range) for AUC_{0-24} and C_{max}, and as median (range) for T_{max}
Source: Extracted from study report R-13640

<u>Reviewer's note</u># 40 mg/kg/day in F monkey for 7 days was tolerated (no mortality) but with emerging GI clinical signs.</td></tr>
<tr><td>R-13627*; non-GLP

Monkey (oral)
7 days
@ 0, 60, 100 mg/kg/day (M+F)
(tosylate salt)

Dosing: once daily

NOAEL = not determined</td><td>Key findings:
• Loose/watery and/or soft feces, inappetence, and excessive salivation @ all doses in M and F
• @ 60 mg/kg: dehydration, decrease in red blood cell parameters in F, serum glutamate dehydrogenase increase in M
• @ 100 mg/kg: ulceration in the pyloric region of the stomach in F, increase in triglyceride.</td></tr>
</table>

Repeat-Dose Toxicity Studies: Non-Pivotal

Study No. & Design	Study findings
	TK: Table 36: PK parameters of elinzanetant following 7-day treatment in monkey. Males 60 mg/kg: Day 1: AUC0-24h (µg.h/mL) 36.6; Cmax (µg/mL) 2.62; Tmax (h) 8.0 60 mg/kg: Day 7: AUC0-24h (µg.h/mL) 82.9; Cmax (µg/mL) 4.94; Tmax (h) 2.0 100 mg/kg: Day 1: AUC0-24h (µg.h/mL) 16.7; Cmax (µg/mL) 1.27; Tmax (h) 8.0 100 mg/kg: Day 7: AUC0-24h (µg.h/mL) 28.9; Cmax (µg/mL) 3.14; Tmax (h) 1.0 Females 60 mg/kg: Day 1: AUC0-24h (µg.h/mL) 12.3; Cmax (µg/mL) 0.619; Tmax (h) 12.0 60 mg/kg: Day 7: AUC0-24h (µg.h/mL) 19.4; Cmax (µg/mL) 1.73; Tmax (h) 5.0 100 mg/kg: Day 1: AUC0-24h (µg.h/mL) 15.7; Cmax (µg/mL) 0.954; Tmax (h) 12.0 100 mg/kg: Day 7: AUC0-24h (µg.h/mL) 21.0; Cmax (µg/mL) 1.98; Tmax (h) 2.0 Source: Excerpted from review by Dr. Frederic Moulin*
R-13639*; GLP Monkey (oral) 29 days [4-week] @ 0, 6, 20, 60 mg/kg/day in M and F (tosylate salt) Dosing: once daily NOAEL = 20 mg/kg/day	Key findings: • 1M and 1F @ 60 mg/kg were sacrificed prematurely on day 6 and 22, respectively. • Euthanized monkeys had abnormal fecal consistency (loose/watery) and reduction in food intake. Dilation of distal nephron elements in the kidney was considered to be a primary adverse test article-related finding. • Other findings include acinar atrophy of the pancreas, cytoplasmic rarefaction in the liver, and hemorrhage in the adventitia and mucosa of multiple regions in the gastrointestinal tract. • Increase in glucose to creatinine ratio in M @ 60 mg/kg TK: Exposures in M and F were similar. Table 37: PK parameters of elinzanetant following 28-day treatment in monkey. **PK parameters** / **6 mg/kg/day** / **20 mg/kg/day** / **60 mg/kg/day** **Male values on day 1** AUC(0-24) [µg·h/mL]: 1.54 / 4.65 / 28.9 Cmax [µg/mL]: 0.371 / 0.607 / 2.24 Tmax [h]: 2 / 2 / 12 **Male values on day 28** AUC(0-24) [µg·h/mL]: 1.7 / 6.86 / 40.2 Cmax [µg/mL]: 0.227 / 0.609 / 2.24 Tmax [h]: 4 / 4 / 5 **Female values on day 1** AUC(0-24) [µg·h/mL]: 0.961 / 5.01 / 11.2

Repeat-Dose Toxicity Studies: Non-Pivotal	
Study No. & Design	**Study findings**
	C_{max} [µg/mL] 0.199 0.794 0.916 T_{max} [h] 2 2 2 **Female values on day 28** $AUC_{(0-24)}$ [µg·h/mL] 1.15 9.88 31.1 C_{max} [µg/mL] 0.248 1.02 2.13 T_{max} [h] 2 4 14 Source: Reviewer-generated table. ***Reviewer's comments:* Gastrointestinal (GI) findings of loose/watery fecal consistency with reduced food intake at 60 mg/kg/day (~4-fold the human therapeutic exposure on an AUC basis) was noted as potentially concerning findings as they led to premature sacrifice in monkeys. These animals also had hemorrhage in the adventitia and mucosa of multiple regions in the gastrointestinal tract. GI effects were also seen in the 13-week and 39-week studies as decribed below.**

Repeat-Dose Toxicity Studies: Pivotal	
Study No. & Design	**Study findings**
R-13629*; GLP **Monkey (oral)** **13 weeks** @ 0, 6, 20, 40 mg/kg/day in M and F (free base form) **Dosing: once daily** **NOAEL =** 40 mg/kg/day Safety margin =2.9-fold (M) and 1.2-fold (F) on AUC basis for MRHD	Mortality: No premature deaths Clinical signs: • Thin appearance and dehydration were occasionally observed for females in all dose groups (including controls) but with greater frequency for females given ≥20 mg/kg. • Abnormal feces (liquid/soft) were noted in many animals across all dose groups at various points throughout the study. The incidence and severity of the findings were comparable between doses. Body weight and Food consumption: • Slight reduction in body weight or lack of body weight gain towards the end of the study was noted in some males and/or females across all dose groups, affecting 40 mg/kg animals more predominantly. • A reduction in food intake/appetite was observed throughout the study at all dose groups (including controls) for all males and females with the exception of a single animal. Hematology and Clinical chemistry: • Decrease in red blood cell count, hemoglobin, hematocrit and reticulocyte counts compared to controls @ 20 and/or 40 mg/kg. • Mild decrease in glucose and mild increase in triglycerides and urea @ 20 and/or 40 mg/kg.

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Repeat-Dose Toxicity Studies: Pivotal

Study No. & Design	Study findings
	Organ Weight and Histopathology: • No test article-related changes in organ weight, macroscopic, or microscopic findings. TK: • $AUC_{(0\text{-}t)}$ values increased from Day 28 to Day 91 at all doses, and systemic exposure to elinzanetant (mean $AUC_{0\text{-}t}$ and C_{max} values) increased greater than dose proportionally, but the inter-animal variability was large.

Table 38: PK parameters of elinzanetant following 91-day (13-week) treatment in monkey.

PK parameters	6 mg/kg/day	20 mg/kg/day	40 mg/kg/day
Male values on day 28			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	0.266	2.21	9.207
C_{max} [µg/mL]	0.0569	0.211	0.642
T_{max} [h]	4	4	6
Male values on day 91			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	0.54	3.65	24.75
C_{max} [µg/mL]	0.037	0.25	1.77
T_{max} [h]	6	4	8
Female values on day 28			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	0.276	2.645	5.192
C_{max} [µg/mL]	0.0548	0.264	0.465
T_{max} [h]	4	4	3
Female values on day 91			
$AUC_{(0\text{-}24)}$ [µg·h/mL]	0.64	4.19	10.33
C_{max} [µg/mL]	0.064	0.321	0.781
T_{max} [h]	7	6	6

Source: Reviewer-generated table.

Repeat-Dose Toxicity Studies: Pivotal	
Study No. & Design	**Study findings**
R-13612[$] [as amended twice]; GLP **Monkey (oral)** **13 weeks** @ 0, 30, 60, 80 mg/kg/day [0, 15, 30, 40 mg/kg BID] in M and F (free base form) **Dosing: BID (6 h apart)** **NOAEL =** 40 mg/kg BID or 80 mg/kg/day Safety margin =1.9-fold (M) and 2.7 -fold (F) on AUC basis for MRHD	Mortality: None Clinical signs: • Thin appearance @ 40 mg/kg BID; Loose/liquid feces in M @ 30 mg/kg BID and F @ 15 mg/kg BID. • Mild and transient decrease in body temperature in 1M @ 40 mg/kg BID. Body weight and food consumption: • Reduced body weight gain in M @ ≥15 mg/kg BID and in M and F @ ≥ 40 mg/kg BID. • Lower food consumption recorded occasionally in animals treated with 30 mg/kg BID and frequently in animals given 40 mg/kg BID when compared with control animals. Clinical chemistry: Reduced ALP and GGT in M and increased mean creatinine levels with reduced chloride levels in F @ 40 mg/kg BID, with no histopathological correlations. Organ weight: • Increase liver weight (relative to body or brain weight) in both M and F @ 40 mg/kg BID, with no corresponding microscopic changes in the liver. • In M, dose-dependent decrease in epididymis and testes mean weight. Note# The male animals were found to have varying degrees of sexual maturity that may have influenced organ weight differences (i.e., 2 controls were sexually mature, whereas all treated males were immature). ***Reviewer's comment. NK1R/NK3R inhibition in KNDy neurons in the hypothalamus reduces the activity of hypothalamic neurons that secrete gonadotropin-releasing hormone (GnRH). The reduced GnRH release suppresses the release of gonadotropins (luteinizing hormone [LH] and follicular stimulating hormone [FSH]) from the anterior pituitary gland. A reduction of the LH and FSH levels due to elinzanetant-induced inhibition of NK1R/NK3R could explain the dose-dependent reduction of the mean weight of epididymis and testes.*** Histopathology: • No test article-related changes in microscopic findings. TK: • High inter-animal variability and some overlap in exposure between doses. • Mean exposure in M was higher than in Fs on both Days 1 and 91 @ 15 mg/kg BID whereas on Day 1 the mean exposure in F @ 30 mg/kg BID was higher than in M.

Repeat-Dose Toxicity Studies: Pivotal

Study No. & Design	Study findings
	Table 39: PK parameters of elinzanetant following 91-day (13-week) treatment in monkeys dosed BID. **PK parameters** / **15 mg/kg BID** / **30 mg/kg BID** / **40 mg/kg BID** **Male values on day 1** $AUC_{(0-24)}$ [µg·h/mL] 7.370 7.340 30.40 C_{max} [µg/mL] 0.609 0.603 1.96 T_{max} [h] 3 24 12 **Male values on day 91** $AUC_{(0-24)}$ [µg·h/mL] 8.440 10.7 16.30 C_{max} [µg/mL] 0.671 0.885 1 T_{max} [h] 7 9 9 **Female values on day 1** $AUC_{(0-24)}$ [µg·h/mL] 2.99 20.5 24.9 C_{max} [µg/mL] 0.313 1.41 1.79 T_{max} [h] 9 24 7 **Female values on day 91** $AUC_{(0-24)}$ [µg·h/mL] 1.670 16.2 24 C_{max} [µg/mL] 0.178 1.370 1.690 T_{max} [h] 1 9 9 Source: Reviewer-generated table.
R-13895[#]; GLP **Monkey (oral)** **39 weeks** @ 0, 30, 60 and 80 mg/kg/day [0, 15, 30 and 40 mg/kg BID], 6 h apart) in M and F for 39-week **Dosing: BID (6 h apart)** **NOAEL =** 80 mg/kg/day (40 mg/kg BID) for M 30 mg/kg/day (15 mg/kg BID) for F Safety margin = 1-fold (M) and 0.35-fold (F) on AUC basis for MRHD	Mortality: None Clinical signs: • Loose and/or liquid feces in M @ 15 and 40 mg/kg BID and F @ 30 and 40 mg/kg BID. • Diarrhea accompanied by additional GI disturbances signs including distended and gassy abdomen and signs of dehydration in some animals. • 2F @ 40 mg/kg BID had diarrhea that led to dehydration, weight loss and general ill-health. minimal inflammatory cell infiltrate in the mucosa of the large intestine was also seen. • 1F @ 30 mg/kg BID had muscle fasciculation during 2 consecutive days towards the end of the treatment period. • Occasional contracted muscles in toes and abnormal locomotion observed for animals in each treated group with a dose-related incidence during the first 2 weeks of treatment. Body weight and food consumption: • Mean body weight gain ~48% lower than controls in F @ 40 mg/kg BID which correlated with GI-related effects (loose stool/diarrhea). • Food consumption information was not provided. Clinical chemistry: • Increased ALT activity in F @ 40 mg/kg BID at week 13 and 26 (2.5-fold) and 39 (3.6-fold) and in M @ 30 mg/kg BID at week 39 (1.8-fold). • Increased plasma urea in F @ 40 mg/kg BID at week 39. • Increased triglycerides in M and F @ 30 and 40 mg/kg BID.

Repeat-Dose Toxicity Studies: Pivotal

Study No. & Design	Study findings

Organ weights:

- Dose-related increase in liver weights in M (up to 68% @ 40 mg/kg BID) and F (up to 38% increase @ 40 mg/kg BID)
- Decreased absolute and relative (to body weight) female reproductive organ weights @ 30 mg/kg BID (ovaries: -67%) and 40 mg/kg BID (uterus and cervix: -43%; ovaries: -55%).

Histopathology:

- Liver: Sinusoid compression in liver, presenting as narrowing of the sinusoidal space in M and @ 40 mg/kg BID and F @ 30 mg/kg BID.
- Large Intestine: Minimal inflammatory cell infiltrate in the mucosa of the cecum or colon of F @ 40 mg/kg BID.
- Ovaries: Corpora lutea and/or follicular activity absent in the ovaries of F @ 30 and 40 mg/kg BID, correlating with a reduction in ovary weight. These changes are consistent with an observed lack of menstrual cycling; however, menstrual status was not monitored for females during the in-life phase this study. These findings are consistent with the expected pharmacological effects of elinzanetant.

TK:

Table 40: PK parameters of elinzanetant following 39-week treatment in monkey.

PK parameters	15 mg/kg, BID	30 mg/kg, BID	40 mg/kg, BID
Male values on day 1			
$AUC_{(0-24)}$ [µg·h/mL]	2.67	6.46	21
C_{max} [µg/mL]	0.256	0.475	1.450
T_{max} [h]	9	9	9
Male value on week 39			
$AUC_{(0-24)}$ [µg·h/mL]	2.4	5.690	8.370
C_{max} [µg/mL]	0.221	0.494	0.793
T_{max} [h]	7	7	8
Female values on day 1			
$AUC_{(0-24)}$ [µg·h/mL]	2.730	6.2	13.4
C_{max} [µg/mL]	0.222	0.491	1.1
T_{max} [h]	8	9	14
Female values on week 39			
$AUC_{(0-24)}$ [µg·h/mL]	3.0	16.90	9.490
C_{max} [µg/mL]	0.332	1.300	0.771
T_{max} [h]	7	4	4

Source: Reviewer-generated table.

Reference ID: 5623053

Repeat-Dose Toxicity Studies: Pivotal	
Study No. & Design	**Study findings**
	As a note# metabolites M27, M22, M18/21, and M30/34 systemic exposures were measured in this study. • Metabolite exposure for M27, M18/21, and M30/34 generally increased in a dose proportional manner with the increase in elinzanetant dose level from 30 to 80 mg/kg/day. • For the M22 metabolite, systemic exposure generally increased in a greater than dose proportional manner on Day 1 from 30 to 80 mg/kg/day elinzanetant. M22 metabolite levels could not be accurately determined at the 30 mg/kg/day dose level at Week 39. At Week 39, increases in M22 systemic exposure were less than dose proportional from 60 to 80 mg/kg/day. • No accumulation of any metabolite was observed after multiple doses of elinzanetant in monkeys.

Note: Safety margins calculated based on clinical exposure at the Maximum Recommended Human Dose (MRHD) of AUC_{0-24} = 8572.0 µg.h/L [from the clinical study number CPM50130 (report number B002427)]
$ Not previously reviewed under IND 129492
* Nonclinical reviews under IND 129492 in DARRTS dated 01/30/2017
** Nonclinical review under IND 129492 in DARRTS dated 10/19/2020 when reviewing the rat SPA (Carci)
# Nonclinical review under IND 129492 in DARRTS dated 08/25/2022 (phase 3 protocol)

7 Genetic Toxicology

Genotoxicity studies conducted with elinzanetant and with metabolites (study reports located under from module 4.2.3.7.5) are included in this section.

Overall, the in-vitro and in-vivo genotoxicity studies with elinzanetant and in-vitro genotoxicity studies with its three principal metabolites (M27, M30/34, and M18/21) showed **negative results.**

Genotoxicity Studies – elinzanetant	
Study No. & Design	**Study findings**
R-13577 (GLP) Ames assay up to 1500 µg/plate (limit of solubility) with elinzanetant (Tosylate salt)	Elinzanetant did not induce mutations in the presence or absence of S9.
R-13579 (GLP) Mutagenicity assay in cultured mouse lymphoma L5178Y cells (up to 80 µg/mL for 3 h and 50 µg/mL for 24 h) with elinzanetant (Tosylate salt)	Elinzanetant was not mutagenic in mouse lymphoma L5178Y cells under treatment conditions (3 h with or without S9 or 24 h without S9 followed by a 2-day expression period).
R-13576 (GLP) Micronucleus Assay in Rats @ 0, 1000, 2000 mg/kg/day, males, oral gavage, for two days with elinzanetant (Tosylate salt)	Elinzanetant did not induce chromosomal aberrations in vivo in male rats. Piloerection and hunched posture were observed on day 2. @ 2000 mg/kg: Systemic exposure mean: 17200 ng/mL, range: 14600 to 19200 ng/mL.

Metabolite Genotoxicity Studies - metabolites	
R-13888* (GLP) Ames assay @ 0, 5, 16, 50, 160, 500, 1600 and 5000 µg/plate M27 (BAY 3462932)	M27 metabolite of elinzanetant did not induce gene mutations at concentrations up to 5000 µg/plate (precipitation observed ≥ 1600 µg/plate) in the absence of S9. No testing was performed in the presence of S-9.
R-13874* (GLP) Micronucleus assay in cultured human lymphocytes. M27 (BAY 3462932)	M27 metabolite of elinzanetant did not induce chromosomal aberrations in the absence of S9 at 3+21 h (up to 80 µg/mL) and 24+0 h (up to 30 µg/mL). No testing was performed in the presence of S9.
R-13867*(GLP) Ames assay @ 5, 16, 50, 160, 500, 1600 and 5000 µg/plate M30/M34 (BAY 3462933)	M30/M34 metabolites of elinzanetant did not induce mutations at concentrations up to 5000 µg/plate (precipitation observed ≥ 1600 µg/plate) in the absence of S9. No testing was performed in the presence of S9.
R-13866*(GLP) Micronucleus assay in cultured human lymphocytes. (up to 60 µg/mL) M30/34 (BAY 3462933)	M30/M34 metabolites of elinzanetant did not induce chromosomal aberrations at 3+24 h up to 60 µg/mL and 24 h up to 30 µg/mL in the absence of S9. No testing was performed in the presence of S9.
PH-42069* (GLP) M18/21 Salmonella/Microsome Test up to 5000 µg/plate M18/21 (BAY 3462934)	M18/21 metabolites of elinzanetant did not induce gene mutations in the salmonella microsome assay up to 5000 µg/plate with or without S-9. (precipitation observed ≥ 1600 µg/plate).
PH-42100* Micronucleus assay in Chinese hamster V79 cells M18/21 (BAY 3462934)	M18/21 metabolites of elinzanetant did not induce chromosomal aberrations in vitro (up to 30 µg/mL for 4 h + 20 h recovery or 24 h treatment without S9, and up to 45 µg/mL for 4 h + 20 h recovery with S9).
* Metabolite genotoxicity assays were deemed valid and negative in the Nonclinical review under IND 129492 in DARRTS dated 08/25/2022.	

8 Carcinogenicity

The following table describes the dose range finding (DRF) studies.

Dose range finding (DRF) studies in mice	
Study No. & Design	**Study findings**
R-14290[##]; non-GLP (DRF study to determine MTD) Reviewed under IND 129492 as study T105245-7 Wild type rasH2 mice: Phase 1: @ 50, 100, 200 mg/kg/day (adaptive DRF study up to 21 days)	Mortality: In Phase 2, 1/24 (M) @ 200 mg/kg/day euthanized (due to broken limb) Clinical signs: None Clinical chemistry: Increase (~3-5X) in Total bilirubin @ 200 mg/kg/day TK: • No sex differences in exposure • Accumulation seen on day 7

Reference ID: 5623053

Dose range finding (DRF) studies in mice

Study No. & Design	Study findings
Phase 2: @ 0, 200 mg/kg/day for 7 days Dosing: BID (6.5 h apart) by oral gavage Conclusion: MTD not reached	Table 41: Summary of the BAY 3427080 TK parameters in mouse (Tg RAS) plasma. Dose Level (mg/kg/day) / Day / Sex / C_{max} (µg/L) / T_{max} (h) / AUC_{0-24} (h*µg/L) / DN AUC_{0-24} (kg*h/L) 200 / 1 / M / 4660 / 1.00 / 58200 / 0.291 F / 4040 / 7.00 / 59700 / 0.299 MF / 3800 / 1.00 / 59000 / 0.295 7 / M / 11200 / 7.00 / 183000 / 0.913 F / 9520 / 7.00 / 168000 / 0.839 MF / 10300 / 7.00 / 175000 / 0.876 Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately. Doses were administered twice daily (6 hours ± 30 minutes apart). Tlast occurred at 24 hours. Source: Excerpted from review by Dr. Leslie McKinney[##] Metabolites TK: • BAY3462932 (M27), BAY 3462933 (M30/34) and BAY 3462934 (M18/21) had a similar T_{max} and similar decline. • Accumulation after repeated dosing was observed for M27 and M18/21, while there was no notable accumulation for M30/34. • No marked differences in exposure were noted for the three metabolites between M and F.
R-14213; non-GLP Reviewed under IND 129492 as study T105362-7 (T105362-7-EXT) Wild type rasH2 mice @ 300, 500/400* mg/kg/day (oral gavage) for 12-14 day Dosing: BID (6.5 h apart) *250 mg/kg/dose on Days 1-3, 200 mg/kg/dose beginning with the 2nd dose on day 5 and continuing BID through 12 of the dosing phase, dependent on survival. NOAEL= not determined. MTD is above 200 mg/kg/day; the MTD was exceeded at 500 mg/kg/day. At 300 mg/kg/day most animals showed clinical signs	Mortality or unscheduled sacrifice: • All M and all F @ HD (500 mg/kg/day). • 1 F @ LD (300 mg/kg/day). Clinical signs: Severe clinical signs including weight loss, hunched posture, decreased activity, piloerection and/or squinting eyes. Body weight: • All M @ HD (500 mg/kg/day) and 12/18 F had body weight loss on day 4. • After dosing holiday and reduction of dose to 200 mg/kg (BID) or 400 mg/kg/day, body weight losses were noted between Days 5 and 7 for 6/13 remaining M and between Days 5 and 8 for 12/18 F. Clinical chemistry: Mild elevations of bilirubin; no correlating histopathology. TK: • No sex-related differences in exposure to parent and metabolites M30/34, M27, and M18/21. • Exposure was dose proportional for parent compound and roughly dose proportional for metabolites. • C_{max} of BAY 3427080 (parent) was observed at 7 h in female mice and between 1 h and 7 h in male mice dosed with 300 mg/kg/day. • Accumulation was noted for the parent compound: $AUC_{(0-24h)}$ fold increase being 2.3 in female and 1.6 in male mice. Even greater accumulation was observed for metabolites: ≤5.6-fold

<table>
<tr><th colspan="2">Dose range finding (DRF) studies in mice</th></tr>
<tr><th>Study No. & Design</th><th>Study findings</th></tr>
<tr><td></td><td>for BAY 3462932 (M27), 1.6-fold for BAY 3462933 (M30/34) and 5.8-fold for BAY 3462934 (M18/21).
• Metabolite exposure was lower than the exposure to the unchanged drug. It was ≤ 12% for M27, 17% for M30/34 and 3.1% for M18/22 compared to the parent compound on day 14.
Table 42: TK parameters for the low dose group (300 mg/kg/day) on day 14.
<table><tr><td>Dosing Day 14</td><td></td><td>Female</td><td></td><td>Male</td><td></td></tr><tr><td>Dose BAY 3427080</td><td>[mg/kg/day]</td><td>300</td><td></td><td>300</td><td></td></tr><tr><td>Dose BID BAY 3427080</td><td>[mg/kg]</td><td>150</td><td></td><td>150</td><td></td></tr><tr><td>Time
[h]</td><td></td><td>gMean
[µg/L]</td><td>gSD</td><td>gMean
[µg/L]</td><td>gSD</td></tr><tr><td>1</td><td></td><td>12200</td><td>1.38</td><td>9990</td><td>1.35</td></tr><tr><td>7</td><td></td><td>15400</td><td>1.46</td><td>9450</td><td>1.64</td></tr><tr><td>24</td><td></td><td>2180</td><td>1.91</td><td>4800</td><td>1.45</td></tr><tr><td>Parameter</td><td>Unit</td><td></td><td></td><td></td><td></td></tr><tr><td>$AUC_{(0-24h)}$</td><td>µg*h/L</td><td>239000</td><td></td><td>187000</td><td></td></tr><tr><td>$AUC_{(0-24h),\ norm}$</td><td>kg*h/L</td><td>0.797</td><td></td><td>0.623</td><td></td></tr><tr><td>t_{last}</td><td>h</td><td>24</td><td></td><td>24</td><td></td></tr><tr><td>C_{max}</td><td>µg/L</td><td>15400</td><td></td><td>9990</td><td></td></tr><tr><td>$C_{max,\ norm}$</td><td>kg/L</td><td>0.0513</td><td></td><td>0.0333</td><td></td></tr><tr><td>t_{max}</td><td>h</td><td>7</td><td></td><td>1</td><td></td></tr><tr><td>C_{last}</td><td>µg/L</td><td>2180</td><td></td><td>4800</td><td></td></tr><tr><td>$C(t_{int})/C_{max}$</td><td>%</td><td>14.2</td><td></td><td>48.0</td><td></td></tr><tr><td>RA-AUClast</td><td>%</td><td>227.6</td><td></td><td>158.5</td><td></td></tr><tr><td>RA-Cmax</td><td>%</td><td>278.5</td><td></td><td>139.9</td><td></td></tr><tr><td>$MR\text{-}AUC_{(0-24h),norm}$ (BAY 3462932)</td><td></td><td>7.6</td><td></td><td>11.9</td><td></td></tr><tr><td>$MR\text{-}AUC_{(0-24h),norm}$ (BAY 3462933)</td><td></td><td>15.6</td><td></td><td>17.2</td><td></td></tr><tr><td>$MR\text{-}AUC_{(0-24h),norm}$ (BAY 3462934)</td><td></td><td>2.2</td><td></td><td>3.1</td><td></td></tr></table>Source: Excerpted from review by Dr. Leslie McKinney##</td></tr>
<tr><td>R-14305; GLP

Reviewed under IND 129492 as study T105264-8

Wild type rasH2 mice @ 0, 20, 60, 200 mg/kg/day (oral gavage) for 28 days

Dosing was done BID (6 h apart)

NOAEL = 20 mg/kg/day [Note# unexplained mortality at all doses; nonetheless, the sponsor set the NOAEL at low dose]

Reviewer's note# study report amended twice. The changes do not appear to affect the final results</td><td>Mortality:
• 1M/1F @ 0 mg/kg/day (M: moribund, F: broken hind limb)
• 1M/1F @ LD (M: body weight loss; F: broken hind limb)
• 2M/1F @ MD (1M/F: body weight loss; 1M: broken limb)
• 1M/3F @ HD (3F: body weight loss; M: broken limb)

Clinical signs: No signs in non-moribund animals.

Body weight:
• 1MD and 3 HD F had marked body weight loss (up to -21%) and were sacrificed in moribund condition.
• Animals that survived to terminal sacrifice showed normal body weights.

Feed consumption: No correlation with body weight loss.

Clinical chemistry: 200 mg/kg/day had increased bilirubin, with no correlative changes in hepatobiliary enzyme activities or microscopic liver findings.

TK:
• Increases in C_{max} and AUC_{0-24} were generally dose proportional to greater-than-dose proportional.</td></tr>
</table>

<table>
<tr><th colspan="2">Dose range finding (DRF) studies in mice</th></tr>
<tr><th>Study No. & Design</th><th>Study findings</th></tr>
<tr><td></td><td>

Sponsor's NOAEL for this study is 20 mg/kg/day corresponded to mean C_{max} and AUC_{0-24} values of 302 ng/mL and 3,990 ng.h/mL, respectively, on Day 28 of the dosing phase.
At the high dose of 200 mg/kg, on day 28, C_{max} and AUC_{0-24} values were 6590 ng/mL and 124000 ng.h/mL, respectively. An exposure multiple of 10.5 X is achieved relative to the proposed clinical human dose for the parent compound based on human 14-day AUC_{0-24} of 11830 ng.h/mL.
Accumulation seen @ HD only.
Metabolites: similar TK as parent compound, with some exceptions - accumulation of BAY 3462932 (M27 and BAY 3462934 (M18/21) were noted @ 200 mg/kg/day

Table 43: Elinzanetant exposure in TgRAS mouse on day 1 and day 28 (study R-14305).
Day 1 AUC_{0-24} ng.h/mL
<table>
<tr><th></th><th>20 mkd</th><th>60 mkd</th><th>200 mkd</th></tr>
<tr><td>M</td><td>6620</td><td>32700</td><td>136000</td></tr>
<tr><td>F</td><td>6620</td><td>26700</td><td>123000</td></tr>
<tr><td>MF</td><td>6620</td><td>29700</td><td>129000</td></tr>
</table>
Day 28 AUC_{0-24} ng.h/mL
<table>
<tr><th></th><th>20 mkd</th><th>60 mkd</th><th>200 mkd</th></tr>
<tr><td>M</td><td>2870</td><td>14900</td><td>88900</td></tr>
<tr><td>F</td><td>5130</td><td>14500</td><td>160000</td></tr>
<tr><td>MF</td><td>3990</td><td>14800</td><td>124000</td></tr>
</table>
mkd= mg/kg/day; M=male, F=female, MF= combined concentration data for all animals (male and female) at each dose level on each interval
Source: Excerpted from review by Dr. Leslie McKinney##
</td></tr>
<tr><td>R-14411; GLP

Transgenic rasH2 Mice @ 0, 150, 200, and 250 mg/kg/day (oral gavage) for 28-day

Dosing: BID (6 h apart)

Reviewed under IND 129492 as study T105617-0 (unaudited draft reviewed under the IND, final report (signed) has been submitted)

NOAEL:

NOAEL set at 200 mg/kg/day for males (M).
NOAEL set at 250 mg/kg/day for females (F)

</td><td>Mortality/unscheduled sacrifice:

1 M @ 200 mg/kg/day (gavage error)
1 F @ 250 mg/kg/day (gavage error),
All M @ 250 mg/kg/day (weight loss, inactivity, clinical chemistry and microscopic findings indicating liver toxicity, as well as skeletal muscle degeneration and loss of adipose tissue)

Clinical signs: Decreased activity, hunched posture, and/or labored respiration

Body weight: Weight loss limited to M @ 250mg/kg/day and associated with poor clinical outcomes but did not correspond with low food consumption.

Clinical chemistry:</td></tr>
</table>

Reference ID: 5623053

<table>
<tr><th colspan="2">Dose range finding (DRF) studies in mice</th></tr>
<tr><th>Study No. & Design</th><th>Study findings</th></tr>
<tr><td></td><td>

Elevated AST, ALT, creatine kinase, and LDH, as well as increased GDH and minimally higher total bilirubin in M @ 250 mg/kg/day that were moribund or prematurely sacrificed.
Elevated total bilirubin (considered by Sponsor to be adaptive metabolic effect and/or inhibition of OATP1B1 transporter protein) @ 200 and 250 mg/kg/day

<u>Gross Pathology</u>:

1 M@ 200 mg/kg/day and 6M @ 250 mg/kg/day had tan discoloration on liver, with correlation to microscopic findings of micro vesicular vacuolation in 4 M @ HD.

<u>Histopathology</u>:

@ 250 mg/kg/day animals showed treatment-related atrophy of adipose tissue and muscle degeneration (biceps femoris). There was also moderate to marked micro vesicular hepatocyte vacuolation (suggestive of lipid accumulation).

<u>TK</u>:

No evidence of sex-related differences in exposure to parent or metabolites, except slightly for M18/21.

Table 44: Elinzanetant exposure in TgRAS mouse on day 1 and day 28 (study R-14411)
<table>
<tr><th>$AUC_{(0\text{-}24)}$ ng.h/mL</th><th colspan="3">Day 1</th></tr>
<tr><th></th><th>150</th><th>200</th><th>250</th></tr>
<tr><td>M</td><td>164000</td><td>160000</td><td>278000</td></tr>
<tr><td>F</td><td>117000</td><td>180000</td><td>234000</td></tr>
</table>
<table>
<tr><th>$AUC_{(0\text{-}24)}$ ng.h/mL</th><th colspan="3">Day 28</th></tr>
<tr><th></th><th>150</th><th>200</th><th>250</th></tr>
<tr><td>M</td><td>98600</td><td>234000</td><td></td></tr>
<tr><td>F</td><td>94400</td><td>110000</td><td>136000</td></tr>
</table>
Note# No samples were obtained on day 28 for M @ HD because they were terminated on Day 10 and Day 11.
Source: Excerpted from review by Dr. Leslie McKinney##
</td></tr>
</table>

Nonclinical review under IND 129492 in DARRTS dated 12/13/2022 (mouse SPA review)

The following table summarizes the findings of the **pivotal carcinogenic studies conducted in transgenic mice and rats**. For the full assessment of the study protocols and reports refer to complete carcinogenicity review in DARRTS dated 02/04/2025, the Executive CAC meeting minutes dated 12/20/2024, and Statistical Review dated 12/12/2024.

Carcinogenicity Studies: Pivotal	
Study No. and Design	**Study Findings**
Mouse	
B003184### Transgenic ras H2 Mice (M and F) 26 weeks @ 0, 10, 30, 85 mg/kg/day in M [0, 5, 15, 42.5 mg/kg BID in M] @ 0, 10, 20, 70 mg/kg/day in F [0, 5, 10, 35 mg/kg BID in F] via oral gavage, with N-methyl-N-nitrosourea single intraperitoneal dose on day 1 as the positive control Oral Dosing: BID (6 h apart)	The mouse carcinogenicity study was conducted at doses recommended by the Executive Carcinogenicity Assessment Committee (Exec CAC) and the overall study was considered adequate. **Key study findings:** • Elinzanetant did not affect the overall survival rate or adverse clinical signs up to the high dose of 85 mg/kg/day in M and 70 mg/kg/day in F. • Oral treatment with elinzanetant doses ranging from 10 to 85 mg/kg/day in M and 10 to 70 mg/kg/day in F compared to vehicle for 26 weeks resulted in no statistically significant neoplastic or non-neoplastic findings. • Negative.
Rat	
B003186### Sprague Dawley Rat (F only) 2 years (104 weeks) @ 0, 7, 20, 60, 80 mg/kg/day in F [0, 3.5, 10, 30, 40 mg/kg BID in F] via oral gavage Dosing: BID (6 h apart)	The rat carcinogenicity study was conducted as per the recommendations of Exec CAC. The study conduct was considered adequate. **Key study findings:** • Oral treatment of F rats with elinzanetant doses ranging from 7 to 80 mg/kg/day compared to vehicle for 104 weeks reduced their body weight gain but had no effect on their survival. • Elinzanetant treatment resulted in the following **neoplastic findings:** ○ Malignant lymphoma in the hematolymphoid system at 80 mg/kg/day. ○ Malignant endometrial adenocarcinoma of the uterus at ≥ 60 mg/kg/day. ○ Combined malignant and benign endometrial tumors ≥ 60 mg/kg/day. ○ Combined malignant and benign endometrial tumors and malignant squamous cell carcinoma of the uterus ≥ 60 mg/kg/day. Note# Refer to Table 45 below (FDA statistical analysis) • The oral dose of **20 mg/kg/day** (NOAEL) was the highest test dose not associated with carcinogenic signals in female rats. Based on AUCs, the clinical exposure margins provided

Carcinogenicity Studies: Pivotal	
Study No. and Design	**Study Findings**
	by the highest noncarcinogenic dose to the MRHD is ~**7.5 X** for elinzanetant and ~0.2 X, 3.7 X, and 0.05 X for the metabolites M27, M30/34, and M18/21, respectively. • The oral dose of **60 mg/kg/day** was the lowest test dose **associated with carcinogenic signals** in female rats. Based on AUCs, the clinical exposure margin provided by this dose to the MRHD is ~**29.4 X** for elinzanetant and ~0.8 X, 7.0 X, and 0.1 X for the metabolites M27, M30/34, and M18/21, respectively. • Additionally, the following **CNS-related signs** were noted in the rats starting at **20 mg/kg/day.** o Increased incidence of whole-body convulsions (≥20 mg/kg/day). o Increased incidence of hunched posture (≥60 mg/kg/day). o Decreased general activity (≥60 mg/kg/day). o Increased sensitivity to touch (≥60 mg/kg/day). o Increased salivation (≥60 mg/kg/day). o Irregular respiration (≥7 mg/kg/day). ***Reviewer's comment: the CNS-related signs observed in the study are discussed separately in the integrated summary section below.***

###Nonclinical review under NDA 219469 in DARRTS dated 02/04/2025

Table 45: Tumor types with statistically significant dose-response relationships and pairwise comparisons in elinzanetant-treated rats.

Organ name	Tumor name	0 mg/kg/day Control (VC) p - Trend	7 mg/kg/day Low dose (LD) p - C vs. LD	20 mg/kg/day Low-mid dose (LM) p - C vs. LM	60 mg/kg/day Mid dose (MD) p - C vs. MD	80 mg/kg/day High dose (HD) p - C vs. HD
Hematolymphoid System	M-Lymphoma	1/100 (72) 0.0020 *	3/100 (67) 0.2831	3/100 (71) 0.3046	6/100 (71) 0.0557	9/100 (72) 0.0087 **
Uterus	M-Adenocarcinoma, Endometrium	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	22/100 (75) 0.00001 **
	M-Carcinoma, Squamous Cell	0/100 (72) 0.0206 *	0/100 (66) NC	1/100 (71) 0.4965	1/100 (69) 0.4894	3/100 (70) 0.1172
	C. Endometrium (B+M)	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	23/100 (75) 0.00001 **
	C. Endometrium (B+M)/ Carcinoma, Squamous Cell	2/100 (72) 0.00001 *	3/100 (67) 0.4658	6/100 (71) 0.1330	16/100 (72) 0.0003 **	25/100 (75) 0.00001 **

Note: X/ZZ (YY): X=number of tumor-bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. **The p-values marked with an asterisk * indicate statistically significant dose-response relationships at p < 0.005 and p < 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparisons at p < 0.01 and p < 0.05 for a common tumor and a rare tumor, respectively.**

Source: Table extracted from FDA Statistical Reviewer Report (dated 12/12/2024 in DARRTS).

9 Reproductive and Developmental Toxicology

A full battery of reproductive and developmental toxicity studies was conducted in rats and rabbits. The studies are summarized below.

9.1 Fertility and Early Embryonic Development (FEED)

Seg I (FEED) Studies: Pivotal

Study No. & Design

R-13611 [reviewed under the IND as study CD2008-01634-00/ G08291] ***; GLP

Female rats
@ 0, 5, 25 and 100 mg/kg/day

Dosing: once daily for 22 days before cohabitation, during cohabitation with untreated males (1 to 14 days) and on Day 0 to 6 postcoitum (pc).

NOAEL (maternal) = 25 mg/kg/day

NOAEL (fetal) = 25 mg/kg/day

Safety margin based on maternal NOAEL = 3 X

$AUC_{0\text{-}24h}$ = 8572.0 µg.h/L [from the clinical study number CPM50130 (report number B002427).

Multiple of Exposure (MOE) For increased pre-post implantation loss @ 100 mg/kg/day
= 14 X

Study findings

- Decreased body weight gain and food consumption @ 100 mg/kg/day during the premating and gestation treatment periods and @ 25 mg/kg/day during the gestation treatment period with decreases in mean food consumption @ 25 and 100 mg/kg/day.
- Increased pre- and post-implantation losses and decreased number of implantations @ 100 mg/kg.
- Decreased number of live fetuses, uterus weight, and fetal body weights @ 100 mg/kg/day.

Table 46: Mean cesarean section observation per litter in the rat FEED study.

Dose	Average Number of Implants	% Pre-implant losses	% Post-implant losses	Average Number of Live Fetuses	Gravid Uterus Weights, % Control	Fetal Weights	
						Females, % Control	Males, % Control
0 mg/kg	15.1	4.5	9.5	13.7	100	100	100
5 mg/kg	15.3	4.6	9.4	13.9	103.4	101.1	103.1
25 mg/kg	15.2	2.3	4.9	14.4	103.4	97.5	98.2
100 mg/kg	**13.5**	**11.5***	**14.6**	**12.3**	**88.2**	**92.4***	**91.4***

*: Statistically significantly different from control, p<0.05

Source: Excerpted from review by Dr. Frederic Moulin***

TK: (not conducted for the study)*

Exposure in female on Week 4	Dose (mg/kg/day)		
	5	25	100
$AUC_{(0\text{-}tlast)}$ (µg·h/mL)	8.05	27.5	116
C_{max} (µg/mL)	0.626	1.80	6.57
Tmax (h)	1	1	2

*Source: Reviewer-generated table using TK values at the 4-week timepoint from 13-week toxicity study in non-pregnant rats [R-13596]

Clinical $AUC_{0\text{-}24h}$ = 8572.0 µg.h/L used to calculate safety margin and MOE [from the clinical study number CPM50130 (report number B002427)].
*** Refer to nonclinical review under IND 129492 dated 08/02/2019 in DARRTS

9.2 Embryonic Fetal Development (EFD)

EFD studies were conducted in rats and rabbits.

<table>
<tr><th colspan="2">Seg II (EFD) Studies: Pivotal</th></tr>
<tr><th>Study No. & Design</th><th>Study findings</th></tr>
<tr><td>R-13610 [Reviewed under the IND as study CD2008/01636/00; G08290] ***; GLP

Female rat
@ 0, 5, 25 or 100 mg/kg/day
Dosing: once daily from GD 6 to 17

NOAEL (maternal) =
25 mg/kg/day

NOAEL (fetal) =
100 mg/kg/day

Safety Margin based on maternal NOAEL= 7X

Safety Margin based on fetal NOAEL = 23 X</td><td>• There was a statistically significant decrease in mean maternal body weight gain @ 100 mg/kg/day along with a statistically significant decrease in mean food consumption.
• There was no test article-related effect on placenta morphology or on mean numbers of corpora lutea, implantations, resorptions, pre- or post-implantation losses, live or dead fetuses, percent live males, or on gravid uterus weight at any dose.
• No test article-related effect on fetal body weights at any dose level.
• The number of fetuses with variations (visceral and skeletal) was higher in the 100 mg/kg/day dose group. These were not considered test article related due to: (i) inconsistent pattern of variations in the affected litters, (ii) incidence of variations in elinzanetant-exposed litters being well below the incidence in historical controls in the same facility, and (iii) lack of dose responsiveness. The finding could be a result of the maternal toxicity at the high dose.

Table 47: Elinzanetant exposure in pregnant female rats.
<table><tr><th rowspan="2">Exposure on GD 17</th><th colspan="3">Dose (mg/kg/day)</th></tr><tr><th>5</th><th>25</th><th>100</th></tr><tr><td>AUC(0-tlast) (µg•h/L)</td><td>8610</td><td>57200</td><td>197000</td></tr><tr><td>Cmax (µg/L)</td><td>758</td><td>3630</td><td>15300</td></tr><tr><td>Tmax (h)</td><td>4</td><td>2</td><td>6</td></tr></table>Source: Reviewer-generated table with TK values excerpted from DRF PPND study (study B003162) which uses the same doses (from table 1 on page 465 of study report).</td></tr>
<tr><td>R-13597
[Reviewed under the IND as study CD2009/0044 7/00; G09062]; GLP

Female rabbits
@ 0, 60, 90, or 140 mg/kg/day
[0, 30, 45, 70 mg/kg BID]

Dosing: BID; from GD 7 to GD19

NOAEL (maternal) = 90 (45 mg/kg BID) produces AUC of 2160 µg.h/L

NOAEL (fetal) = 140 (70 mg/kg BID) produces AUC of 10600 µg.h/L

Safety margin (Maternal) = 0.25 X

Safety margin (Fetal) = 1.23 X</td><td>• Maternal toxicity (euthanasia, marked body weight loss, and decreased food consumption) @ 140 mg/kg/day. 4 Dams had to be euthanized.
• No test article-related effects on developmental or fetal growth parameters at any dose and no test article-related effect on mean fetal body weight, fetal malformations or variations at any dose.
• TK measured in the study is shown in the table.

Table 48: Elinzanetant exposure in female rabbits in EFD study.
<table><tr><th rowspan="2">Exposure on GD 19</th><th colspan="3">Dose (mg/kg/day)</th></tr><tr><th>60</th><th>90</th><th>140</th></tr><tr><td>AUC(0-tlast) (µg•h/L)</td><td>1250</td><td>2160</td><td>10600</td></tr><tr><td>Cmax (µg/L)</td><td>110</td><td>206</td><td>953</td></tr><tr><td>Tmax (h)</td><td>9</td><td>9</td><td>10</td></tr></table>Source: Reviewer-generated table.</td></tr>
<tr><td colspan="2">Clinical AUC0-24h = 8572.0 µg.h/L used to calculate safety margin and MOE [from the clinical study number CPM50130 (report number B002427).</td></tr>
</table>

Reference ID: 5623053

DRF and TK Studies in Pregnant Rabbits: Non-pivotal studies

R-13608 [D08289][$]
GSK1144814: Oral Dose Range Study in Female Rabbits

Study conducted in 3 parts/stages)

Part 1
Female rabbit @ 0, 15, mg/kg/day, once daily for 13 days from day 6 postcoitum (p.c.) and 125 mg/kg/day, once daily for 8 days from day 6 p.c.

NOAEL **=** 15 mg/kg/day

Part 2
Female rabbits @ 0, 30, 60 mg/kg/day, once daily from day 6 p.c.

NOAEL (maternal) = 60 mg/kg/day

Part 3
Female rabbit @ 0, 90 mg/kg/day once daily or 140, 180 mg/kg/day (given 70, 90 mg/kg BID) for 13 days from day 6 p.c.

NOAEL = not established

Part 1

- Maternal toxicity (moribundity, excessive body weight loss up to ~10%, marked decreases in food consumption) resulting in early termination (day 14 or day 15) of the group @ 125 mg/kg/day.

Part 2

- No test article-related findings.

Part 3

- Decrease in maternal body weight (~6%) @ 90 mg/kg/day. Doses 140 and 180 mg/kg/day not well tolerated.
- Decrease in maternal body weight gain during the treatment period @ 140 mg/kg/day. Abortion on day 17 (1 in 4 rabbits).
- Maternal toxicity (moribundity, excessive body weight loss ~5 to 11%, and marked decreases in food consumption) resulting in abortion (3 in 4 rabbits) and early sacrifice (day 15) @ 180 mg/kg/day.

B002328 [T105246-8-EXT/ 8469581][$]

Oral Gavage Study with BAY 3427080 (NT814) in Pregnant Female Rabbits, Including Toxicokinetics

Female rabbits
@ 0, 60, 90, 140 mg/kg/day
[0, 30, 45 and 70 mg/kg BID]
Dosing: BID; from GD 7 to 11

[$]Not previously reviewed under IND 129492.

- Metabolites M27, M30/34 and M18/21 exposure measured.
- Exposure to elinzanetant assessed by $AUC_{(0\text{-}24h)}$ on GD 11 increased greater than dose proportionally with increasing dose; whereas C_{max} did not increase between the 60 and 90 mg/kg/day doses but was greater than dose-proportional between 90 and 140 mg/kg/day.
- The dose-normalized exposure to metabolites was equal or less than 59.4 % for BAY 3462932 (M27), 29.4 % for BAY 3462933 (M 30/34) and 26.9 % for BAY 3462934 (M18/21) of the dose-normalized exposure to BAY 3427080.

Table 49: Summary of elinzanetant exposure and metabolite ratio on gestation day 11.

Dose BAY 3427080	[mg/kg/day]	60	90	140
Parameter	Unit			
$AUC_{(0\text{-}24h)}$	µg*h/L	1010	1650	4580
$AUC_{(0\text{-}24h),\ norm}$	kg*h/L	0.0168	0.0183	0.0327
t_{last}	h	24	24	24
C_{max}	µg/L	92.2	109	475
$C_{max,\ norm}$	kg/L	0.00154	0.00121	0.00339
t_{max}	h	10	9	10
C_{last}	µg/L	14.9	41.6	48.8
$C(t_{int})/C_{max}$	%	16.2	38.2	10.3
$MR\text{-}AUC_{(0\text{-}24h),norm}$	% BAY 3462932	56.7	51.6	53.2
$MR\text{-}AUC_{(0\text{-}24h),norm}$	% BAY 3462933	29.3	28.0	26.2
$MR\text{-}AUC_{(0\text{-}24h),norm}$	% BAY 3462934	23.6	21.1	18.5
$MR\text{-}C_{max,\ norm}$	% BAY 3462932	59.4	55.1	57.2
$MR\text{-}C_{max,\ norm}$	% BAY 3462933	29.4	28.2	26.0
$MR\text{-}C_{max,\ norm}$	% BAY 3462934	26.9	21.2	18.6

Extracted from study report (page 20).

[$] Not previously reviewed under IND 129492

9.3 Prenatal and Postnatal Development (PPND)

A PPND study was conducted in the rat. The key findings from the dose-range finding (DRF) and pivotal study are described below. Refer to full review attached in the Appendix.

<table>
<tr><th colspan="2">Seg III (PPND) Studies: DRF and Pivotal</th></tr>
<tr><th>Study No. & Design</th><th>Study findings</th></tr>
<tr><td>B003162 or T105436-9/8500238[$]; DRF study; GLP

Female rats
@ 0, 5, 25, 100 mg/kg/day once daily (QD) and 50 mg/kg BID
Dosing: once daily or BID from GD 6 to lactation day (LD) 4

Maternal NOAEL = 25 mg/kg/day

Fetal NOAEL = not determined (decrease in pup viability index at lowest dose tested)</td><td>Key findings:
Mortality: @ 100 mg/kg/day QD group and 50 mg/kg BID group.
Clinical observations: dystocia (e.g., piloerection, rough pelage, hunched posture, and decreased activity), decreased body weight and body weight gain, and decreased food consumption were observed in dams found in moribund condition.
Litters: Increase in total litter loss and decreased pup viability (by PND 5) in all elinzanetant-treated groups.
Gestational outcomes: Increased gestation length, post-implantation loss, decreased number of liveborn pups delivered, decreased pup body weights, and pups found with no milk in stomach.
Table 50: Elinzanetant exposure in pregnant rats on GD17.<table><tr><th rowspan="2">Exposure on GD 17</th><th colspan="3">Dose (mg/kg/day)</th></tr><tr><th>5</th><th>25</th><th>100</th></tr><tr><td>AUC(0-tlast) (µg*h/L)</td><td>8610</td><td>57200</td><td>197000</td></tr><tr><td>Cmax (µg/L)</td><td>758</td><td>3630</td><td>15300</td></tr><tr><td>Tmax (h)</td><td>4</td><td>2</td><td>6</td></tr></table>Reviewer-generated table from Bioanalytical and TK Analyses report in appendix 10.4 of the study report (Table 1 on page 456).</td></tr>
<tr><td>B003187 [T105437-0/ 8500239][$]; Pivotal Study; GLP

Female rats
@ 1.5, 5, 15 mg/kg/day
Dosing: once daily from GD 6 to LD 21

Maternal and Fetal NOAEL = 1.5 mg/kg/day corresponds to AUC of 2000

Safety margin: At the NOAEL of 1.5 mg/kg/day for developmental toxicity, there is no safety margin for the AUC0-24 of 8572 ng•h/mL (Elinzanetant) obtained from clinical study B002427.</td><td>Dams (F0)
No effects seen on maternal mortality, clinical observations, or other outcomes.
Higher number of dams with still born pups in elinzanetant treatment groups.
Litters (F1)
Increase in total litter deaths and stillborn pups @ 5 and 15 mg/kg/day.
There was a decrease in viability index, i.e, % alive on PND 4 versus PND 0 (83% @ 5 and 15 mg/kg/day compared with 96% in controls and 1.5 mg/kg/day).
Increased incidence of neonatal pups with no milk band or milk in the stomach was observed both by clinical observation and at necropsy, respectively, @ 5 and 15 mg/kg/day.</td></tr>
</table>

Reference ID: 5623053

Table 51: Natural delivery and litter data summary.

Dose (mg/kg/day)	0	1.5	5	15
F0 females				
No. pregnant	22	19	21	22
No. sacrificed moribund due to total litter loss	1	1	3	3
F1 Litters				
No. pups delivered	289	230	279	285
Liveborn	267	225	263	273
Stillborn	22*	5	16	12
No. pup deaths - PND 0 to 4	10	10	45	48
Viability Index (%)	96.3	95.6	82.9	82.4
No. pup deaths - PND 4 to 22	10	17	9	13
Weaning Index (%)	94.3	89.4	94.0	92.1

*The high number of stillbirths in the control group is due to 1 control dam (R0001) that had 18 stillborn pups (complete litter).
Source: Reviewer-generated table.

Table 52: Summary of pup clinical observations (F1 generation) in the rat PPND study.

Dose (mg/kg/day)	0	1.5	5	15
Number of litter/pups evaluated	21/233	18/206	20/226	20/236
No milk band present (physical appearance)	Pups: 0/233 Litters: 0/21	Pups: 0/206 Litters: 0/18	Pups: 17/226 Litters: 3/20	Pups: 13/236 Litters: 3/20
Cool to touch (temperature)	Pups: 0/233 Litters: 0/21	Pups: 1/206 Litters: 1/18	Pups: 25/226 Litters: 3/20	Pups: 14/236 Litters: 2/20

Source: Reviewer-generated table.

- Increase in female pup body weight was observed and considered test-article related but not adverse.
- No effects on developmental markers or sexual maturation in the F1 generation pups were noted.
- Increased sensitivity to touch was noted in F1 generation female pups with an incidence of 2/21, 2/21, 5/20 and 6/20 in control, LD, MD, and HD, respectively.

***Reviewer's comment**: Although no neurobehavior findings were noted, the dose-dependent increase in sensitivity to touch in female pups could be an adaptive behavior change in response to decreased maternal care or a CNS-related effect. More studies would be necessary to fully elucidate the mechanistic basis of this finding.*

Reference ID: 5623053

- Metabolites in pup plasma: Metabolites M27 (BAY 3462932), and M18/21(BAY 3462934) were detected in the F1 pup plasma at 24-h post-dosing of the dams with elinzanetant doses ≥5 mg/kg/day on lactation day 4. Major human metabolite M30/34 (BAY 3462933) was detected in the plasma of pups from dams treated with elinzanetant doses ≥1.5 mg/kg/day.

Table 53: Elinzanetant exposure in pregnant rats on GD 20.

Exposure on GD 20	Dose (mg/kg/day)		
	1.5	5	15
$AUC_{(0-24)}$ (µg*h/L)	2000	8960	36200
C_{max} (µg/L)	134	700	2940
Tmax (h)	6	4	6

Reviewer-generated table from Bioanalytical and TK Analyses report in appendix 10.4 of the study report (Table 26 on page 1226).

***Reviewer's comment*: During review of the study report, the Nonclinical team noted several discrepancies in summary tables throughout the report. The raw data were used to recreate tables, interpret the findings, and derive the Nonclinical review team's final conclusions from the study.**

$ Not previously reviewed under IND 129492.

10 Special Toxicology Studies

Mechanistic Study: Effect on muscle disposition in male rats

Study No & Designs

R-13644 [QL24QG][$] – non GLP

Male rats
14 days
@ 200 mg/kg/day (once daily) and 25 mg/kg ,100 mg/kg BID

Dosing: once daily and BID

Note # (b) (4) rats used, study conducted in (b) (4)

Study Findings

Key Findings:

- Piloerection and red staining around nose @ all doses with no dose dependent severity.
- Multifocal, minimal degeneration of the skeletal muscle observed @ 200 mg/kg once daily (1 in 10 rats) and @ 100 mg/kg BID (3 in 10 rats).
- Minimal, focal fibrosis in 1 in 10 rats @ 100 mg/kg BID. (Applicant notes that this could be early signs of skeletal muscle pathology (degeneration/necrosis)).
- Elinzanetant accumulation was noted in skeletal muscle (8 to 10-fold compared to plasma).

Table 54: Concentrations of elinzanetant in plasma and skeletal muscle tissue in male rats on day 15.

Group	Daily dose	Dose and frequency	Group mean concentration [ng/mL ± SD]	
	[mg/kg/day]	[mg/kg/occasion]	Plasma	Tissue
1	200	200	997.2 ± 230.4 [a]	8579.6 ± 5689.0 [a]
2	200	100 bid	686.5 ± 177.2 [b]	6267.0 ± 4952.8 [b]
3	50	25 bid	249.7 ± 127.1 [b]	1882.2 ± 846.9 [b]

bid: *bis in die* (twice a day); SD: standard deviation.
bid dosing was approx. 6 hours apart
a = approx. 24 hours after the last dosing occasion.
b = approx. 18 hours after the last dosing occasion.

	Source: Module 2.6.6 toxicology written summary (table 8-1). ***Reviewers' comment*: The Applicant notes that the purpose of this study was to reproduce, in an accelerated time window of 14 days, the skeletal muscle findings recorded in the 13-week oral toxicity study in rat [R-13628] and to explore the mechanistic basis of the finding. However, the severe skeletal muscle degeneration seen @ 150 mg/kg BID or 300 mg/kg/day (300 mg/kg/day up to day 9 followed by 175 mg/kg/day for remaining dosing phase) in the 13-week repeat-dose toxicity study could not be reproduced in this study. Refer to study summary for R-13628 under rat repeat dose toxicity study.**

$ Not previously reviewed under IND 129492

Dependence Studies*	
Study No & Designs	**Study Findings**
B003002 (T105225-5) Male Cynomolgus monkey @ 40 mg/kg oral	• Elinzanetant failed to serve as a clear discriminative stimulus post 30 days treatment indicating limited abuse potential.
B003288 (T105226-6/ 2603-021) Male Cynomolgus monkey @ 0,0.01, 0.05, 0.195 mg/kg per injection. Cocaine as positive control	• Elinzanetant did not initiate or maintain self-administration in experimentally naïve male cynomolgus monkeys maintained to self-administer IV cocaine
B003013 (T105227-7 /2603-019) Male Cynomolgus monkey @ 0, 15, 40 mg/kg BID (oral) and 1.95 mg/kg/dose IV. Methamphetamine (IM) as positive control.	• No significant behavioral, cardiovascular, or physiological withdrawal syndrome post elinzanetant treatment

*These studies have been fully reviewed by Control substance Staff (CSS). Refer to review filed in DARRTS.

The following table summarizes studies conducted with impurities. An integrated assessment is located earlier in this review in Section 2.5 Comments on Impurities/Degradants of Concern.

Impurities	
Study No & Designs	**Study Findings**
PH-42298 [T105216-5][$]- GLP Rats (oral); M and F 4 weeks Test article: (b) (4) ((b) (4) @ 20, 40, 80 mg/kg/day NOAEL = (b) mg/kg/day	Notes# • (b) (4) impurity and degradation product of elinzanetant (BAY 3427080) • (b) (4) are stated to be formed from (b) (4) (b) (4)

	(b) (4) Key findings • No effect on clinical signs, body weight, and mortality. • Statistically significantly increased water intake @ 80 mg/kg/day on day 15 and 22 (13 to 17% increase in males and ~23% increase in females). No change on day 29. • Statistically significant decrease (~15%) of glucose in males @ 80 mg/kg/day and total bilirubin was statistically significantly increased in females (~70%) starting @ 20 mg/kg/day. • Statistically significantly increased relative and absolute liver weights in females @ 40 mg/kg/day (10% absolute and 13.52% relative weight) but with no histopathological correlate @ 80 mg/kg/day (9% absolute and 12% relative weight) • No TK was conducted. • Structure of (b) (4) (b) (4) Source : Module 3.2.P.5.5 (Characterization of Impurities)

PH-42303 [T105174-8] $; non-GLP

Rat (oral); F only
Single Dose
Test article: (b) (4)
((b) (4)
@ 20, 40, 80 mg/kg/day

- Single oral administration (b) (4) ((b) (4) was well tolerated.
- TK data showed that (b) (4) and degradation product of BAY 3427080, after systemic uptake is cleaved in the body at least partly into elinzanetant [BAY 3427080].
- Study report notes that repeated measurements of plasma samples revealed decreasing concentrations of (b) (4)

Table 55: PK of (b) (4) in rat.

		Females		
Dose	(mg/kg/d)	20	40	80
AUC(0-24)	[mg·h/L]			(b) (4)
AUC(0-24)norm	[kg·h/L]			
Cmax	[mg/L]			
Cmax,norm	[kg/L]			
$t_{1/2}$	[h]			
tmax	[h]			
MRT	[h]			

Table 56: PK of BAY 3427080 (elinzanetant) in rat.

		Females		
Dose	(mg/kg/d)	20	40	80
AUC(0-24)	[mg·h/L]			(b) (4)
AUC(0-24)norm	[kg·h/L]			
Cmax	[mg/L]			
Cmax,norm	[kg/L]			
$t_{1/2}$	[h]			
tmax	[h]			
MRT	[h]			

Source: study report PH-42303

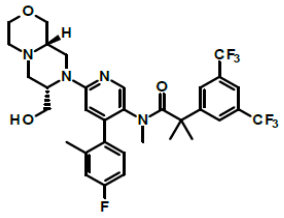
R-14064 [8440176] $; non-GLP

Bacterial Reverse Mutation Test (Ames assay)
Test Article: (b) (4)
@ 0, 6, 15, 50, 150, 500, 1500, 5000 µg/plate (±S9 mix).

- (b) (4) is a starting material/intermediate of elinzanetant BAY 3427080 [See Figure 18 below].

Key findings

- No evidence of mutagenic activity.
- Toxicity (observed as thinning of the background lawn of non-revertant colonies, together with a reduction in revertant colony numbers) was seen in all strains following exposure to (b) (4) in strains TA100 and TA1537 at 1500 µg/plate and above, and in strains WP2 uvrA (pKM101), TA98 and TA1535 at 5000 µg/plate in absence of S9 mix.
- Toxicity was seen in strains TA98, TA100, TA1535 and TA1537 at 1500 µg/plate and above, and in strain WP2 uvrA (pKM101) at 5000 µg/plate in presence of S9 mix.

	Figure 15: Key building blocks of the synthesis of Elinzanetant drug substance.  Elinzanetant drug substance (b) (4) Source: Figure extracted from Module 3.2.S.2.3 to depict the (b) (4) starting materials ((b) (4)) for the synthesis of Elinzanetant drug substance.
B002884 [T106064-7][$]; GLP Bacterial Reverse Mutation Test (Ames assay) Test Article: (b) (4) @ 0, 16, 50, 160, 500, 1600, 5000 µg/plate (±S9 mix).	• (b) (4) was considered mutagenic in the preincubation modification of the salmonella/microsome test with increases seen in TA 1535 and TA 100 strains. • Bacteriotoxic effect seen at concentrations 500 µg/plate. ***Reviewer's Comment.*** (b) (4) ***(synonymous name:*** (b) (4) ***) is noted as intermediate in the starting material*** (b) (4) ***Exact structural matches could not be located in the Quality sections. As per the discussion with CMC reviewer, Dr. Lawrence Perez, the only*** (b) (4) ***in the synthesis of the starting material*** (b) (4) ***is the final product (i.e., compound*** (b) (4) ***There is possibility that the Applicant is referring to compound*** (b) (4) ***(IUPAC name:*** (b) (4) (b) (4) ***In Section 3.2.S.2.3 Drug Substance, the Applicant states that*** (b) (4) ***.'*** ***The data from the batch analyses of the starting materials*** (b) (4) ***and*** (b) (4) ***(see section 3.2.S.2.3.10-*** (b) (4) ***does not list data for impurity*** (b) (4) ***(nor for*** (b) (4) ***which is also found to be mutagenic) in the starting materials. Unspecified impurities are controlled at levels below*** (b) (4) ***% in the elinzanetant drug***

	substance specification [Refer to Table 4-1 in module 2.3.S]. This is considered acceptable.
B002889 [T106065-8][$]; GLP Bacterial Reverse Mutation Test (Ames assay) Test Article: (b) (4) @ 0, 16, 50, 160, 500, 1600, 5000 µg/plate (±S9 mix).	Note# (b) (4) is noted as (b) (4) (b) (4) which is another intermediate in the synthesis towards starting material (b) (4) Key findings • No mutagenic activity in any of the strains tested, with and without S9 mix.
B003093 [T106139-0] [$] ; GLP Bacterial Reverse Mutation Test (Ames assay) Test Article: (b) (4) @0, 16, 50, 160, 500, 1600, 5000 µg/plate (±S9 mix)	Key findings • Mutagenic in strain TA98 with S9 mix. ***Reviewer's comment:*** (b) (4) ***(synonymous names:*** (b) (4) (b) (4) ***) is noted as an intermediate in the*** (b) (4) ***route towards the starting material*** (b) (4) ***in the manufacture of elinzanetant. As with*** (b) (4)***, this compound is also not specified in the drug substance specification and hence should be controlled under unspecified impurities at levels below*** (b) (4) ***%. Additionally, the applicant notes*** (b) (4)

[$] Not previously reviewed under IND 129492

An in-vitro phototoxicity study was conducted and is summarized below. Refer to full review attached in the Appendix.

Phototoxicity	
Study No & Designs	**Study Findings**
R-13578 [8382675][$] ; GLP In vitro 3T3 Neutral Red Uptake phototoxicity assay Mouse Balb/c 3T3 clone A31 cells Test Article: Elinzanetant @ 0.316, 1, 3.16, 20, 31.6, 100 µg/mL ±UV-A light	Elinzanetant is noted to absorb light in the visible part of the spectrum; hence, an in-vitro 3T3 NRU (Neutral Red Uptake) phototoxicity assay was performed. Key findings • Cytotoxicity was observed at the highest 4 concentrations of elinzanetant analyzed (1.00 to 31.6 µg/mL) in presence of UV irradiation, resulting in an IC_{50} of 0.845 µg/mL and a no-observed-effect-concentration (NOEC) of 0.316 µg/mL. • The MPE (mean photo effect) value for the positive control, chlorpromazine, was 0.662 and that for elinzanetant was 0.442; as the MPE value was ≥0.15, elinzanetant was phototoxic in this assay. • The Applicant assessed the tissue distribution of elinzanetant in two whole-body autoradiography studies conducted in rats: study WD2008-00842-00 (study report R-13624) and study KINE 220019-EXT (study report R-14368). • Detailed multiple of exposure (MOE) calculations taking into account the exposures in eye and skin and the % unbound of elinzanetant are noted in the appendix section.

	Reviewer's comments: ***1. The Pharm/Tox review team estimated the most conservative multiple of exposure for phototoxicity to be approximately 7-fold.*** ***2. Although the MOEs calculated by the Applicant and by the Pharm/Tox review team appear reasonable, they should be interpreted with caution because elinzanetant concentrations in human pigmented tissues are derived based on the distribution of elinzanetant to rat pigmented tissues (eyes and skin) following a single treatment. No information is available to determine the extent of tissue accumulation in melanin-containing tissues following repeated treatment with elinzanetant.*** ***3. Elinzanetant has several characteristics that, per the Guidance for Industry: S10 Photosafety Evaluation of Pharmaceuticals (January 2015), available at https://www.fda.gov/media/85076/download, make it a potential phototoxicant:*** • ***It absorbs photons in the ultraviolet (UV) spectrum (290-700 nm).*** • ***It distributes to and accumulates in melanin-rich tissues (see below; Study Report R-13624; Study Report R-14368).*** • ***It is cytotoxic in the in-vitro Balb/c 3T3 neutral red uptake phototoxicity assay, with an IC50 of 0.845 µg/mL and an NOEC of 0.316 µg/mL in presence of UV-A (Study Report R-13578).*** ***4. In the pooled safety analysis of the 4 studies (SWITCH-1, and OASIS 1, 2 and 3), 5 women under elinzanetant 120 mg and 1 woman under placebo treatment reported photosensitivity reaction (PTs). Of the 5, one had to withdraw because of photosensitivity reaction (onset day 290). The other 4 cases resolved despite continued treatment with elinzanetant 120 mg, and no actions were taken for these events.***

$ Not previously reviewed under IND 129492 [Refer to Appendix for full review].

11 Integrated Summary and Safety Evaluation

Bayer submitted NDA 219469 for elinzanetant (BAY 3427080) in soft gel capsule dosage form for the indication to treat moderate to severe VMS associated with menopause. The recommended oral dose of elinzanetant is 120 mg (two 60 mg capsules) taken orally once daily at bedtime. Bayer has submitted a full nonclinical program for elinzanetant to support their NDA under the 505 (b)(1) pathway as an NME (New Molecular Entity).

Pharmacology

Elinzanetant is an NK1R/NK3R antagonist. Inhibition of NK1R/NK3R on KNDy neurons can decrease neuronal activity involved in thermoregulation, which is thought to contribute to the VMS associated with menopause.

Elinzanetant has ~10-fold higher affinity to NK1R compared to NK3R, with mean pKi values of 9.43 and 8.42 for NK1R and NK3R, respectively. Elinzanetant has three principal metabolites M27, M30/34, and M18/21, which also act as noncompetitive antagonists at NK1R and NK3R.

In-vitro selectivity assays/ (b) (4) screen including a wide range of receptors, ions channels, transporters, and enzymes to identify potential off-target effects of elinzanetant yielded only a few notable findings. Elinzanetant and its three principal metabolites may have the potential to inhibit estrogen and progesterone receptors (ER and PR, respectively). Radioligand binding and functional assays with elinzanetant produced equivocal results. In study R-13674, elinzanetant had no effect on radioligand binding to ER and PR, and in study R-14344, elinzanetant (up to 30 µM) had no effect on the activity of recombinant human PR-B. However, in study 14343, elinzanetant inhibited radiolabeled estradiol and progesterone binding to recombinant human ERβ and to recombinant human PR-B, respectively; the IC_{50}s were 22.5 µM and 0.64 µM, respectively. The metabolites M27, M30/M34 (major metabolite), and M18/21 inhibited radiolabeled progesterone binding to recombinant human PR-B with IC_{50}s of 1.34 µM, 1.20 µM, and 1.69 µM, respectively.

Elinzanetant did not generate major safety signals in a complete battery of safety pharmacology studies (cardiovascular, respiratory, and CNS). Refer to Table 57 below.

Table 57:Safety pharmacology studies with elinzanetant.

Study	Effects of Elinzanetant/ Metabolite	NOAEL	Safety Margin*
In vitro (elinzanetant)			
R-13675 in vitro hERG @ 1.91 µM	▪ No inhibition of hERG tail current	-	-
R-13679 in vitro KCNH2 (hERG) assay@ 0.0228 – 50 µM	▪ IC_{50} = 31 µM (= 20726.6 µg/L)	-	~4,820X
In vitro (metabolites: M 27, M 30/34, M 18/21)			
PH-42243 in vitro human cardiac ion channels# with M 27 (BAY 3462932) @ 10 µM	▪ No inhibitory effect on the hERG potassium channel, hNav1.5 sodium channel, thCav1.2 L-type calcium channel, hKvLQT1 potassium channel, hKv4.3 potassium channel, and hKir2.1 potassium channel	-	-
PH-42244 in vitro human cardiac ion channels# with M 30/34 (BAY 3462933) @ 10 µM		-	-
PH-42245 in vitro human cardiac ion channels# with M 18/21 (BAY 3462934) @ 10 µM		-	-
In vivo (elinzanetant)			
R-13668 (GLP) Central Nervous System (CNS) in rats @ 0, 5, 25, and 100 mg/kg elinzanetant (tosylate salt)	▪ 25 mg/kg increased defecation and urination at 4 and 24 h, respectively. ▪ 100 mg/kg increased. response to finger approach and rearing at 24 h. ▪ No seizures, tremors, or twitches. ▪ No effect on body temperature.	100 mg/kg $C_{max, unbound}$ = 98 µg/L in males on Day 1 in the 4-week rat Study [R-13595]	23X
R-13670 (GLP) Cardiovascular System (CVS) in monkeys @ 0, 6, 20, and 60 mg/kg elinzanetant (tosylate salt)	▪ Mild increase in heart rate (~15%), mild decrease in body temperature (~0.6°C), which was both reversible. No effect on ECG @ 60 mg/kg. ▪ Mild decrease in body temperature (reversible) @ 20 mg/kg.	20 mg/kg $C_{max, unbound}$ = 18 µg/L in males at 20 mg/kg on Day 1 in the 4-week monkey study [R-13639]	4X
R-13676 (GLP) Respiratory in rats @ 0, 5, 25, and 100 mg/kg elinzanetant (tosylate salt)	▪ No change in tidal volume, respiratory rate, minute volume, pulmonary resistance, or body temperature.	100 mg/kg $C_{max, unbound}$ = 98 µg/L at 100 mg/kg in males on Day 1 in the 4-week rat study [R-13595]	23X

* $C_{max, unbound}$ = 4.3 µg/L at 120 mg, QD, obtained from Study No. B002427#. Molecular weight of elinzanetant = 668.6 g/mol. Specific human cardiac ion channels: the hERG potassium channel, hNav1.5 sodium channel, thCav1.2 L-type calcium channel, hKvLQT1 potassium channel, hKv4.3 potassium channel, and hKir2.1 potassium channel.

Pharmacokinetics (PK)

Absorption, distribution, metabolism, and excretion of elinzanetant were assessed in whole-body autoradiography studies rats and non-radiolabeled assays in rats, monkeys, and dogs.

Clearance differed between species. It was low in rats with differential clearance between male and female rats. Significant accumulation of elinzanetant was observed over the dose range tested in female rats, but not in male rats. Bioavailability was moderate in male and female rat (77% and 47%), and low in monkey and dog (19%). High clearance was seen in dog, with low bioavailability (19%). Hence, monkeys (also with low bioavailability of 19% but moderate clearance compared to dog) were chosen as the second nonclinical species for chronic toxicity studies besides rats. No notable accumulation in monkeys post repeat dosing was observed.

Plasma protein binding was high across all preclinical species tested (99.5 to 99.9%) and higher in human (>99.9%) for elinzanetant as well as the principal metabolites (M27, M30/34 and M18/21). No concentration dependence of the unbound fraction (fu) of elinzanetant was observed.

Elinzanetant was brain penetrant in the mouse, rat and monkey with brain:blood ratios of 0.5:1, 0.1:1 to 0.5:1 and 0.6:1 respectively. Elinzanetant distributes more into plasma than into the blood cells resulting in a Cb/Cp [blood-to-plasma concentration ratio] range of 0.574 to 0.663 in human blood and of 0.6-0.7 in the animals' species.

Distribution: In rat whole-body autoradiography studies, radioactivity showed high distribution to most tissues. Highest levels were noted in liver, kidney, adrenal gland, abdominal and brown fat, bulbo-urethral gland, pancreas, lacrimal glands, harderian gland and mucous gland, whereas brain had lower levels which did not change with time (no accumulation). After 35 days, radioactivity was still present in brown fat, uveal tract/retina, spleen and adrenal cortex.

The brain to blood ratio of elinzanetant is 0.1 to 0.5:1 in rats and 0.6:1 in monkeys. In pregnant rats, the organ distribution was similar to non-pregnant rats. Fetal and associated tissue concentrations were generally much lower than maternal blood, except for amnion, placenta, and brain. $AUC_{(0\text{-}tlast)}$ ratio of placenta/maternal blood was 1.3, fetus average/amniotic fluid was 18.3 and fetal brain/maternal brain was 2.4.

Metabolism: Elinzanetant is metabolized primarily by oxidation at the methyl-phenyl moiety as well as at the morpholine ring leading mainly to metabolites M27, M30/34, and M18/21. Based on clinical data, M30/34 (~11%) is considered as the major human metabolite. Exposure to all three principal metabolites were investigated in toxicological studies. Dedicated studies, including chronic repeat dose studies, were also conducted with M27 as it was considered disproportionate in rat.

Reference ID: 5623053

Excretion: Major route of elimination was via feces and bile in both rat and monkeys. Similarly in humans, metabolic profiling in plasma, feces and urine demonstrated ~40% elinzanetant in plasma, ~90% of the administered dose was excreted via feces (about 50% unchanged and ~40% was metabolites) and negligible amount in urine (<0.5%). Radioactivity was secreted into the milk of lactating SD rats to a moderate extent (6.1% of dose within 48 h post administration).

Toxicology

The major findings from pivotal repeat dose findings in rat and monkey are summarized below:

Table 58. Key findings and safety margins/multiples of exposure from pivotal repeat-dose toxicity studies.

Study	Key Findings	NOAEL and Systemic Exposures $AUC_{(0-24)}$	Safety Margin*
Rat – 26 weeks (Elinzanetant) F @ 20, 50, 80 mg/kg/day M @ 50,120, 180 mg/kg/day **[Study R-13894]**	• Decreased hematocrit and red cell distribution width in both sexes @ 180 mg/kg in M and 80 mg/kg in F. • Decreased hemoglobin concentration @ 180 in M. • Increased ALT at week 13 in M @ 180 mg/kg/day. Increased AST in F @ 50, 80 mg/kg/day at week 26. • Increased bilirubin in treatment groups. • Decreased cholesterol @ 20 and 180 mg/kg/day in M. • Increased protein and glucose concentration in the urine from @ 180 mg/kg/day in M and 80 mg/kg/day in F. • Increase (dose dependent) in the relative weight of the adrenal gland, heart, kidney, liver and decrease in thymus weight in M. • Increased relative weight of the adrenal, heart, kidney and liver @ 80 mg/kg/day in F. Histopathology • Lung: Increased (dose dependent) macrophage infiltrations in the alveoli was noted in both sexes. • Kidney: tubular basophilia, hyaline casts and cortical scars in M correlated with increased kidney weights.	80 mg/kg/day (females) $AUC_{(0-24)}$ = 311000 ng.h/mL Week 26 120 mg/kg/day (males) $AUC_{(0-24)}$ = 76100 ng.h/mL Week 26	36 X (females) 8.8 X (males)

Reference ID: 5623053

Study	Key Findings	NOAEL and Systemic Exposures $AUC_{(0-24)}$	Safety Margin*
Rat – 26 weeks (M27 metabolite) @ 0, 5, 10, 20 mg/kg/day for 13 (Interim) or 26 weeks (main study) in F and M **[Study R-13953]**	• No treatment-related changes in clinical signs. • Decreased BW gain compared to control @ 10 and 20 mg/kg in F from week 13 to termination. Overall, BW gain (Week 0-26) was unaffected by treatment. • Increased leucocyte subpopulation counts in treated groups @ 20 mg/kg F in Week 13/14 and 26, @ 20 mg/kg M in Week 13 and 26. • Bilirubin concentration was increased in all treated female groups (up to 4x control at 20 mg/kg) in Week 13/14 and 26 and in 20 mg/kg males (up to 2x control) in Week 13 and 26. There were no correlating findings of hemolysis, cholestasis, organ weight changes, macroscopic, or microscopic changes in the liver at 13 or 26 weeks. • No treatment-related changes in histopathology.	20 mg/kg/day $AUC_{(0-24)}$ = 38300 ng.h/mL (Females) 13700 ng.h/mL (Males)	15 X (females) 5.4 X (males)
Monkey – 39 weeks (Elinzanetant) @ 0, 30, 60 and 80 mg/kg/day (given 0, 15, 30 and 40 mg/kg BID, 6 h apart) in F and M	• GI disturbance and related clinical signs in M @ 30 and 80 mg/kg/day and F@ 60 and 80 mg/kg/day. • @ 80 mg/kg/day in 2 females, GI symptoms were very severe with histopathology- minimal inflammatory cell infiltrate in the mucosa of the large intestine. • 1 female @ 60 mg/kg/day had muscle fasciculation during 2 consecutive days towards the end of the treatment period. • Decreased body weight in females • Increased ALT, plasma urea, and triglycerides @ 60 mg/kg/day and and/or 80 mg/kg/day. Organ weight • Increase in liver weight in M and F @ HD. • Decreased absolute and relative (to body weight) female reproductive organ weights in F @ 80 mg/kg/day and ovary weights @ 60 mg/kg/day.	30 mg/kg/day (female) AUC_{0-24} = 3000 ng.h/mL 80 mg/kg/day (male) AUC_{0-24} = 8370 ng.h/mL	0.35 X (females) 1 X (males)

Study	Key Findings	NOAEL and Systemic Exposures $AUC_{(0-24)}$	Safety Margin*
	Histopathology • Sinusoid compression in liver, presenting as narrowing of the sinusoidal space in M and F @ 80 mg/kg/day and 60 mg/kg/day, respectively. • Pharmacological effects seen in females: Corpora lutea and/or follicular activity was absent in the ovaries of F @ 60 mg/kg/day and 80 mg/kg/day.		

*Based on AUC_{0-24} of 8572 ng·h/mL for elinzanetant and AUC_{0-24} of 2496.3 ng·h/mL for M27 at MRHD (120 mg) obtained from Clinical Study B002427

Reproductive and developmental toxicity

A full package of reproductive and developmental toxicity studies was conducted in rats and rabbits. In reproductive and developmental toxicity studies, elinzanetant administration prior to or during pregnancy caused fetal harm in rats in the form of pre- and post-implantation loss, reduced litter size or total litter loss, decrease in fetal body weight, and decrease in neonatal pup viability. No teratogenicity was observed in the reproductive and developmental studies with elinzanetant in rats or rabbits.

Key findings from the studies along with the safety margins / multiples of exposure are summarized in the table below and is also summarized as a finding of safety concern based on nonclinical finding below.

Table 59: Key findings and safety margins/multiples of exposure from reproductive and developmental toxicity studies.

Study	Key findings	No Observed Adverse Effect Level (NOAEL)	Systemic Exposures AUC (0-24)	Safety Margin/MOE*
FEED study, rat 0, 5, 25, 100 mg/kg/day, QD, from 22 days before mating to post-coitum day 6 R-13611 [Note# No TK collected in FEED study. Systemic exposures from study 13596 used to calculate safety margin and MOE]	▪ Increased preimplantation and post-implantation losses @ 100 mg/kg/day	25 mg/kg/day (maternal and fetal)	27500 µg.h/L (Week 4 at 25 mg/kg/day, from Study 13596)	3X
			11600 µg.h/L (Week 4 at 100 mg/kg/day, from Study 13596)	MOE = 14X for increased pre-post implantation loss at 100 mg/kg/day
EFD study, rat 0, 5, 25, 100 mg/kg/day, QD, from gestation day (GD) 6 to GD 17 R-13610	▪ Decreased body weight gain and food consumption (maternal) @ 100 mg/kg/day	25 mg/kg/day (maternal)	57200 µg.h/L	6.7X (maternal)
		100 mg/kg/day (fetal)	197000 µg.h/L	23X (fetal)
EFD study, rabbit 0, 60, 90, 140 mg/kg/day (as 0, 30, 45, 70 mg/kg, BID) from GD7 to GD19 R-13597	▪ Decreased body weight and food consumption (maternal) @ 140 mg/kg/day leading to poor heath and premature sacrifice in 4 dams.	90 mg/kg/day (maternal)	2160 µg.h/L	0.25X (no safety margin for maternal exposure)
		140 mg/kg/day (fetal)	10600 µg.h/L	1.2X
PPND study, rat 0, 1.5, 5, 15 mg/kg/day, QD, from GD 6 to lactation day (LD) 21. B003187	▪ Increased number of dams with stillborn pups in elinzanetant treatment groups. ▪ Increased litter deaths and decrease of pup viability between postnatal days 0 to 4 @ 5 mg/kg/day and 15 mg/kg/day	1.5 mg/kg/day (maternal and fetal)	2000 µg.h/L (at 1.5 mg/kg/day)	0.2X (no safety margin for maternal and fetal exposure and for metabolites in rat pup plasma)
			8960 µg.h/L (at 5 mg/kg/day)	MOE = 1X for increased litter deaths at 5 mg/kg/day

The table below is a summary of safety margins from all pivotal toxicology studies.

Table 60: Summary of safety margins from pivotal toxicology studies

Study	Sex/Age	NOAEL (mg/kg/day)	Exposure (µg.h/L)	Safety Margin*
26-week repeat-dose toxicity study in rats	Female	80	311000	36X
	Male	120	76100	8.8X
26-week repeat-dose toxicity in rats (with metabolite M27)	Female	20	38300	15X
	Male	20	13700	5.4X
39-week repeat repeat-dose toxicity in monkeys	Female	30	3000	0.35X
	Male	80	8370	1X
2-year carcinogenicity study in female rats	Female	20	64000	7.5X
Fertility and early embryonic development study in rats	Maternal and Fetal	25	27500	3X
Embryofetal development study in rats	Maternal	25	57200	6.7X
	Fetal	100	197000	23X
Embryofetal development study in rabbits	Maternal	25	2160	0.25X
	Fetal	100	10600	1.2X
Pre- and postnatal development in rats	Maternal and Fetal	1.5	2000	0.2X

* Safety margins calculated based on clinical exposures at the elinzanetant MRHD of 120 mg/day: Elinzanetant $AUC_{(0-24)}$ = 8572.0 µg.h/L; M27 $AUC_{(0-24)}$ = 2496.3 µg.h/L [from the clinical study number CPM50130 (report number B002427)].

Integrated Summary of Potential Safety Concern based on Nonclinical Findings

The main clinically relevant nonclinical safety signals are discussed in the next sections and include: (i) central nervous system (CNS)-related signals, including tremors and convulsions, (ii) skeletal muscle degeneration, (iii) malignant adenocarcinoma of the uterus, the combination of malignant and benign endometrial tumors and squamous cell carcinoma of the uterus, and lymphomas of the hematolymphoid system, (iv) phototoxic signals, (v) gastrointestinal (GI)-related signals, and (vi) reproductive and developmental toxicity signals. The potential for hepatotoxicity with elinzanetant, based on the integrated assessment of liver-related signals detected in the nonclinical studies and a comparative quantitative structure-activity relationship analysis of elinzanetant and the NK3R inhibitor fezolinetant are also discussed below.

CNS-related safety signals

Convulsions were noted in two nonclinical studies – a 2-year carcinogenicity study (B003186) conducted in female Sprague-Dawley (SD) rats (Envigo – formerly Harlan, US) and a 13-week repeat-dose toxicity study (R-13628) conducted in male and female SD rats (Envigo, Netherlands). Table 61 summarizes the CNS-related findings from these studies. The substrain of SD rats from Envigo is referred to as SD:Hsd. The rat substrains and their sources are noted here for context as the discrepant findings between the different studies could potentially be linked to the substrain of rats and their origins.

The CNS-related findings from studies B003186 and R-13628 are elaborated in the subsequent paragraphs.

Table 61:Summary of CNS-related findings in rat studies with safety margins and multiples of exposure.

Rat Study	CNS-Related Effects of Elinzanetant	NOAEL/ LOAEL	Safety Margin[a]	MOE
13-week study (R-13628 [RH17GJ]) Female (F) and male (M) SD:Hsd rats (Envigo, Netherlands) F: 0, 10, 25, or 50 mg/kg, BID, 13 weeks M: 0, 25, 60, or 150 mg/kg (highest dose decreased to 87.5 after day 9), BID, 13 weeks	**Females** At all doses: Spasms (up to 3 min) and tremors (starting ~day 24); convulsions (starting ~day 35): 2/16 @ 20 mg/kg/day; 3/16 @ 50 mg/kg/day; 3/21 @ 100 mg/kg/day [3 more F @ 100 mg/kg with decreased activity, hunched posture, and piloerection were euthanized by day 12] **Males** 50 and 120 mg/kg/day: 1/16 @ each dose had tremors, whole body rigidity, spams (1-3 min), involuntary muscle contractions (convulsions), and stiff tail 300 mg/kg/day: 5 found dead (days 9-11); 6 euthanized for severe clinical signs (days 9-12): decreased activity, hunched posture, abnormal gait, piloerection, prostration **Females and Males** 1. There were no brain histopathological findings associated with the convulsions. 2. CNS-unrelated finding: Skeletal muscle degeneration and necrosis in the highest dose groups (discussed below).	No NOAEL	ND	N/A
		LOAELs: **F**: 20 mg/kg/day Estimated AUC on treatment day 34: 35111 µg•h/L **M**: 50 mg/kg/day Estimated AUC on treatment day 34: 31930 µg•h/L	N/A	4X[b]

Rat Study	CNS-Related Effects of Elinzanetant	NOAEL/ LOAEL	Safety Margin[a]	MOE
Carcinogenicity study (B003186 [T105128-7]) Female SD:Hsd rats (Envigo, IN, USA) 0, 3.5, 10, 30, or 40 mg/kg, BID, 104 weeks	**At ≥60 mg/kg/day**: ▪ Increased incidence of whole-body convulsions (first noted at day 162). ▪ Increased incidence of hunched posture ▪ Increased sensitivity to touch. ▪ Decreased general activity. ▪ Increased salivation. **At ≥7 mg/kg/day**: ▪ Irregular respiration.	NOAEL: 20 mg/kg/day $AUC_{(0-24)}$s: 64000 µg•h/L measured on day 358	7.5X	N/A
		LOAEL: 60 mg/kg/day Estimated AUC on day 162: 149399 µg•h/L	N/A	17X[c]

LOAEL= Lowest Observed Adverse Effect Level; MOE = Margin of Exposure; NOAEL= No Observed Adverse Effect Level; N/A= Not applicable; ND = Not determined since a NOAEL was not established; [a]Safety margins are ratios of the AUC_{0-24h} at NOAEL to the clinical $AUC_{(0-24)}$ of 8572 ng•h/mL at the MRHD (clinical study B002427). [b]MOE estimated using extrapolated AUC values for day 34, when convulsions were first observed in male and female rats at the LOAELs [For details, refer to Table 32 and the reviewer's comment in the same section under repeat-dose toxicity study description for study R-13628]. [c]MOE estimated using extrapolated AUC value for day 162, when convulsions were first observed at the LOAEL (60 mg/kg/day) in female rats.

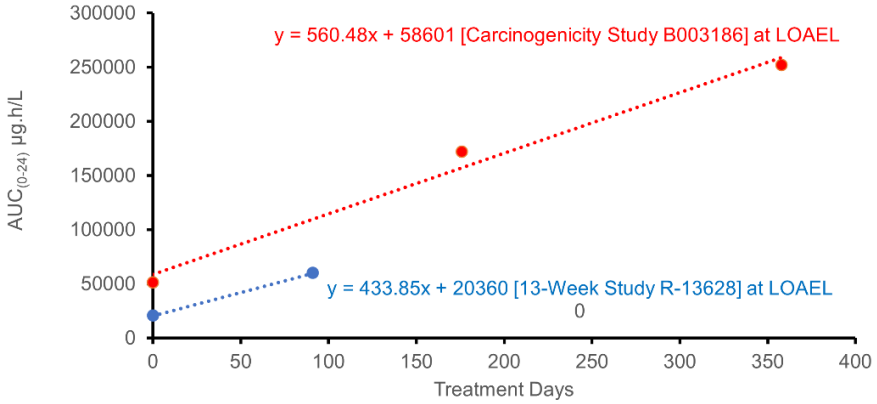
Source: Reviewer-generated table.

In the 13-week repeat-dose toxicity study R-13628, male SD:Hsd rats (Netherlands) were treated with oral elinzanetant (free base) doses of 0, 25, 60, or 150 mg/kg (highest dose reduced to 87.5 after day 9), BID (twice daily), and female SD:Hsd rats (Netherlands) were treated with doses of 0, 10, 25, or 50 mg/kg, BID. Treatments were delivered by oral gavage for 13 weeks. Muscle spasms (lasting up to 3 min) and tremors were noted around day 24 after start of treatment and were followed by convulsions (starting around treatment day 34) in 2 out of 16 females at 20 mg/kg/day, 3 out of 16 females at 50 mg/kg/day, and 3 out of 21 females at 100 mg/kg/day. Likewise, 1 out of 16 males in the groups that received the low and mid doses (50 and 120 mg/kg/day, respectively) had tremors, whole-body rigidity, spasm (lasting up to 1-3 min), stiff tail, and involuntary muscle contractions (convulsions). In male rats, rigidity and spasms were first noted on treatment day 31 and convulsions were first noted on treatment day 34. Male rats treated with the highest tested dose (300/175 mg/kg/day) died prematurely after presenting with reduced activity, hunched posture, abnormal gait, piloerection, and prostration.

In the 13-week repeat-dose toxicity study R-13628, exposures [$AUC_{(0-24)}$] were measured on treatment days 1 and 91. Using the linear regression of the time-dependent increase in $AUC_{(0-24)}$s (Figure 16), the $AUC_{(0-24)}$ generated in female rats

treated with the LOAEL (20 mg/kg/day) when convulsions were first observed (treatment day 34) was estimated to be approximately 35111 µg•h/L. Using the same approach, the $AUC_{(0-24)}$ generated in male rats treated with the LOAEL (50 mg/kg/day) on treatment day 34 was estimated to be approximately 31930 µg•h/L. Within the study, elinzanetant exposures capable of inducing convulsions were relatively consistent between sexes and were ~4-fold higher than the clinical exposure of 8572 µg•h/L generated by the MRHD of elinzanetant (120 mg/day) in women.

Figure 16. Linear regressions of systemic exposures in female rats treated orally with the elinzanetant doses of 20 mg/kg/day, BID, for 13 weeks in Study R-13628 and 60 mg/kg/day, BID, for 2 years in the carcinogenicity study B003186



The dotted lines represent the linear regression of the $AUC_{(0-24)}$s measured in the two studies. For the linear regression, the first day of treatment was considered as day 0. In the regression equations shown in the graph, y represents $AUC_{(0-24)}$ and x represents treatment days.

Source: Reviewer-generated graph

In the 2-year carcinogenicity study, female SD:Hsd rats (U.S.) were treated with oral elinzanetant (free base) doses of 0, 3.5, 10, 30, or 40 mg/kg, BID, for total doses of 0, 7, 20, 60, or 80 mg/kg/day, over the course of 104 weeks. At doses ≥7 mg/kg/day, there was an increased incidence of irregular respiration. At doses ≥60 mg/kg/day, there was an increased incidence of reduced general activity, increased sensitivity to touch, vocalization, hunched posture, and convulsions (Table 62). At doses ≥60 mg/kg/day, prodromal signs of convulsions (e.g. increased sensitivity to touch and decreased activity) generally preceded detection of convulsions, which were first noted around days 162 and 106 after start of treatment with the doses of 60 mg/kg/day and 80 mg/kg/day, respectively.

Table 62: Incidence of clinical signs per treatment group in 2-year carcinogenicity study.

Clinical Signs	Vehicle control	Elinzanetant Doses (mg/kg/day)			
		7	20	60	80
Total Number of Rats/Group	**101**	**100**	**100**	**102**	**100**
Involuntary movements					
Convulsions, whole body <1 minute	7	7	9	27	26
Convulsions, whole body >1 minute	2	0	5	11	9
All convulsions (# associated deaths)	8 (1)	7 (1)	9 (5)	30 (20)	28 (11)
Hunched posture	7	6	2	13	10
Decreased activity	3	5	4	10	16
Increased sensitivity to touch	4	6	2	18	12
Respiration					
Irregular	1	4	3	8	10
Audible	1	1	2	3	4
Fast	1	2	2	6	4
Excessive salivation					
Clear	1	2	2	8	5
Colorless	0	0	0	0	3

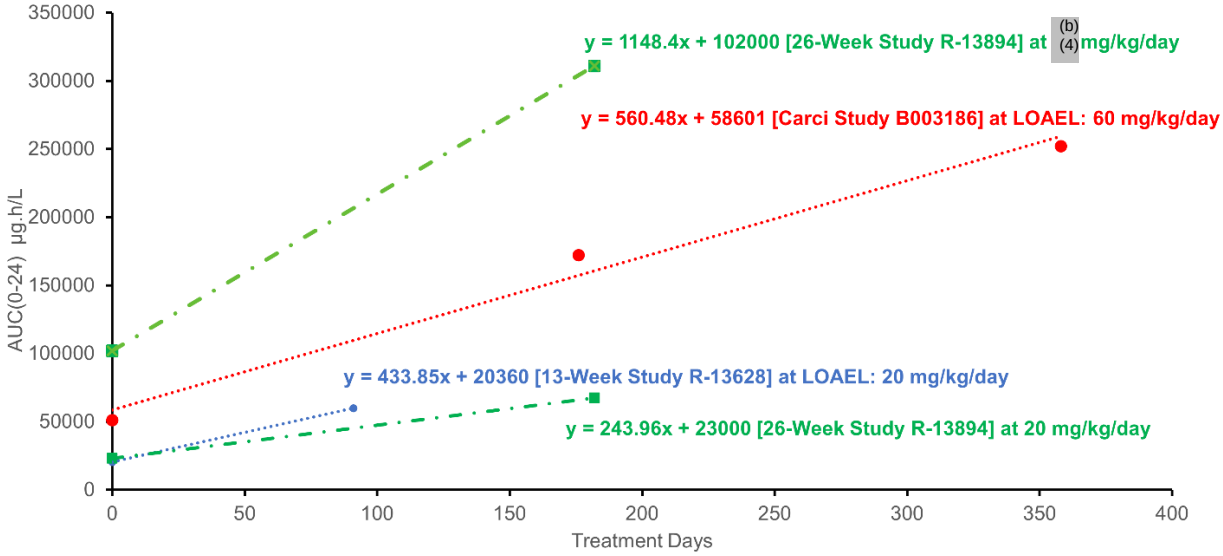
Note# Numbers in each row represent the number of animals presenting the listed clinical sign.
Source: Reviewer-generated table using data from the Applicant's study report B003186.

Source: Reviewer-generated table

In the carcinogenicity study, exposures were assessed on treatment days 1, 176, and 358. Using the linear regression of the time-dependent increase in $AUC_{(0\text{-}24)}$s at the oral LOAEL for convulsions in this study (60 mg/kg/day) (Figure 16), systemic exposure was estimated to be ~149399 µg•h/L at the time when convulsions were first noted in elinzanetant-treated female rats (treatment day 162).

Using the linear regression of the time-dependent increase in systemic exposure in female rats treated for 2 years with the elinzanetant dose of 80 mg/kg (
Figure 17, exposure was estimated to be ~150076 µg•h/L at the time convulsions were first noted at this dose (treatment day 106). Thus, within this study, exposures needed to induce convulsions in female rats were relatively consistent between doses and were ~17-fold higher than the clinical exposure of 8572 µg•h/L generated by the MRHD of elinzanetant (120 mg/day) in women.

Figure 17. Linear regressions of systemic exposures in female rats treated by oral gavage twice daily with the elinzanetant doses of 60 and 80 mg/kg/day for 2 years in the carcinogenicity study B003186 and with the elinzanetant dose of 20 mg/kg/day for 13 weeks in study R-13628 and for 26 weeks in study R-13894



The dotted lines represent the linear regression of the $AUC_{(0\text{-}24)}$s measured in the two studies. For the linear regressions, the first treatment day was considered day 0. In the regression equations shown in the graph, y represents $AUC_{(0\text{-}24)}$ and x represents treatment days.

Source: Reviewer-generated graph

Convulsions were not reported in the13-week repeat-dose toxicity study R-13596 and the 26-week repeat-dose toxicity study R-13894 conducted in male and female SD rats treated with elinzanetant (free base). In the 13-week study R-13596, SD rats were from Charles River (Canada) and were treated once daily with the oral doses of 0, 5, 25, or 100 mg/kg. The substrain of SD rats from Charles River is referred to as SD:Crl. In the 26-week study R-13894, SD:Hsd rats were from Envigo (UK); in this study, female rats were treated twice daily with the oral dose of 0, 10, 25, or 40 mg/kg, and male rats were treated twice daily (BID) with the oral dose of 0, 25, 60, or 90 mg/kg. In both studies, the treatments were delivered by oral gavage.

On treatment day 1, systemic exposures of female rats treated BID with 20 mg/kg/day were comparable between the 13-week repeat-dose toxicity study in which rats developed convulsions (R-13628) and the 26-week repeat-dose toxicity study in which rats were also treated twice daily with elinzanetant but did not develop convulsions (R-13894) (

Figure 17). As reported in other studies conducted by the Applicant, elinzanetant accumulated with the repeated daily treatment in the studies discussed here (

Figure 17). However, throughout the treatment duration, systemic exposures measured in the 13-week study R-13628 became slightly higher than those measured in the 26-week study R-13894 (

Figure 17).

As discussed in previous paragraphs, on treatment day 34, when convulsions were first noted in female rats treated with the dose of 20 mg/kg/day in the 13-week study R-13628, systemic exposure was estimated to be approximately 35111 µg•h/L. At the same dose (20 mg/kg/day), in the 26-week study R-13894, systemic exposure was estimated to approximate 35111 µg•h/L on treatment day 50 and was as high as 59840 µg•h/L on the last treatment day (day 182). However, convulsions were not observed throughout the treatment of female rats with the dose of 20 mg/kg/day in the 26-week study R-13894.

Likewise, on treatment day 106, when convulsions were first noted in female rats treated with the dose of 80 mg/kg/day in the 2-year carcinogenicity study, systemic exposure was estimated to be 150076 µg•h/L. At the same dose (80 mg/kg/day), in the 26-week study R-13894, systemic exposure was estimated to approximate 150076 µg•h/L on treatment day 42 and was as high as 311000 µg•h/L on the last treatment day. Yet, convulsions were not observed throughout the treatment of female rats with the dose of 80 mg/kg/day in the 26-week study R-13894. Therefore, the apparently inconsistent CNS effects between studies could not be fully accounted for by insufficient systemic exposures.

It is unclear why convulsions were inconsistently observed across the different studies or why convulsions were associated with higher exposures in elinzanetant-treated female rats in the 2-year carcinogenicity study than in the 13-week study R-13628. It is possible that the differential seizure susceptibility of different substrains of SD rats (SD:Crl vs SD:Hsd) and of SD:Hsd rats from different sources (UK, Netherlands, and U.S.) could have accounted for, or contributed to, the discrepant findings from the toxicity studies in SD rats treated with elinzanetant. According to a study published by Langer and collaborators[6], SD:Crl rats are less susceptible than SD:Hsd rats to developing seizures in response to electrical stimulation of the basolateral amygdala

[6] Langer M, Brandt C, Löscher W. Marked strain and substrain differences in induction of status epilepticus and subsequent development of neurodegeneration, epilepsy, and behavioral alterations in rats: Strain and substrain differences in an epilepsy model in rats. Epilepsy Res. 2011 Oct;96(3):207-224.

(BLA). In addition, SD:Hsd rats from the Netherlands are less susceptible than SD:Hsd rats from Germany to developing seizures in response to BLA electrical stimulation.

Biological Plausibility of Elinzanetant-Induced Seizures in Rats

Considering the current knowledge that NK1R/NK3R activation increases neuronal excitability[7,8] and the Applicant's finding that, in acute habenula slices from guinea pigs, elinzanetant inhibited neuronal firing induced by the NK3R agonist NKB (Study R-13877), it is unlikely that elinzanetant-induced inhibition of NK1R/NK3R would lead to the development of convulsions.

The Applicant has reported that, at 10 µM, the elinzanetant metabolite BAY 3462933 (M30/34) inhibits [^{3}H]tert-butylbicycloorthobenzoate ([^{3}H]TBOB) binding to gamma-amino butyric acid type A ($GABA_A$) receptors in Wistar rat brain membrane preparations by ~55% (R-14018). $GABA_A$ receptor antagonists (e.g., picrotoxin and bicuculline) are well known for their proconvulsant effects.[9] Considering that, in female rats treated with the elinzanetant dose of 60 mg/kg/day, C_{max} and $AUC_{0\text{-}24h}$ of BAY 3462933 (M30/34) were 2.09 µM and 46.8 µM•h, respectively, on treatment day 358, BAY 3462933 (M30/34)-induced inhibition of $GABA_A$ receptors could have contributed to the proconvulsant effects of elinzanetant in rats.

Additionally, BAY 3462933 (M30/34) inhibits [^{3}H]progesterone binding to PR-B with a Ki of 0.96 µM. Two other metabolites of elinzanetant – BAY 3462932 (M27) and BAY 346934 (M18/21) – also inhibit PR-B with Kis of 1.08 µM and 1.35 µM, respectively. According to binding studies, interactions of elinzanetant with PR-B are equivocal (see Secondary Pharmacology above). However, in one study, elinzanetant inhibited binding of [^{3}H]progesterone to PR-B ectopically expressed in insect Sf9 cells with an IC_{50} of 0.64 µM. PR-B inhibition by the elinzanetant metabolites (and, possibly, elinzanetant itself) may contribute to the proconvulsant properties of elinzanetant because PR antagonists and null mutations of the genes that encode PR-A and PR-B reportedly suppress the anticonvulsant effects of progesterone.[10,11]

Reviewer's comments.

- ***On January 16, 2025, the nonclinical team consulted with the PTCC Neurotoxicology Assessment Subcommittee on whether a safety margin <10X (specifically 7.5X, based on the findings of the 2-year carcinogenicity study) would be reasonable for***

[7] Stacey AE, Woodhall GL, Jones RS. Neurokinin-receptor-mediated depolarization of cortical neurons elicits an increase in glutamate release at excitatory synapses. Eur J Neurosci. 2002 Nov;16(10):1896-906.

[8] Gallopin T, Geoffroy H, Rossier J, Lambolez B. Cortical sources of CRF, NKB, and CCK and their effects on pyramidal cells in the neocortex. Cereb Cortex. 2006 Oct;16(10):1440-52.

[9] Sigel E, Steinmann ME. Structure, function, and modulation of GABA(A) receptors. J Biol Chem. 2012 Nov 23;287(48):40224-31.

[10] Lonsdale D, Nylen K, McIntyre Burnham W. The anticonvulsant effects of progesterone and its metabolites on amygdala-kindled seizures in male rats. Brain Res. 2006 Jul 26;1101(1):110-6.

[11] Shiono S, Sun H, Batabyal T, Labuz A, Williamson J, Kapur J, Joshi S. Limbic progesterone receptor activity enhances neuronal excitability and seizures. Epilepsia. 2021 Aug;62(8):1946-1959.

the CNS-related safety signal of convulsions and whether it would be advisable to request a post-marketing nonclinical evaluation of the CNS findings to better define safety margins for this safety signal.

- ***The Neurotoxicology Subcommittee indicated that it is rather common to not see histopathological changes even when there is evidence of seizures in animals. Seizures of prolonged duration may be accompanied by histopathological changes, but shorter seizures may not.***
- ***The Neurotoxicology Subcommittee considered it acceptable to set NOAELs based on convulsions and prodromal signs, including spasms and tremors. The margins would be to the highest dose with no observed clinical CNS signs.***
- ***The Neurotoxicology Subcommittee considered that additional nonclinical studies may not help better define the safety margins for the safety signal of convulsions.***
- ***Finally, the Neurotoxicology Subcommittee agreed that describing the nonclinical findings of convulsions in the subsection (13.2) in section 13 of the drug product labeling is appropriate. The Neurotoxicology Subcommittee further recommended that, if human findings warrant the addition of the potential for elinzanetant to increase the incidence of seizures to the "Warnings and Precautions" section of the labeling, they should be linked to the nonclinical findings described in section 13.***

Summary and conclusion

Based on the totality of evidence, the CNS-related findings in the rat were determined to be related to elinzanetant treatment. The mechanism of the CNS-related findings in elinzanetant-treated rats has not been determined; however, as discussed above, PR-B inhibition by the elinzanetant metabolites (and, possibly, elinzanetant itself) and $GABA_A$ receptor inhibition by the metabolite BAY 3462933 could contribute to the convulsions observed in elinzanetant-treated rats. These findings were discussed with internal neurotoxicology experts (PTCC Neurotoxicology Assessment Subcommittee), and it was determined that, at the time of this review, additional nonclinical studies were not needed to better define safety margins for this safety signal.

Skeletal muscle degeneration

In the 13-week repeat-dose toxicity study (R-13628 [RH17GJ]) conducted in SD:Hsd rats (Envigo, Netherlands), male rats (11/11) and female rats (3/10) that died prematurely following treatment with the highest test doses of elinzanetant (300 mg/kg/day and 100 mg/kg/day, respectively) presented with moderate to severe degeneration and necrosis of the skeletal muscles in the leg, tongue, and/or larynx

Reference ID: 5623053

(Table 63). Muscle degeneration/necrosis was not noted in elinzanetant-treated rats that presented with convulsions.

Table 63: Incidence of skeletal muscle degeneration in male and female rats euthanized due to overt toxicity induced by the highest test doses of elinzanetant.

Findings	**# of Affected Rats/Total # Rats**	
	Male Rats (300 mg/kg/day)	Female Rats (100 mg/kg/day)
Skeletal Muscle Degeneration/Myofiber	11/11	3/6
Larynx Degeneration/Necrosis, Muscle	9/11	1/6
Tongue Degeneration/Necrosis, Myofiber	11/11	1/6

Source: Reviewer-generated table using data from study report R-13628 [RH17GJ].

Skeletal muscle degeneration/necrosis correlated with increased transaminases, lactate dehydrogenase, and creatine kinase and was considered the primary cause of death or early termination of rats treated with the highest test doses of elinzanetant. Three additional female rats died prematurely following treatment with the highest test dose (100 mg/kg/day); however, the cause of death was undetermined for these 3 female rats, which presented no remarkable histopathological findings. As a note, rats with the skeletal muscle degeneration findings were different from the rats that had CNS-related findings (as described above).

The finding of skeletal muscle degeneration was not observed in other repeat-dose toxicity studies conducted in rats and other animal species. In addition, the finding was not reproduced in a separate study that the Applicant designed and conducted specifically to investigate the mechanistic basis of the finding.

Summary and conclusion

Biological plausibility of elinzanetant to cause skeletal muscle degeneration/necrosis is unclear. A mechanistic study that the Applicant conducted in male rats (R-13644) to mimic the effects recorded in the 13-week repeat-dose toxicity study (R-13628 [RH17GJ]) failed to reproduce the severe skeletal muscle degeneration. The most conservative multiple of exposure for this finding derived from the 13-week repeat-dose study at 100 mg/kg/day in female rats is 16X the human therapeutic exposure on an AUC basis. The clinical relevance of this skeletal muscle finding is unknown.

Genotoxicity and Carcinogenicity

In-vitro and in-vivo genotoxicity studies with elinzanetant and its three main metabolites (M27, M30/34, and M18/21) showed negative results.

There were no neoplastic findings in the 26-week transgenic mouse study (B003184).

Reference ID: 5623053

Positive carcinogenicity findings were present in the 2-year rat study (B003186). Female rats were treated orally with elinzanetant doses ranging from 7 to 80 mg/kg/day compared to vehicle for 104 weeks. Elinzanetant dose dependently reduced body weight gain (body weights were 9%, 9%,17%, and 19% lower at 7, 20, 60, 80 mg/kg/day, respectively, compared to control at terminal sacrifice), but had no effect on overall survival. Elinzanetant treatment resulted in neoplastic findings in the uterus and the hematolymphoid system as described in Table 64 below, along with safety margins based on clinical exposure.

Table 64: Summary of neoplastic findings in rat and transgenic mouse studies.

Study	Carcinogenic Effects of Elinzanetant	NOAEL/ NOEL	Safety Margin[a]
Rat – 2 years (B003186) @ 7, 20, 60, 80 mg/kg/day in F	Statistically significant increases in the incidence of: ▪ Malignant lymphoma in the hematolymphoid system @ 80 mg/kg/day. ▪ Malignant adenocarcinoma of the uterus @ ≥60 mg/kg/day. ▪ Combined malignant and benign endometrial tumors @ ≥60 mg/kg/day. ▪ Combined malignant and benign endometrial tumors and malignant squamous cell carcinoma of the uterus @ ≥60 mg/kg/day.	NOAEL: 20 mg/kg/day (females)	7.5X
Transgenic mouse – 6 months (B003184) @ 10, 30, 85 mg/kg/day in M @ 10, 20, 70 mg/kg/day in F	No neoplastic findings	NOEL: 70 mg/kg/day (females) 85 mg/kg/day (males)	N/A

NOAEL = No Observed Adverse Effect Level; NOEL = No Observed Effect Level; N/A= Not applicable; [a]Safety margins are ratios of the AUC_{0-24} at the NOAEL or NOEL to the clinical AUC_{0-24} of 8572 ng•h/mL for the MRHD of elinzanetant (120 mg/day) obtained from clinical study B002427. Safety margins based on AUC_{0-24} are not calculated for transgenic mice.

Source: Reviewer-generated table.

Biological Plausibility of Elinzanetant-Induced Endometrial Carcinomas in Rats

The main metabolites of elinzanetant – BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 346934 (M18/21) – inhibit [^{3}H]progesterone binding to PR-B with Kis of 1.08 µM, 0.96 µM, and 1.35 µM, respectively. Considering that C_{max} and AUC_{0-24h} of BAY 3462933 (M30/34) were 2.09 µM and 46.8 µM•h, respectively, in female rats treated with the elinzanetant dose of 60 mg/kg/day, it is possible that inhibition of PR-B by BAY 3462933 (M30/34) contributes to the increased incidence of endometrial cancers in rats treated with elinzanetant doses ≥60 mg/kg/day.

As mentioned in the subsections “Secondary Pharmacology” and “CNS-related signals” above, elinzanetant produced equivocal signals in binding studies assessing its interactions with PRs. In one study, elinzanetant inhibited [^{3}H]progesterone binding to PR-B in a concentration dependent manner, with an IC_{50} of ~0.64 µM. It is, therefore, plausible that inhibition of PR-B by the parent drug may also contribute to the increased incidence of endometrial cancers in elinzanetant-treated rats.

According to nonclinical pharmacological studies conducted by the Applicant (see Section 4.2 Secondary Pharmacology), the elinzanetant metabolite BAY 3462933 (M30/34) at 10 µM inhibited by ~50-60% binding of [^{3}H]estradiol to human estrogen receptor α (ERα) ectopically expressed in Sf9 cells, an ovarian cell line. The Applicant did not conduct studies to determine how the metabolite regulates ERα activity in different organs. As described in the literature, selective estrogen receptor modulators can act as ER agonists or antagonists depending on their tissue-selective interaction with the receptor. For instance, while tamoxifen acts as an ER antagonist in the breast, it acts as an ER agonist in the uterus.[12] An agonistic action of BAY 3462933 (M30/34) on ERα in the uterus could contribute to the increased incidence of uterine adenocarcinomas in female rats treated with elinzanetant doses ≥60 mg/kg/day. On the other hand, an antagonistic action of BAY 3462933 (M30/34) on ERα in breast, pituitary, and thyroid tissues could contribute to the apparent reduction in the incidence of mammary gland neoplasms and hyperplasia, pituitary adenomas, and thyroid C-cell adenomas in female rats treated with elinzanetant doses ≥60 mg/kg/day for 2 years. Although not statistically significant, the incidence of these tumors in elinzanetant-treated female rats was >50% lower than in vehicle-treated female rats.

The primary mechanism of action of elinzanetant may also be an important factor contributing to its carcinogenic potential, particularly when treatment spans ages when sex hormones are regularly cycling as it did in the 2-year carcinogenicity in female rats. In this study, twice daily treatment of female rats with elinzanetant started at adolescence (~2 months of age) and continued through adulthood and reproductive senescence. As discussed earlier in this review, inhibition of NK1R/NK3Rs in the hypothalamus can reduce the activity of KNDy neurons, which are known to synapse onto GnRH-releasing neurons (see Figure 1). Reduced KNDy neuron activity can lead to reduced activity of GnRH-releasing neurons and, thereby, contribute to suppression of the activity of the hypothalamic-pituitary-gonadal (HPG) axis (see Figure 1). As discussed below, findings consistent with suppression of the HPG axis were reported in healthy premenopausal women treated with elinzanetant in a randomized, single-blinded, placebo-controlled clinical study.[13]

[12] Grese TA, Sluka JP, Bryant HU, Cullinan GJ, Glasebrook AL, Jones CD, Matsumoto K, Palkowitz AD, Sato M, Termine JD, Winter MA, Yang NN, Dodge JA. Molecular determinants of tissue selectivity in estrogen receptor modulators. Proc Natl Acad Sci U S A. 1997 Dec 9;94(25):14105-10.

[13] Pawsey S, Mills EG, Ballantyne E, Donaldson K, Kerr M, Trower M, Dhillo WS. Elinzanetant (NT-814), a Neurokinin 1,3 Receptor Antagonist, Reduces Estradiol and Progesterone in Healthy Women. J Clin Endocrinol Metab. 2021 Jul 13;106(8):e3221-e3234.

In the clinical study published by Pawsey et al.,[13] 33 healthy premenopausal women were examined during two consecutive menstrual cycles and received a 21-day treatment with elinzanetant (40 mg, 80 mg, or 120 mg, oral) during the second cycle. The authors reported that treatment with elinzanetant caused a dose-dependent reduction of LH levels during the second menstrual cycle compared to the first (though the finding did not reach statistical significance). The largest reduction in serum LH levels was noted at the elinzanetant oral dose of 120 mg/day and was accompanied by a significant reduction of estradiol and progesterone levels during the second menstrual cycle compared to the first. Reduced levels of estradiol remained within the therapeutic window of 30 to 50 pg/mL thought to be important to minimize vasomotor symptoms and bone loss.[13] However, levels of progesterone were sufficiently reduced to increase the duration of the luteal phase of the cycle and prolong bleeding during the menstrual cycle.[13] Thus, treatment of premenopausal women with elinzanetant resulted in a hormonal imbalance with relative estrogen dominance.

Considering the findings of the clinical study by Pawsey et al.,[13] it is possible that, in the 2-year carcinogenicity study, the life-long elinzanetant treatment covering ages when sex hormones were regularly cycling in the female rats caused a hormonal imbalance with relative estrogen dominance that could, in turn, have contributed to a reduction of the potential protective effect of progesterone against development of sex hormone-sensitive tumors such as endometrial adenocarcinomas.

Summary and conclusion

In the 2-year carcinogenicity study in female rats, the highest noncarcinogenic dose of elinzanetant was 20 mg/kg/day (7.5X the human therapeutic exposure on an AUC basis) and the lowest dose found to be carcinogenic was 60 mg/kg/day (~29X the human therapeutic exposure on an AUC basis). The neoplastic findings were observed in the uterus and the hematolymphoid system of the female rat.

Phototoxicity

Elinzanetant has several characteristics that, per the *Guidance for Industry: S10 Photosafety Evaluation of Pharmaceuticals* (January 2015)[14], make it a potential phototoxicant.

- Elinzanetant absorbs photons in the ultraviolet (UV) spectrum (290-700 nm).
  - One peak was detected at 321.4 nm with a calculated molar extinction coefficient (MEC) of 3762.3 $L \cdot mol^{-1}$, which exceeds the threshold of 1000 $L \cdot mol^{-1}$ for phototoxicity (Study Report R-13578).
- Elinzanetant distributes to and accumulates in melanin-rich tissues (Study Report R-13624; Study Report R-14368).
- Elinzanetant is cytotoxic in the in-vitro Balb/c 3T3 neutral red uptake phototoxicity assay, with an IC_{50} of 0.845 µg/mL in presence of UV-A (Study Report R-13578).

[14] https://www.fda.gov/media/85076/download

Summary and conclusion
Based on the in-vitro phototoxicity assay, the most conservative MOE for phototoxicity was approximately 7-fold. Refer to full review in the appendix for details on the calculations. The MOE should be interpreted with caution because elinzanetant concentrations in human pigmented tissues are derived based on the distribution of elinzanetant to rat pigmented tissues (eyes and skin) after a single dose and no additional in-vivo animal photosensitivity studies have been conducted.

GI-related signals

GI-related signals were noted with elinzanetant treatment in repeat-dose toxicity studies in rats and monkeys.

In rats treated orally with elinzanetant for 7 days [study R-13586], histopathological findings of mucosa degeneration along with regeneration of the gastric mucosa, isthmus regenerative hypertrophy, and/or hyperplasia of the isthmus epithelium were observed at 300 mg/kg/day in both male and female rats. Minimal multifocal degeneration/ regeneration was also noted at 100 mg/kg/day in female rats. In a 13-week repeat-dose toxicity study with 4-week recovery (study R-13628), rats with decreased food consumption died prematurely [3 males at 300 mg/kg/day and 2 females at 100 mg/kg/day] and had alterations in the large intestine consisting of distended colon or cecum and/or hard content in the colon.

In monkeys, GI-related adverse effects consisted of findings of loose feces, decreased food consumption, and excessive salivation starting at 60 mg/kg/day (10-fold the human therapeutic exposure on an AUC basis) in a 7-day oral repeat dose study [study R-13627]. Ulceration in the pyloric region of the stomach was seen in females at 100 mg/kg/day (2.4-fold the human therapeutic exposure on an AUC basis). In a 4-week oral repeat-dose toxicity study [study R-13639], 2 monkeys (1 male and 1 female) that were prematurely sacrificed treated with 60 mg/kg/day (4-fold the human therapeutic exposure on an AUC basis) had abnormal fecal consistency (loose/watery) and reduction in food intake along with histopathological findings of hemorrhage in the adventitia and in mucosa of multiple regions in the GI tract.

Similar findings were noted in the 13-week studies [R-13629 and R-13612] and the 39-week study [study R-13895], with abnormal feces (liquid/soft) and/or diarrhea observed in many animals across all dose groups (highest dose tested was 80 mg/kg/day) at various points throughout the study. In the 13-week study, monkeys treated with once daily oral elinzanetant doses ≥20 mg/kg/day (≥0.5-fold the human therapeutic exposure on an AUC basis) presented with increased incidence of thin appearance and dehydration; these findings are indicative of GI disturbances. In the 13-week study, monkeys treated with twice daily oral elinzanetant doses ≥30 mg/kg/day (≥0.2-fold the human therapeutic exposure on an AUC basis) presented with diarrhea and doses ≥80 mg/kg/day (≥2.3-fold the human therapeutic exposure on an AUC basis) presented with thin appearance. In the 39-week study, 2 female monkeys treated twice daily with oral doses ≥60 mg/kg/day (2-fold the human therapeutic exposure on an AUC basis) and

male monkeys treated twice daily with oral doses ≥30 mg/kg/day (0.7-fold the human therapeutic exposure on an AUC basis) had diarrhea that led to dehydration, weight loss, and general ill-health.

Summary and conclusion
The multiples of exposure for the GI effects in monkeys is low, with observed findings starting at the oral elinzanetant doses equivalent to 0.2-fold the human therapeutic exposure at the MRHD.

Reproductive and developmental toxicity
In reproductive and developmental toxicity studies, elinzanetant administration prior to or during pregnancy caused fetal harm in rats in the form of pre- and post-implantation loss, reduced litter size or total litter loss, decrease in fetal body weight, and decrease in neonatal pup viability. No teratogenicity was observed in any of the conducted studies.

In a fertility and early embryonic development study in rats, there was an increase in the percentage of pre- and post-implantation embryo loss and decrease in fetal body weights at 40-fold the human therapeutic exposure when rat dams were treated orally prior to mating and through the early embryonic period.

In a pre- and postnatal developmental study in rats, a higher incidence of still born pups, an increase in total litter loss, a decrease in pup viability between postnatal days 0 and 4, and an increase in the number of neonatal pups without milk in the stomach were observed in the mid- and high-dose groups, with maternal systemic exposures that were within the range of human therapeutic exposure. Decreased maternal care was also a clinical observation in these treatment groups. Whether the neonatal effects were due to decreased maternal care or other potential elinzanetant-related effects on the offspring could not be definitively concluded from this study.

In an embryofetal development study in rabbits, maternal toxicity was noted in the form of marked body weight loss and decreased food consumption at systemic exposures that were within the range of human therapeutic exposure.

No teratogenicity was observed in the reproductive and developmental studies with elinzanetant in rats or rabbits.

Biological Plausibility of Pregnancy Losses and Stillbirths in Rats Exposed to Elinzanetant During Gestation
The pregnancy losses and stillbirths noted in rats exposed to elinzanetant during gestation may be related, at least in part, to NK1R/NK3R inhibition. The inhibition of NK1Rs and NK3Rs can reduce the activity of GnRH-releasing neurons in the hypothalamus and, consequently, suppress the HPG axis leading to an adverse imbalance of the hormones needed to sustain pregnancy. In rats, drugs that act as GnRH receptor inhibitors (e.g., relugolix) are known to cause pregnancy loss and

stillbirth.[15] However, studies have not been conducted to examine this mechanistic relationship resulting in hormonal imbalance in the rat or rabbit after elinzanetant treatment.

Summary and conclusion
Based on findings from animal reproduction studies, elinzanetant may cause pregnancy loss or stillbirth when administered during pregnancy. Fetal malformations were not observed in these animal studies.

Potential for liver toxicity

In the pivotal chronic toxicity studies conducted by the Applicant, including a 26-week study in Sprague-Dawley rats (R-13894) and a 39-week study in monkeys (R-13895), elinzanetant increased levels of the liver-associated enzymes ALT, AST, and ALP. Specifically, in male rats treated orally with the dose of 180 mg/kg/day (90 mg/kg, BID), ALT increased by ~2 fold, and in female rats treated orally with ≥50 mg/kg/day (≥25 mg/kg, BID), AST increased by ~2 fold. In male and female monkeys treated orally with the dose of 40 and 30 mg/kg, BID, respectively, ALT increased by ~1.8 fold (male monkeys) to ~3.6 fold (female monkeys). In these studies, the increased enzyme activity was not associated with histopathological findings that are typically indicative of adverse liver tissue damage.

Liver damage was reported in non-pivotal short-term studies in rats and monkeys. Specifically, following a 7-day oral treatment with elinzanetant tosylate doses of 100 and 300 mg/kg/day, SD rats presented with hepatocellular necrosis and lobular hepatocellular hypertrophy (Study 13586). In addition, following a 4-day oral treatment with the elinzanetant dose of 300 mg/kg/day, monkeys (n = 2; 1 male and 1 female) presented with hepatocellular vacuolation and/or single-cell necrosis (Study 13580). The discrepancy in the liver-associated histopathology findings between the chronic and short-term studies is unclear. However, upregulation of certain cytochrome P450 (CYP) enzymes is thought to contribute to drug-induced liver injury (Jaeschke et al. 2002[16]), and the Applicant reports that elinzanetant and its metabolites are CYP inducers. Thus, the initial injury that develops following short-term treatment with elinzanetant could result at least in part from upregulation of CYPs and could be subsequently resolved by adaptative responses. In this context, hepatic adaptation to an initial drug-induced liver injury has been reported with other drugs (Eakins et al. 2015[17]).

Following a consult request from the OND/Drug-Induced Liver Injury (DILI) team, the CDER Computational Toxicology Consultation Service (CTCS) team conducted a

[15] Myfembree [estradiol, norerthindrone acetate, relugolix] approved labeling (last revised on 07/17/2024, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/214846s008lbl.pdf.

[16] Jaeschke H, Gores GJ, Cederbaum AI, Hinson JA, Pessayre D, Lemasters JJ. Mechanisms of hepatotoxicity. Toxicol Sci. 2002 Feb;65(2):166-76.

[17] Eakins R, Walsh J, Randle L, Jenkins RE, Schuppe-Koistinen I, Rowe C, Starkey Lewis P, Vasieva O, Prats N, Brillant N, Auli M, Bayliss M, Webb S, Rees JA, Kitteringham NR, Goldring CE, Park BK. Adaptation to acetaminophen exposure elicits major changes in expression and distribution of the hepatic proteome. Sci Rep. 2015 Nov 26;5:16423.

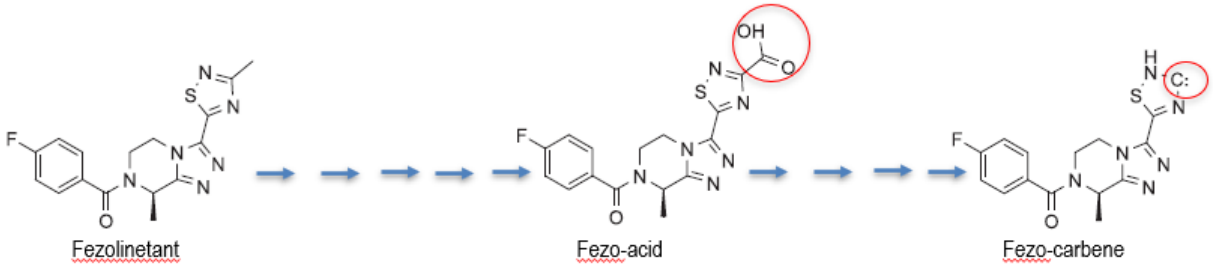
quantitative structure-activity relationship [(Q)SAR] analysis to assess whether the chemical structure of elinzanetant has structural features that could predict its hepatotoxic potential. The team concluded that, based on their (Q)SAR analysis, elinzanetant is predicted to be equivocal for the endpoints of liver damage and cholestasis, negative for liver enzyme abnormalities, and positive for bile duct disorders and gall bladder disorders. Refer to the internal memo from the CTCS team appended in the review.

Hypothetical hepatotoxicity predictions for elinzanetant considering findings from fezolinetant

Fezolinetant is an NK3R antagonist approved under the brand name VEOZAH [NDA 216578; approval date: 5/12/2023] for the treatment of moderate to severe VMS due to menopause (). In the pre-approval clinical trial database, elevations of hepatic enzymes were seen with fezolinetant but there were no cases meeting Hy's law criteria or with elevated bilirubin levels. The approved fezolinetant labeling thus included a warning for its potential to elevate liver enzymes, and FDA recommended monitoring and follow-up of hepatic function and injury in patients taking fezolinetant. After receiving post-marketing reports of serious hepatotoxicity in patients taking fezolinetant, FDA revised labeling in 2024 to add a Boxed Warning for serious hepatotoxicity that occurred within 40 days of starting treatment and recommended monthly testing of hepatic function for the first three months of treatment and additional follow up testing at 6 and 9 months after initiation of treatment.

In February 2025, Nuthi et al.[18] published an article reporting that a reactive carbene metabolite could contribute to the hepatotoxicity of fezolinetant. The authors hypothesized that the high electrophilicity of a carbene metabolite that can be generated from the fezolinetant metabolite referred to as fezo-acid, as illustrated in Figure 18, is likely to favor the carbene reaction with thiol groups in the liver to produce thiol adducts that can be hepatotoxic.

Figure 18: Generation of the fezo-carbene metabolite by decarboxylation of the fezolinetant metabolite fezo-acid



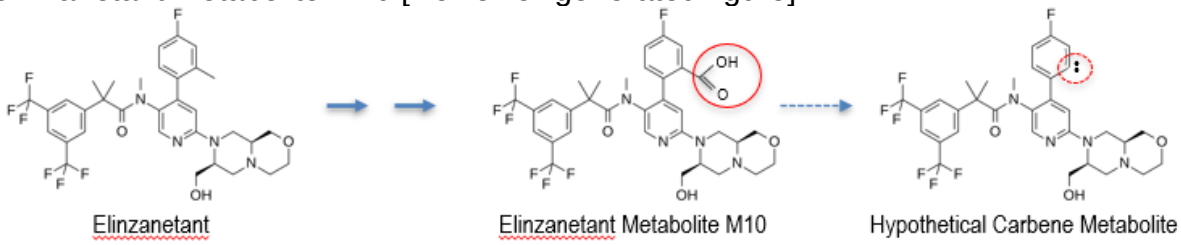
Note# Reviewer-generated figure based on Nuthi et al. 2025. The red circles highlight the carboxylic acid group in the fezo-acid structure and the neutral carbon atom with a valence of two and two unshared valence electrons in the fezo-carbene structure.

[18] Nuthi A, Mishra G, Dixit VA. Carbene reactive metabolite explains the hepatotoxicity of the hot flashes drug fezolinetant: A DFT investigation. Bioorg Chem. 2025 Apr;157:108291.

The Nonclinical Team consulted with the CTCS team to determine if the mechanism hypothesized in this paper could help further inform the (Q)SAR assessment to predict the hepatotoxic potential for elinzanetant and its metabolites. The CTCS team's overall conclusion indicated that elinzanetant is unlikely to be converted into a carbene metabolite and is not predicted to have a hepatotoxic potential comparable to that of fezolinetant. The following is a summary of the CTCS assessment:

1. The elinzanetant acid metabolite M10 could hypothetically undergo decarboxylation to form a carbene metabolite (Figure 19). However, per Nuthi et al., in part due to stabilization of charges by resonance, decarboxylation would be more likely for heteroaromatic rings (as the thiadiazole ring that has the -COOH group in fezo-acid) than for a benzene ring (as the ring that has the -COOH group in the elinzanetant metabolite M10). Without empirical evidence, it is difficult to predict whether decarboxylation of the benzene group in the M10 metabolite can happen in vivo.

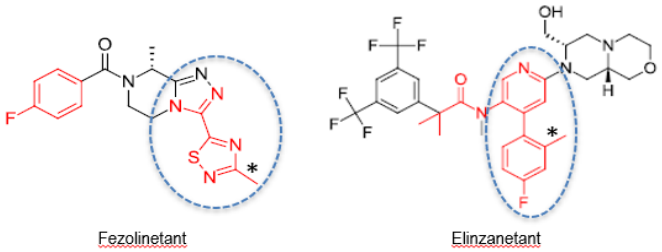
Figure 19. Hypothetical carbene metabolite generated by decarboxylation of the elinzanetant metabolite M10 [Reviewer-generated figure].



The red circles highlight the carboxylic acid group in the elinzanetant M10 metabolite and the neutral carbon atom with a valence of two and two unshared valence electrons in the hypothetical carbene metabolite.

2. Both elinzanetant and fezolinetant have bi-aryl structural alerts (Figure 20). However, in part because the dissimilar aromatic ring types between the two compounds cause the alerts to be weighed differently for each molecule, the (Q)SAR models predict elinzanetant to be negative and fezolinetant to be positive for liver enzyme abnormalities.
3. The presence of a methyl substituent (that could undergo enzymatic oxidative hydrolysis) in the bi-aryl alert is not a requirement for a bi-aryl substructure to be identified as an alert by the hepatotox (Q)SAR models. Thus, the possibility of carbene generation is not a requirement for bi-aryl substructures to be identified as structural alerts for hepatotoxicity.

Figure 20: (Q)SAR-identified structural alerts in fezolinetant and elinzanetant



Note# Figure modified by reviewer from the CTCS consult report issued on December 19, 2024.

The blue circles highlight the bi-aryl substructures in the structural alerts (substructures in red font) in fezolinetant and elinzanetant. The stars mark the methyl groups that could undergo enzymatic oxidative hydrolysis to carboxylic acids.

4. Additional (Q)SAR analysis on M10 or any other metabolites is unlikely to yield additional useful information because the liver tox model training sets are largely populated with drug substances with information from post-market reporting and do not include many metabolites or impurities.

Summary and conclusion

There were no histopathological findings indicating hepatotoxicity in the pivotal, long-term repeat-dose toxicity studies in rats and monkeys. The findings of hepatocellular necrosis and lobular hepatocellular hypertrophy, hepatocellular vacuolation, and/or single-cell necrosis seen in short-term toxicity studies at high doses have multiples of exposure of 21X (average of males and females) in rats, 13X in male monkeys, and 2.7X in female monkeys as compared to the human therapeutic exposure on an AUC basis. Considering the comparative (Q)SAR analysis by the CTCS team, the likelihood of generation of a reactive carbene metabolite that can form hepatotoxic thiol adducts is low for elinzanetant compared to fezolinetant due to their dissimilar structures. Therefore, from the nonclinical perspective, the potential for hepatotoxicity with the maximal recommended human dose of elinzanetant is lower than with fezolinetant.

Conclusion

Elinzanetant is an NK1R/NK3R antagonist, and inhibition of NK1R/NK3R activity in hypothalamic KNDy neurons is proposed to contribute to the suppression of hot flashes experienced by women with VMS during menopause. The complete package of nonclinical studies submitted to support this application are adequate and PharmTox supports the approval of this application.

12 Appendix/Attachments

The full review for the rat PPND studies, in-vitro phototoxicity study, consult report from CTCS and Q(SAR) is included below.

Prenatal and Postnatal Development in the Rat (GLP; Pivotal Study)

Study title: BAY 3427080: An Oral Gavage Study of Prenatal and Postnatal Development, Including Maternal Function in the Rat (GLP)

Study no.:	B003187; T105437-0
Study report location:	SDN 1, 07/26/2024
Conducting laboratory and location:	(b) (4) (b) (4)
Date of study initiation:	01/25/2023
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BAY 3427080, 7486-P54 / 20-002, 100.5%

Methods

Doses: 0, 1.5, 5, 15 mg/kg/day

Group[a]	Number of Mated Females (F0)	Dose Level[b] (mg/kg/day)	Dose Concentration[b] (mg/mL)	Dosing Schedule
1 (Control)	22	0	0	GD 6 through LD 20
2 (Low)	22	1.5	0.75	GD 6 through LD 20
3 (Mid)	22	5	2.5	GD 6 through LD 20
4 (High)	22	15	7.5	GD 6 through LD 20

GD = Gestation Day; LD = Lactation Day.
a Group 1 was administered vehicle control item only.
b Animals were dosed at a dose volume of 2 mL/kg.

Frequency of dosing: Once daily

Dose volume: 2 mL/kg/day

Route of administration: Oral gavage

Formulation/Vehicle: 1% aqueous methylcellulose (400 cps at 2%)

Species/Strain: female Crl:CD(SD) rats, 10 to 12 weeks old

Number/Sex/Group: 22 females/group (see table above)

Satellite groups: TK: n = 3 F_0 animals/group/time point

Group	Set	Phase Day	Time Points[a]
1, 2, 3, 4	Three animals/ group/time point	GD 6	Predose and 1, 2, 4, 6, 8, and 24 hours postdose
		GD 20	1, 2, 4, 6, 8, and 24 hours postdose
		LD 4	24 hours postdose

GD = Gestation Day; LD = Lactation Day.
a Blood collection times were approximate.

Deviation from study protocol: Deviations do not appear to affect the overall outcome of the study. Clinical observations and food consumptions were missed at a few timepoints (up to 4 occasions). Additionally, bladders were not collected from some F_0 animals during necropsy (up to 5 rats per dose group).

Dosing Solution Analysis: The mean sample concentration results from almost all dose formulation preparations were ± 15% of the theoretical concentration, except 1 batch (which was used for dosing day 22-28 (6 days) and was below the specification at 78.6 %).

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Observations and Results

F0 Dams

Mortality: 1 control, 1 LD (1.5 mg/kg/day), 3 MD (5 mg/kg/day), and 3 HD (15 mg/kg/day) females sacrificed following total litter loss.

Findings were as follows:

1 Control: Clinical observations of piloerection and decreased activity were observed for this female on GD 22. Study report notes no body weight loss or decrease in food consumption was noted prior to lactation day 0. All the pups in this litter were considered to have been stillborn (based on failure of the lung float test). There were no findings at necropsy.

1 LD: All pups were partially cannibalized. Fetal material found in stomach of dam. No clinical observations or macroscopic changes at necropsy.

3 MD: Two females (Animals R0210 and R0214) had a clinical observation of not attending to litter on lactation days 0 and 1 or lactation days 1 and 2, respectively. Animal R0214 had a body weight loss of 13 g over lactation day 0 to 1 (despite having a pregnancy on par with the other females), and all pups were observed to be cool to the touch with no visible milk band. Three other pups from this dam were, or were thought to be, cannibalized. All pups in the litter from Animal R0215 were found dead on lactation day 1. Many of these pups were found at necropsy to have no milk in the stomach. There were no macroscopic observations at necropsy for any of these dams.

3 HD: All 3 females sacrificed due to total litter loss on lactation day 2. Animal R0304 was noted with thin body condition on lactation day 1 and a body weight loss of 7 g over lactation day 0 to 1. Animal R0305 had no BAY 3427080-related clinical observations, significant body weight loss, or decreased food consumption prior to lactation day 2. No pups in either of these litters survived to lactation day 2. Animal R0320 was noted with hunched posture on lactation day 1 and 2 and piloerection on lactation day 2. All pups in this litter were observed to be cool to the touch with no visible milk band on lactation day 1 and 2. There were no macroscopic observations at necropsy for this dam.

F0 Maternal clinical observations

Besides the clinical observation in dams sacrificed due total litter loss noted above, there were no clinical observations noted during the gestation and lactation period for any of the treatment groups.

Body weight

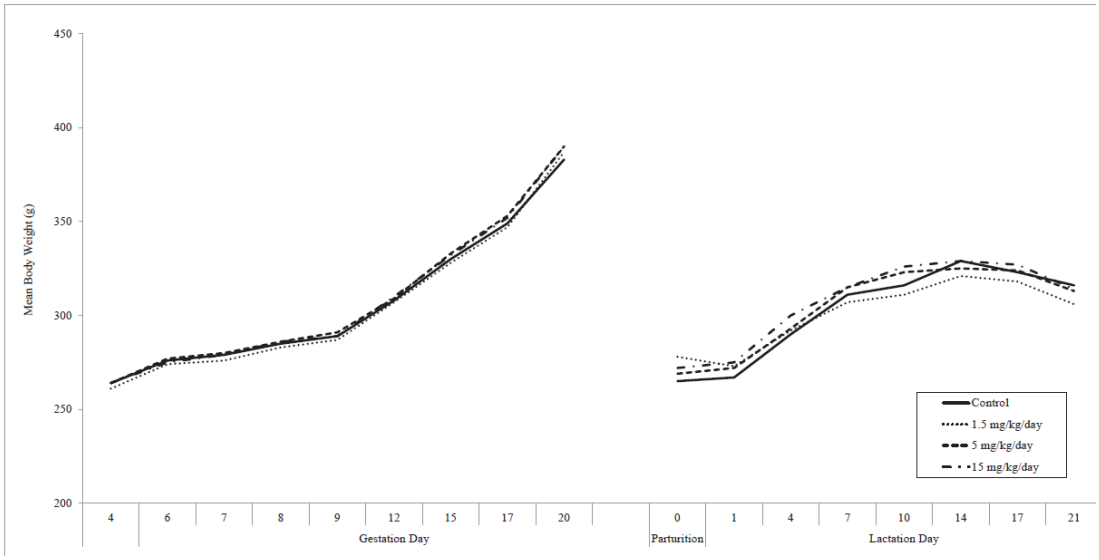
Gestation and Lactation

Gestation:

No treatment-related effect on body weight or body weight gain during gestation.

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Figure 21: Maternal body weight (F0 generation).



Source: Extracted from study report

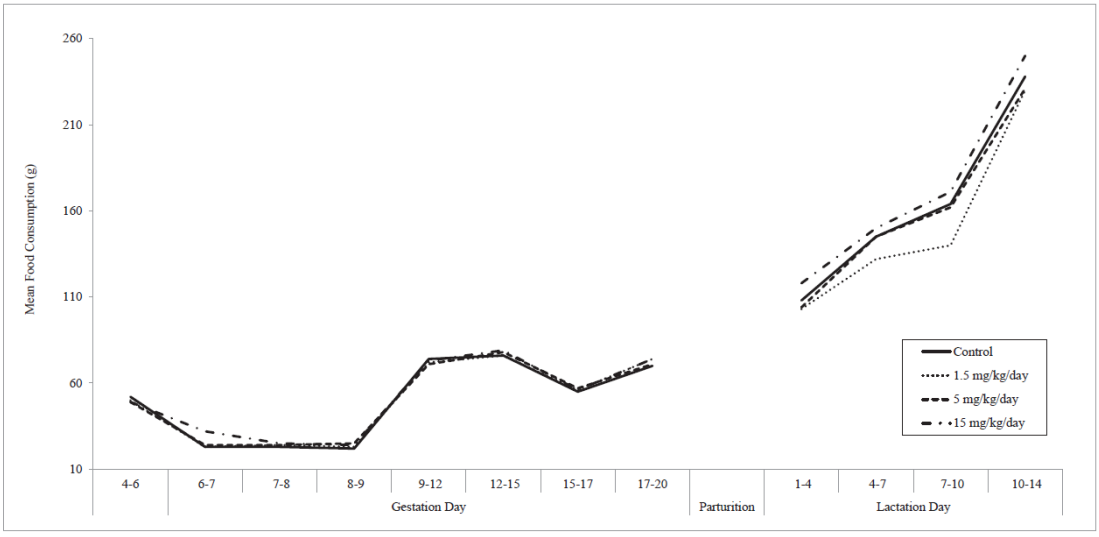
Lactation:

Mean lactation body weight gain was lower than controls from lactation day 1 to 21 in 1.5 mg/kg/day and 15 mg/kg/day (-32.7%) groups. There was no dose responsiveness, hence the Applicant considers this finding incidental.

Reviewer's Comment. A dose-response relationship could have been masked because the most affected rats in the MD and HD groups died by lactation day 2.

Food consumption

Figure 22: Maternal food consumption (F0 generation).



Source: Extracted from study report

Gestation

- No treatment-related effects on food consumption.

Lactation

- Mean maternal food consumption was reduced at 1.5 mg/kg/day for the intervals of lactation day 7 to 10 (-14.6%, p≤ 0.05), and lactation day 1 to 14 (-8%, p≤ 0.05). These reductions in food consumption appear to correlate with lower body weight gain in the 1.5 mg/kg/day group.
- No reduction seen in the 5 mg/kg/day and 15 mg/kg/day groups.

Natural delivery and Litter observations

- An increase in total litter loss was observed at 5 mg/kg/day and 15 mg/kg/day.
- No change in mean gestation duration (number of days to parturition) or mean post-implantation loss.

Table 65: Natural delivery and litter data summary.

Dose (mg/kg/day)	0	1.5	5	15
F0 females				
No. pregnant	22	19	21	22
No. sacrificed moribund due to total litter loss	1	1	3	3
F1 Litters				
No. pups delivered	289	230	279	285
Liveborn	267	225	263	273
Stillborn	22*	5	16	12
No. pup deaths - PND 0 to 4	10	10	45	48
Viability Index (%)	96.3	95.6	82.9	82.4
No. pup deaths - PND 4 to 22	10	17	9	13
Weaning Index (%)	94.3	89.4	94.0	92.1

*The high number of stillbirths in the control group is due to 1 control dam (R0001) that had 18 stillborn pups (complete litter).

Source: Reviewer-generated table

Reviewer's comments:
During review of the study report several tabular discrepancies were noted in the full study report. The raw data were re-interpreted to derive final conclusions from the study as well as to construct Table 65 above.

The study report tables and summary table in the toxicology written summary also notes an error in the total % females with stillborn pups in the control group (i.e., incorrect value of 4.76%). The % of females with stillborn pups are actually 9.09% (2 in 22; Animal R0001 and Animal R0013). Based on the historical control information at the end of the DRF PPND study report [B003162 / T105436-9], the control value is within the range of

Reference ID: 5623053

historical controls for this laboratory. The number of stillborn pups in control, LD, MD, and HD groups were noted to be 22, 5, 16, and 12, respectively. The high number of stillborn pups in the control (22) are largely driven by the complete litter loss in one control female (Animal# R0001) that had 18 stillborn pups.

Viability index:
Decrease in viability index (% alive PND 4 versus PND 0; 83% in MD and HD compared with 92% in controls and LD), and decrease in lactation/weaning index (pup survival from PND 4 to PND 21; 88%, 82 and 81% in LD, MD and HD, respectively, compared with 91% in controls)

Reviewer's note: Complete litter loss and decrease in pup viability (PND 5) was also observed in the DRF study [B003162 / T105436-9] in all doses tested, where F0 animals were administered 5, 25, or 100 mg/kg/dose once daily or 0 (vehicle) or 50 mg/kg/dose twice daily (BID). This finding is considered test article related.

Maternal Macroscopic Pathology
There were no dose-dependent findings in tissues that were evaluated (cervix, liver, ovary, oviduct, skin, stomach, urinary bladder, uterus, vagina).

F1 Generation

Clinical observations

- Missing milk band in pups in the MD (17/226) and HD (13/236) groups, and pups were cool to touch (25/226, 14/236) in litters that experienced total litter loss.
- Thinning of pelage (fur) in 4, 19 and 5 animals in LD, MD and HD respectively.

Table 66: Summary of pup clinical observations (F1 generation) in the rat PPND study.

Dose group (mg/kg/day)	0	1.5	5	15
Number of litter/pups evaluated	21/233	18/206	20/226	20/236
No milk band present (physical appearance)	Pups: 0/233 Litters: 0/21	Pups: 0/206 Litters: 0/18	Pups: 17/226 Litters: 3/20	Pups: 13/236 Litters: 3/20
Cool to touch (temperature)	Pups: 0/233 Litters: 0/21	Pups: 1/206 Litters: 1/18	Pups: 25/226 Litters: 3/20	Pups: 14/236 Litters: 2/20

Source: Reviewer-generated table based of table 8.11 from study report (page 91).

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Pup body weight

Mean female pup body weights were statistically higher than controls in the HD group from PND 4 (prior to culling) all the way up to PND 17 ($p<0.05$).

Table 67: Body weight of male and female pups from dams that were treated with vehicle or elinzanetant from GD6 through lactation day 20.

DOSE LEVEL		Control 0 mg/kg/day	GROUP 2 1.5 mg/kg/day	GROUP 3 5 mg/kg/day	GROUP 4 15 mg/kg/day
pup Weight/Litter (grams)					
Day 4 FEMALES - Postcull	MEAN	9.68	10.38	10.13	10.93*H
	S.D.	1.16	1.78	1.78	1.43
	N	21	18	18	19
Day 7 MALES	MEAN	16.56	16.94	17.02	17.70
	S.D.	1.25	2.40	1.97	1.83
	N	21	18	18	19
Day 7 FEMALES	MEAN	15.91	16.40	16.21	17.60*H
	S.D.	1.33	2.34	1.99	1.92
	N	21	18	18	19
Day 10 MALES	MEAN	24.70	24.79	25.17	26.01
	S.D.	1.45	2.84	2.13	2.21
	N	21	18	18	19
Day 10 FEMALES	MEAN	23.88	24.26	24.17	26.04+H
	S.D.	1.48	2.61	2.22	2.32
	N	21	18	18	19
Day 14 MALES	MEAN	35.41	35.25	35.91	37.18
	S.D.	1.76	3.29	2.60	3.07
	N	21	18	18	19
Day 14 FEMALES	MEAN	34.41	34.56	34.60	37.36+H
	S.D.	1.67	2.93	2.70	2.98
	N	21	18	18	19
Day 17 MALES	MEAN	43.43	43.13	43.66	45.36
	S.D.	2.17	3.63	3.05	3.89
	N	21	18	18	19
Day 17 FEMALES	MEAN	42.44	42.28	42.05	45.29*H
	S.D.	2.17	3.16	3.07	3.72
	N	21	18	18	19
Day 21 MALES	MEAN	59.42	59.19	58.71	60.59
	S.D.	3.69	5.31	4.93	4.91
	N	21	18	18	19
Day 21 FEMALES	MEAN	57.96	57.96	56.44	60.90
	S.D.	3.72	4.76	4.58	4.48
	N	21	18	18	19

N = Number of Litters.
+H = Dunnett Exact Homogeneous Test Significant: 0.01 level
*H = Dunnett Exact Homogeneous Test Significant: 0.05 level

Source: Extracted from study report (Table 8.12 on page 95)

***Reviewer's comment**: Applicant notes that this effect could be test article related but considered non-adverse since it did not affect any other parameters in the female pup. The weights were comparable to controls by PND 21*.

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Necropsy
As in the clinical observation pups, there were no other findings except no milk in stomach. Other findings were sporadic (aorta blood vessel-supernumerary branch, fluid filled thoracic cavity, urinary bladder distended).

Table 68. Necropsy observations in the F1 generation.

Summary of Pup Necropsy Observations - F0 Generation

	DOSE LEVEL	CONTROL 0 mg/kg/day	GROUP 2 1.5 mg/kg/day	GROUP 3 5 mg/kg/day	GROUP 4 15 mg/kg/day
Animal-no milk in stomach pup Incidence	N	0	0	21	20
	%	0.0	0.0	46.7	23.6
Litter Incidence	N	0	0	5	3
	%	0.0	0.0	71.4	42.9

Source: extracted from study report (Table 8.13 on page 98)

Reflex and Physical Development
No effect on sexual development (balano-preputial separation in males and vaginal opening in females) at any dose levels.

Neurobehavioral Data
No treatment-related effects were observed on locomotor activity (basic movements, X+Y ambulations, rearing, and habituation on PND 56), auditory startle on PND 62, or Morris water maze performance on PND 63 at any dose level. Statistically significant values were observed occasionally but lacked dose dependence.

Reviewer's Comments.

1. ***The statistical significance identified for some of the neurobehavioral data is considered spurious because it is based on uncorrected p-values from t-tests used for pairwise comparisons of multiple groups in repeated-measure designs.***
2. ***The findings of no significant neurobehavioral alterations in 56- to 63-day-old pups that were exposed to elinzanetant in utero and through lactation suggest that, if elinzanetant can affect the neurobehavioral domains assessed by the Applicant, its effects are not long lasting.***

Clinical observation during maturation, pairing and post pairing.
Increase in sensitivity to touch in MD and HD females and increase in vocalization in males during maturation were observed. The sensitivity to touch was not observed during gestation for F0 females.

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Table 69: Summary of clinical observations in the F1 generation.

Test Item	Dose Unit	1	2	3	4
BAY 3427080	mg/kg/day	0	1.5	5	15

Phase: Maturation
Phase: Pairing
Phase: Post Pairing

Category / Observation	Group/Sex: / Number in Group:	1/M 21	2/M 21	3/M 20	4/M 20	1/F 21	2/F 21	3/F 20	4/F 20
NORMAL									
No remarkable observations		21	21	20	20	21	21	20	20
Activity									
general activity, increased		0	0	0	0	0	1	0	0
Behavior - other									
aggression to handler		0	0	0	1	0	0	0	1
sensitivity to touch, increased		0	0	0	1	2	2	5	6
vocalization		0	1	2	3	9	5	9	11

Source: Table from the Applicant's report.

<u>Reviewer's comment</u>: Increased sensitivity to touch was noted in F1 generation female pups with an incidence of 2/21, 2/21, 5/20 and 6/20 in control, LD, MD and HD, respectively. Although no neurobehavior findings were noted, the dose dependent increase in sensitivity to touch in female pups could be an adaptive behavior change in response to decrease maternal care or a CNS related effect. More studies would be necessary to fully elucidate the mechanistic basis of this finding.

Body weight
No statistically significant changes in body weight in males during maturation and pairing & in females during maturation, pairing, post pairing and gestation.

Food consumption
There was slight increase in food consumption (day 0 to day 56) in females in all treatment groups (+6.3% to +12%), with only MD (+12%) showing statistically significance.

Reproductive Performance:
There were no treatment-related effects on the reproductive performance of the F1 generation. The mating indices and fertility index % for the treatment groups were within the historical controls.

Macroscopic observation
No treatment-related effects on macroscopic observations for the F1 generation.

Cesarean section data
No dose-dependent effects

Toxicokinetics

Table 70: PK of elinzanetant and its metabolites at GD6 and GD20 in pregnant rats.

	Pregnant female - GD 6				Pregnant female - GD20		
	Dose groups (mg/kg/day)				Dose groups (mg/kg/day)		
	1.5	5	15		1.5	5	15
Elinzanetant (parent)							
$AUC_{(0-24)}$ µg*h/L	2070	6990	25700		2000	8960	36200
C_{max} µg/L	152	617	1800		134	700	2940
BAY 3462932 (M27)							
$AUC_{(0-24)}$ µg*h/L		18.7	112		6.2#	98.1	371
C_{max} µg/L		3.25	7.36		1.29#	6.358	32.1
BAY 3462933 (M30/34)							
$AUC_{(0-24)}$ µg*h/L	1310	2970	5410		1460	5010	10800
C_{max} µg/L	82.3	202	352		90.3	263	651
BAY 3462934 (M18/21)							
$AUC_{(0-tlast)}$ µg*h/L		2.88#	9.30		29#	114	200
C_{max} µg/L		0.962	1.6		1.77#	6.12	14.5

#: limited evaluation possible due to incomplete profile and high variability of concentration near LLOQ

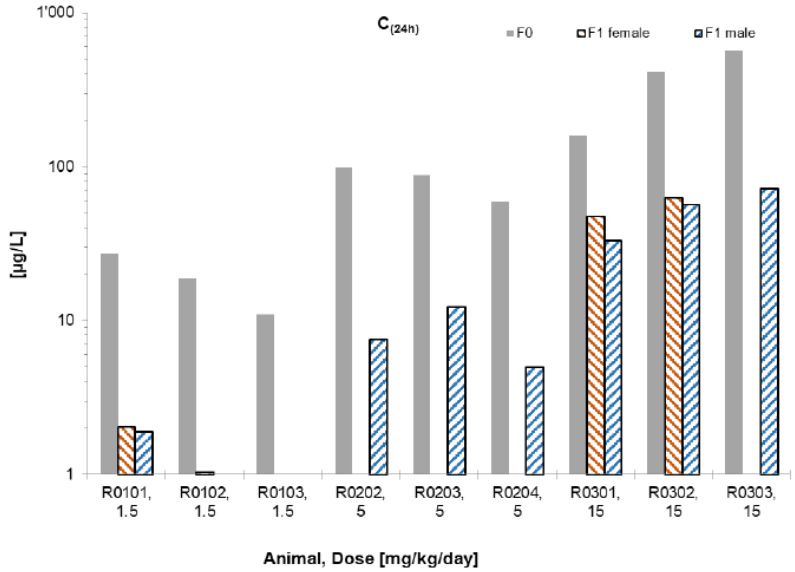
[Table generated by reviewer using tables 26, 27, 28, and 29 from Bioanalytical and TK Analyses report in appendix 10.4 of the study report of the PPND main study B003187]

Pup to Dam systemic exposure ratio (Applicant's summary):
It is noted that there were no female pups available for MD group for TK analysis.

- When comparing the 24-h plasma levels of pooled or individual pups (F1) with those of the respective dams (F0) on lactation day 4 and PND 4, respectively, the concentration ratios increased with dose, with pup-to-individual dam-ratios (F1-F/F0) from 5.6% to 29.9% for BAY 3427080 (Figure 23).

Reference ID: 5623053

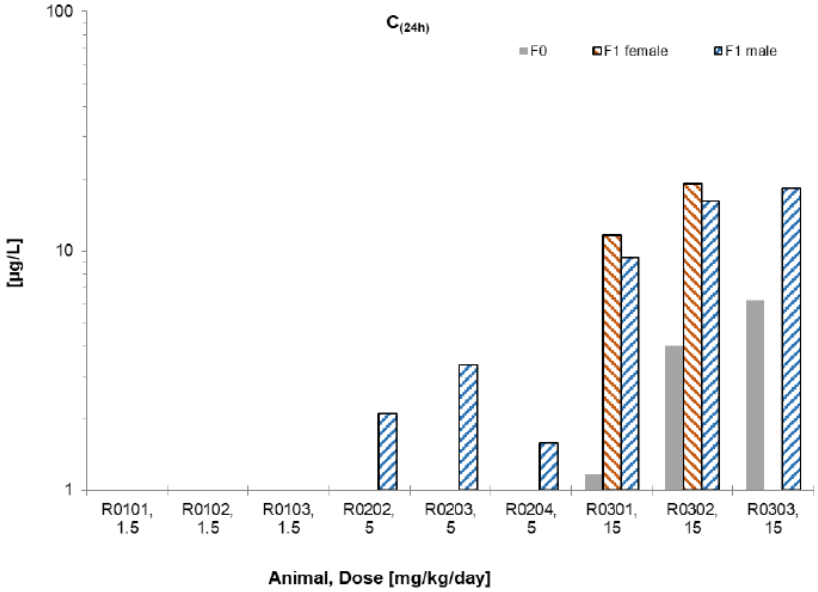
Figure 23: Plasma concentrations of elinzanetant in female F1 and male F1 pups and the F0 dams at 24 h post-dose on PND/lactation day 4 after once daily oral gavage of the dams during pregnancy and lactation.



Source: Extracted from study report

- For the metabolite BAY 3462932, the dam 24 h plasma levels could only be determined for the high dose group. The concentrations in pups were markedly higher than in dams, with pup-to-individual dam-ratios from 293% to 991% for animals dosed with 15 mg/kg/day (Figure 24).

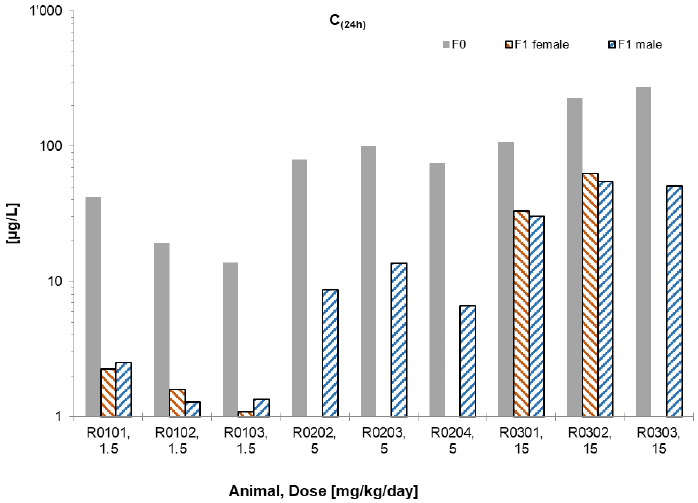
Figure 24: Plasma concentrations of BAY 3462932 in female F1 and male F1 pups and F0 dams at 24 h post-dose on PND/lactation day 4 after once daily oral gavage of the dams during pregnancy and lactation.



Source: Extracted from study report

- For the metabolite BAY 3462933, the pup-to-individual dam-ratios slightly increased with dose from 5.4% to 30.7% (Figure 25).

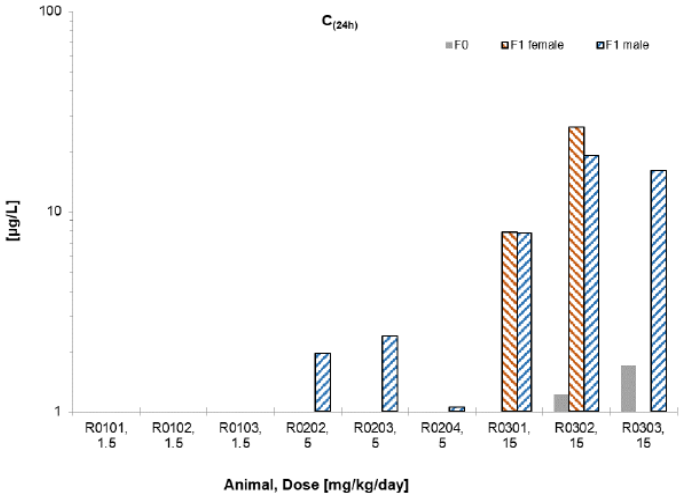
Figure 25: Plasma concentrations of BAY 3462933 in female F1 and male F1 and the F0 dams at 24 h post-dose on PND/lactation day 4 after once daily oral gavage of the dams during pregnancy and lactation.



Source: Extracted from study report

- For the metabolite BAY 3462934, the dam 24 h plasma levels could only be determined for the high dose group. The pup-to-individual dam-ratios were markedly high with values from 947% to 2170% (Figure 26).

Figure 26: Plasma concentrations of BAY 3462934 in female F1 and male F1 pups and the F0 dams at 24 h post-dose on PND/lactation day 4 after once daily oral gavage of the dams during pregnancy and lactation.



Source: Extracted from study report

Reviewer's comment: The reason for higher exposure of M27 (BAY 3462932) and M18/21 (BAY 3462934) in the pups compared to dams is unclear and is not explained by the Applicant. The finding is consistent with elinzanetant radioactivity detected in the milk of lactating rats treated with radiolabeled elinzanetant (study B003245).

NOAEL and Multiples of exposure

- The Applicant sets the NOAEL for **maternal toxicity**, **F1 maturation, and F1 reproductive function** for this study at the highest dose tested or 15 mg/kg/day (BAY 3427080 C_{max} of 2940 µg/L and $AUC_{0\text{-}tlast}$ of **36200** µg*h/L), which provides a safety margin of **4.2-fold on an AUC basis** [based on $AUC_{0\text{-}24h}$ of 8572 ng•h/mL (Elinzanetant) obtained from clinical study B002427].

  Reviewer's comment: This reviewer agrees with the NOAEL set at 15 mg/kg/day for F1 maturation and reproductive function. However, based on maternal findings of body weight loss, clinical signs of not attending to offspring, and general poor health observed in 3 F0 dams at 5 mg/kg/day and 3 F0 dams at 15 mg/kg/day, the maternal toxicity NOAEL should be set at the low dose of 1.5 mg/kg/day.

- The Applicant set the NOAEL for **developmental toxicity** at the low dose or 1.5 mg/kg/day (corresponding to maternal BAY 3427080 C_{max} of 134 µg/L and $AUC_{(0\text{-}24h)}$ of 2000 µg*h/L on GD 20), based on the increase in litter loss and clinical observation of missing milk bands.

  Reviewer's comment:

  1) ***This Reviewer agrees with a NOAEL for developmental toxicity of 1.5 mg/kg/day.***
  2) ***At the NOAEL of 1.5 mg/kg/day for developmental toxicity there is no safety margin (0.23 X) based on $AUC_{0\text{-}24h}$ of 8572 ng•h/mL (Elinzanetant) obtained from clinical study B002427.***
  3) ***Metabolite coverage in F0 rats: Based on $AUC_{0\text{-}24h}$ of 2496 ng•h/mL (M27), 4570 ng•h/mL (M30/34), 2326 ng•h/mL (M18/21), obtained from clinical study B002427, there is no coverage for any of the metabolites in the dams.***

Reference ID: 5623053

Prenatal and Postnatal Development in the Rat (GLP; DRF Study)

Study title: BAY 3427080: Oral Gavage Range-Finding Study of Pre- and Postnatal Development in the Rat (GLP)

Study no.:	B003162; T105436-9
Study report location:	SDN 1, 07/26/2024
Conducting laboratory and location:	(b) (4) (b) (4)
Date of study initiation:	12/08/2022
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BAY 3427080, 7486-P54 / 20-002, 100.5%

Key Study Findings

- Sprague Dawley rats were administered a daily via oral gavage of 0 (vehicle: 1% aqueous methylcellulose), 5, 25 and 100 mg/kg/day (once daily; QD) and 50 mg/kg BID of BAY 3427080 from implantation (GD 6) to lactation day 4.
- Mortality occurred at 100 mg/kg/day once daily and 50 mg/kg/day (twice daily) groups. Clinical observations of dystocia (e.g., piloerection, rough pelage, hunched posture, and decreased activity), decreased body weight and body weight gain (-16% to -34%), and decreased food consumption (up to -47% on GD18 to 21).
- Other toxicities included increased gestation length (23.5 or 23.6 days compared to 23 days in control) and post implantation loss (up to ~49%), decreased number of liveborn pups delivered (~7 compared to ~11 in control), decreased number of litters remaining on lactation day 4 (% viability as low as 5% compared to 94% in control), decreased pup body weights (up to 27%), and pups found with no milk in stomach (with 33, 15, 2, and 11 pups affected in groups administered 5, 25, or 100 mg/kg/day or 50 mg/kg/dose BID).
- Increase in total litter loss and decreased pup viability (by PND 5) in all elinzanetant treated groups: 3 in 5 mg/kg/day, 2 in 25 mg/kg/day, and 5 in 100 mg/kg/day. Additionally, decrease in activity, slow respiration and cool to touch were noted in groups starting at 5 mg/kg/day.
- Applicant set the maternal NOAEL at 25 mg/kg/day once daily (BAY 3427080 C_{max} of 3630 µg/L and $AUC_{(0\text{-tlast})}$ of 57200 µg*h/L on GD 17).
- NOAEL for developmental toxicity was not established due to litter loss in all treatment groups.

Reference ID: 5623053

Toxicokinetics

Table 71: PK of elinzanetant and its metabolites at GD6 and GD17 in pregnant rats.

	Pregnant female - GD 6					Pregnant female – GD17			
	Dose groups (mg/kg/day)					Dose groups (mg/kg/day)			
	5	25	100	100 (50 BID)		5	25	100	100 (50 BID)
Elinzanetant (parent)									
$AUC_{(0\text{-}tlast)}$ µg*h/L	6490	34000	158000	134000		8610	57200	197000	213000
C_{max} µg/L	633	2410	8800	8850		758	3630	15300	13500
BAY 3462932 (M27)									
$AUC_{(0\text{-}tlast)}$ µg*h/L	19.2	154	573	608		24.5	328	1580	2090
C_{max} µg/L	4.0	10.2	27.1	32.3		5.3	24.9	104	113
BAY 3462933 (M30/34)									
$AUC_{(0\text{-}tlast)}$ µg*h/L	3120	5780	11000	11800		3400	8530	22400	26900
C_{max} µg/L	224	358	571	641		243	515	1320	1430
BAY 3462934 (M18/21)									
$AUC_{(0\text{-}tlast)}$ µg*h/L	5.05	12.8	59.7	79.1		10.5	64.7	187	294
C_{max} µg/L	1.84	2.25	3.12	3.84		2.57	4.57	10.5	15.2

[Table generated by reviewer using tables 27, 28, 29, and 30 from Bioanalytical and TK Analyses report in appendix 10.4 of the study report of the DRF study]

Phototoxicity Study Review and Risk Assessment

Study title: NT-814: In Vitro Balb/c 3T3 Neutral Red Uptake Phototoxicity Assay

Study no.:	R-13578 [conducting lab study ID# 8382675]
Study report location:	SDN1; eCTD 0001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Feb 09, 2018
GLP compliance:	Yes
QA statement:	Is there a signed QA statement? Electronic sig (QA statement attached)
Type of study:	In vitro Phototoxicity

Key Study Findings

- NT-814 was assayed for phototoxicity to Balb/c 3T3 fibroblast cells using the Neutral Red Uptake assay.
- NT-814 was phototoxic in this in vitro test system when tested up to the limit of solubility in culture medium.
- The multiples of exposure based on IC_{50} for plasma exposure, eye exposure and skin exposure are 198-fold, 99-fold and ~40-fold, respectively based on the human C_{max} data obtained from PK modeling study [B002427]

Method

Drug: NT-814; Purity 99.4±0.3% assay (HPLC)
Vehicle: 1% dimethyl sulphoxide (DMSO) in Hanks's balanced salt solution (HBSS).

Reference ID: 5623053

Concentration: 8 concentrations including a maximum concentration of 100 µg/mL was tested in the absence and presence of UV-A light (Table 72).

Table 72: Summary of in-vitro phototoxicity assay testing conditions.

UV-A	Concentration of Treatment Solution (mg/mL)	Final Concentration (µg/mL)
- and +	0.00316	0.0316
	0.0100	0.100
	0.0316	0.316
	0.100	1.00
	0.316	3.16
	1.00	10.0
	3.16	31.6
	10.00	100

Cell culture: Mouse fibroblasts (Balb/c 3T3 clone A31)
Results:

1) Visual evaluation:
   - Following treatment with NT-814 in the absence of UV-A, no evidence of toxicity was observed however, cell rounding was observed at the highest two concentrations tested (31.6 to 100 µg/mL).
   - Evidence of concentration-related toxicity at the highest five concentrations of NT-814 in the presence of UV-A (1 and 100 µg/mL) and cell rounding was observed at all concentrations tested.
   - Precipitation was observed at the time of treatment at the highest concentration tested (100 µg/mL). This concentration was therefore excluded from analysis and the highest concentration analyzed was **31.6 µg/mL** in both the absence and presence of UV-A light.

2) Neutral Red Uptake Assay and Phototoxicity
   - Chlorpromazine induced an acceptable positive response with a PIF (photo-irritation factor) value of 22.46 [PIF = IC_{50} in the absence of UV-A/IC_{50} in the presence of UV-A].
   - Treatment of cultures with NT-814 resulted in a minimal decrease in cell survival, in the absence of UV-A light. In the presence of UV-A light, cytotoxicity, as indicated by a decrease in Neutral Red uptake, was observed at the highest four concentrations of NT-814 analyzed (**1.00 to 31.6 µg/mL**). As there was no IC_{50} value in the absence of UV A, the PIF could not be calculated.

Table 73: IC_{50} and PIF calculations from in vitro phototoxicity assay

Test Article	IC_{50} Absence of UV-A (µg/mL)	IC_{50} Presence of UV-A (µg/mL)	PIF Value	MPE Value
Chlorpromazine	42.467	1.892	22.46**	0.662
NT-814	-*	0.845	-*	0.442

* The cell survival at the highest concentration analysed (31.6 µg/mL) was more than 50% and hence IC_{50} and PIF values could not be calculated.

** PIF >6, therefore positive control response was acceptable. A MPE value was used to assess the phototoxicity of the test article.

Source: Extracted from study report.

Reference ID: 5623053

- Mean Photo Effect (MPE) was used for evaluation. An MPE value of 0.442 was calculated for NT-814 and as this MPE value was ≥0.15, the test article was considered to be phototoxic in this assay. [Note# The MPE is based on comparison of the complete concentration response curves. It is defined as the weighted average across a representative set of photo effect values (OECD, 2004)].

Tissue Distribution

The Applicant assessed the tissue distribution of elinzanetant in two whole-body autoradiography studies conducted in rats: study WD2008-00842-00 (study report R-13624) and study KINE 220019-EXT (study report R-14368).

In study WD2008-00842-00, male Lister Hooded pigmented rats were treated with radiolabeled elinzanetant tosylate (in 1% Methylcellulose (w/v)-containing sterile water) via the oral or IV route of administration and euthanized at various times for measurements of radioactivity concentrations in tissues. The oral dose delivered to the rats was 10 mg/kg.

Radioactivity concentrations in blood, pigmented skin, and uveal tract/retina peaked between 2 and 8 h (Table 74). At 35 days following the oral treatment, radioactivity was still quantifiable in about half of the tissues, with highest concentrations generally present in brown fat, uveal tract (choroids, ciliary body and iris)/retina, spleen, and adrenal cortex. The extent of the persistence of radioactive drug-related material in the uveal tract/retina following either route of administration suggested some long-term association of drug-related material with melanin.

Table 74: Concentrations of radioactivity in tissues of male lister hooded pigmented rats after a single oral administration of [^{14}C]GSK1144814 tosylate at a target dose level of 10 mg free base/kg.

	µg equivalents of GSK1144814 free base/g of tissue					
	2 h	**8 h**	**1 day**	**3 days**	**10 days**	**35 days**
Blood (Cardiac)	1.58	1.02	0.233	0.050	BLQ	BLQ
Skin (Pigmented)	4.97	5.11	2.26	0.432	0.146	0.073
Uveal tract/ Retina	1.89	1.63	1.12	0.515	0.416	0.210

Source: Adapted from the study report R-13624 – Table 1, pg 23.

The ratios of tissue:blood radioactivity at 8-h posttreatment rounded to the nearest integer are approximately 5 for pigmented skin and 2 for uveal tract/retina (Table 75).

Table 75: Tissue:blood radioactivity concentration ratios in male lister hooded pigmented rats after a single oral administration of [^{14}C]GSK1144814 tosylate at a target dose level of 10 mg free base/kg

	Tissue:blood radioactivity concentration ratios					
	2 h	**8 h**	**1 day**	**3 days**	**10 days**	**35 days**
Skin (Pigmented)	3.1	5.0	9.7	8.6	NC	NC
Uveal tract/ Retina	1.2	1.6	4.8	10.3	NC	NC

NC = not calculated.
Source: Adapted from the study report R-13624 – Table 3, pg 25

The calculated ratios shown in Table 75 appear to account for the Applicant's statement that "*elinzanetant concentrations in the eye can be up to 2-fold higher and pigmented skin concentrations can be up to 5-fold higher than in blood*" [Nonclinical Overview, pg 19]. However, according to the Applicant's statement in the Pharmacokinetics Written Summary, the Applicant considered study WD2008-00842-00 not relevant for this NDA because "*the study was performed with a higher than clinical[ly] relevant oral dose of the tosylate salt of elinzanetant and only in male Lister-hooded rats*."

In study KINE 220019-EXT, female pigmented Long-Evans rats and albino Sprague-Dawley rats were treated orally with radiolabeled elinzanetant (2 mg/kg in 10% ethanol, 40% polyethyleneglycol 400 (PEG400), and 50% MilliQ water) and euthanized at various times for measurements of radioactivity concentrations in tissues.

In this study, concentrations of radioactivity in the tissues and blood of pigmented female rats at 8, 24, 72, and 168 h were found to be similar to tissues of albino female rats. Radioactivity was still present in the pigmented eye uvea (0.019 µg-equiv/g) at day 35 (840 h) post-dose, a finding that suggests long-term retention or irreversible tissue binding of elinzanetant in pigmented tissues (Table 76).

Table 76: Concentrations of radioactivity in tissues of female Long-Evans rats after a single oral administration of [^{14}C] BAY 3427080 at 2 mg/kg

	µg equivalents of BAY 3427080/g of tissue					
	8 h	**24 h**	**3 days**	**7 days**	**14 days**	**35 days**
Blood (Cardiac)	0.378	0.079	BQL	BQL	BLQ	BLQ
Skin (Pigmented)	0.409	0.117	0.086	0.016	BQL	BQL
Uveal tract/ Retina	0.329	0.170	0.073	0.064	0.045	0.019

Source: Adapted from the study report R-14368 – Table 8, pg 34

The finding that elinzanetant can accumulate in pigmented tissue was consistent between study WD2008-00842-00 (study report R-13624) and study KINE 220019-EXT (study report R-14368).

In study KINE 220019-EXT, the Applicant estimated the total exposure ($AUC_{8h\text{-}last}$) in the different tissues. As shown in Table 77, total exposures were markedly higher in the eye wall pigmented uvea and the highly pigmented skin than in the blood of female Long-Evans rats.

Table 77: Tissue:blood radioactivity exposure ratios in female Long-Evans pigmented rats after a single oral administration of [^{14}C] BAY 3427080 at 2 mg/kg

	$AUC_{(8h\text{-}tlast)}$ (µg-equiv•h/g)	**Tissue:Blood ratios**
Blood (cardiac)	3.656	1
Skin (Pigmented)	13.976	4
Uveal tract/Retina	41.684	11

Source: Reviewer-generated table using data from study report R-14368 – Table 12, pg 40

Although as mentioned above, the Applicant questions the relevance of study WD2008-00842-00 for this NDA, the Applicant appears to have derived potential multiples of exposure (MOEs) for phototoxicity using: (i) the accumulation of elinzanetant in pigmented tissue estimated on the basis of study WD2008-00842-00 (2x in the eyes and 5x in the skin), (ii) the IC_{50} for elinzanetant to induce cytotoxicity in-vitro in the presence of UV-A (0.845 µg/mL), and (iii) the NOEC (0.316 µg/mL).

Calculation of MOEs [using estimated eye and skin accumulations from Study WD2008-00842-00 (2x for eyes and 5x for skin)]:

- IC_{50} in presence of UV-A = 0.845 µg/mL
- NOEC in the presence of UV-A = 0.316 µg/mL
- C_{max} in clinical study = 1423 µg/L or 1.423 µg/mL (Clinical Report B002427, Table 21.3.1, Pg 521)
- Considering the unbound fraction of elinzanetant (~0.3% in human based on study#), the C_{max} exposure = 0.3% of 1.423 µg/mL= 0.00426 µg/mL.
- The distribution data in the quantitative whole-body autoradiography study (melanin binding) indicate that elinzanetant concentrations in the eye can be up to 2-fold higher and pigmented skin concentrations can be up to 5-fold higher than in blood.
- Hence, in the eyes, concentration = 2 x 0.00426 µg/mL= 0.00852 and in the skin, concentration = 5 X 0.00426 µg/mL= 0.0213

MOEs (IC_{50}/C_{max}):

- Based on plasma exposure= 0.845/0.00426 = 198-fold
- Based on eye exposure = 0.845/0.00852 = 99-fold
- Based on skin exposure = 0.845/0.0213 = ~40-fold

MOEs (NOEC/C_{max}):

- Based on plasma exposure= 0.316/0.00426 = 74-fold
- Based on eye exposure =0.316/0.00852 = 37-fold
- Based on skin exposure =0.316/0.0213 = 15-fold

Calculation of MOEs [using estimated eye and skin accumulations from Study KINE 220019-EXT (11x for eyes and 4x for skin)]:

- IC_{50} in presence of UV-A = 0.845 µg/mL
- C_{max} in clinical study = 1423 µg/L or 1.423 µg/mL (Clinical Report B002427, Table 21.3.1, Pg 521)
- Considering the unbound fraction of elinzanetant (~0.3% in human based on study#), the C_{max} exposure = 0.3% of 1.423 µg/mL= 0.00426 µg/mL.
- Based on study KINE 220019-EXT, elinzanetant concentrations in the eye and pigmented skin can be up to 11-fold and 4-fold higher, respectively, than in blood.
- Hence, in the eyes, concentration = 11 x 0.00426 µg/mL = 0.04686 µg/mL, and in the skin, concentration = 4 X 0.00426 µg/mL = 0.01704 µg/mL.

MOEs (IC_{50}/C_{max}):

- Based on plasma exposure= 0.845/0.00426 = 198-fold
- Based on eye exposure = 0.845/0.04686 = 18-fold
- Based on skin exposure = 0.845/0.01704 = 49.5-fold

MOEs (NOEC/C_{max}):

- Based on plasma exposure= 0.316/0.00426 = 74-fold
- Based on eye exposure =0.316/0.04686 = 7-fold
- Based on skin exposure =0.316/0.01704 = 19-fold

***Reviewer's comments*.**

1. ***Based on the calculations from the review team, the multiples of exposure obtained from the in-vitro phototoxicity range from 7-fold (using the NOEC from the in-vitro study and the potential eye exposure based on study KINE 220019-EXT) to as much as 198-fold (using the IC_{50} from the in-vitro study and the plasma exposure).***

   Using the tissue exposures measured in WD2008-00842-00, the Applicant calculates slightly different multiples of exposure. Based on IC_{50}, the Applicant notes potential for phototoxicity at about 234-fold the maximum clinical plasma concentration of elinzanetant. Based on NOEC, the Applicant notes potential for phototoxicity at about 73-fold the maximum clinical concentration. They also note, that based on the distribution data in the quantitative whole-body autoradiography (QWBA) study (melanin binding), the expected maximum clinical concentration in the eye as well as in pigmented skin is still 37- or 15-

Reference ID: 5623053

***times* below the NOEC of the phototoxicity assay. The Applicant concludes that no clinically relevant phototoxicity is to be expected in these tissues.**

2. ***Although the MOEs calculated by the Applicant and by the review team appear to be high, they should be interpreted with caution because elinzanetant concentrations in human pigmented tissues are derived based on the distribution of elinzanetant to pigmented tissues (eyes and skin) in rats treated with a single dose of elinzanetant. There is no data to inform the extent of melanin-containing tissue accumulation after repeated dosing with elinzanetant.***

3. ***Elinzanetant has several characteristics that, per the Guidance for Industry: S10 Photosafety Evaluation of Pharmaceuticals (January 2015), available at https://www.fda.gov/media/85076/download, make it a potential phototoxicant:***
   a. ***It absorbs photons in the ultraviolet (UV) spectrum (290-700 nm).***
      i. ***One peak was detected at 321.4 nm with a calculated molar extinction coefficient (MEC) of 3762.3 $L \cdot mol^{-1}$, which exceeds the threshold of 1000 $L \cdot mol^{-1}$ for phototoxicity (Study Report R-13578).***
   b. ***It distributes to and accumulates in melanin-rich tissues (see below; Study Report R-13624; Study Report R-14368).***
   c. ***It is cytotoxic in the in-vitro Balb/c 3T3 neutral red uptake phototoxicity assay, with an IC_{50} of 0.845 µg/mL and an NOEC of 0.316 µg/mL in presence of UV-A (Study Report R-13578).***

4. ***Considering its light absorption characteristics, its ability to induce cytotoxicity in the in-vitro Balb/c 3T3 neutral red uptake phototoxicity assay, and its ability to distribute to and accumulate in melanin-rich tissues, elinzanetant should be considered a potential phototoxicant.***

5. ***In the pooled safety analysis of the 4 studies (SWITCH-1, and OASIS 1, 2 and 3), 5 women under elinzanetant 120 mg and 1 woman under placebo treatment reported photosensitivity reaction (PTs). Of the 5, one had to withdraw because of photosensitivity reaction (onset day 290). The other 4 cases resolved despite continued treatment with elinzanetant 120 mg, and no actions were taken for these events.***

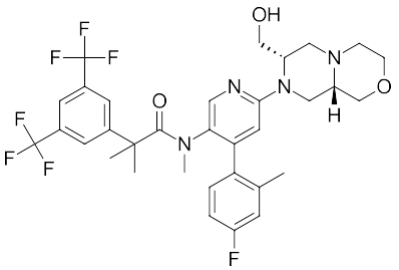
CTCS consult report and (Q)SAR consult report (appended below)

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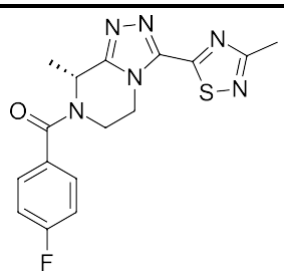
To: **Ling Lan (CDER/OND/OII/DHN)**
cc: **Eileen Navarro Almario (CDER/OND/OII/DHN)**
From: **Jahan Cooper and Naomi Kruhlak (CDER/OTS/OCP/DARS: Computational Toxicology Consultation Service)**
Re: **NDA 219469 - Hepatobiliary toxicity (Q)SAR analysis for Elinzanetant**
Date: **December 19, 2024**

Elinzanetant, the active pharmaceutical ingredient (API) from NDA 219469 and **fezolinetant** (NDA 216578), another API in the same drug class, were evaluated by the CDER/OTS/OCP/DARS Computational Toxicology Consultation Service (CTCS) for hepatobiliary toxicity using (Q)SAR models. Three software programs were used to generate (Q)SAR predictions for five hepatobiliary endpoints: Derek Nexus 6.4.1 (DX), Leadscope Model Applier 2023.0.3-3 (LMA), and CASE Ultra 1.9.2.1 (CU).
These are the most recent versions of the software. All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusions.

Elinzanetant is an investigational new drug being evaluated for treatment of vasomotor symptoms of menopause. **Elinzanetant** and **fezolinetant** are neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonists, and **fezolinetant** was recently approved for treatment of menopausal symptoms.
Fezolinetant contains a warning in its drug label for potential elevated liver enzymes and recommends monitoring and follow-up for hepatic function and injury (FDA, 2023). At least one case of drug-induced liver injury was reported following approval of **fezolinetant** (NIDDK, 2024).
(b) (4)
Therefore, CTCS was consulted to perform a (Q)SAR assessment of potential hepatobiliary toxicity for both NK1/3 antagonists and comment on their structural similarities.



Elinzanetant



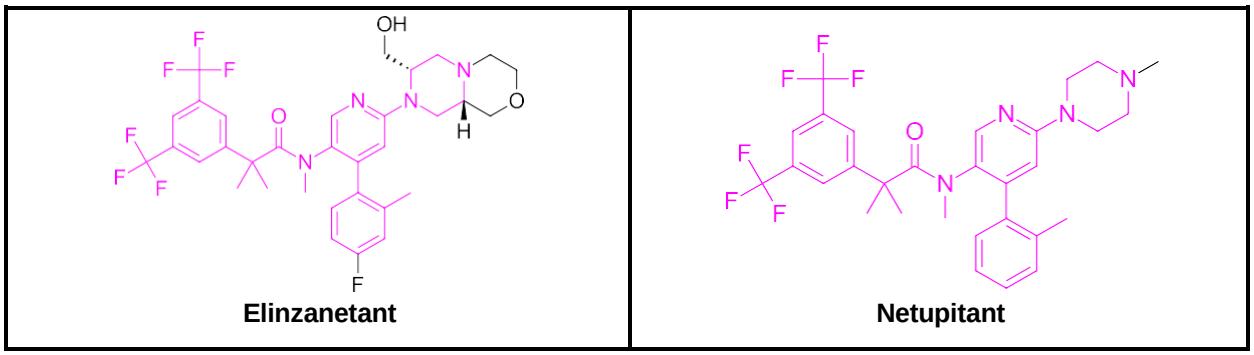
Fezolinetant

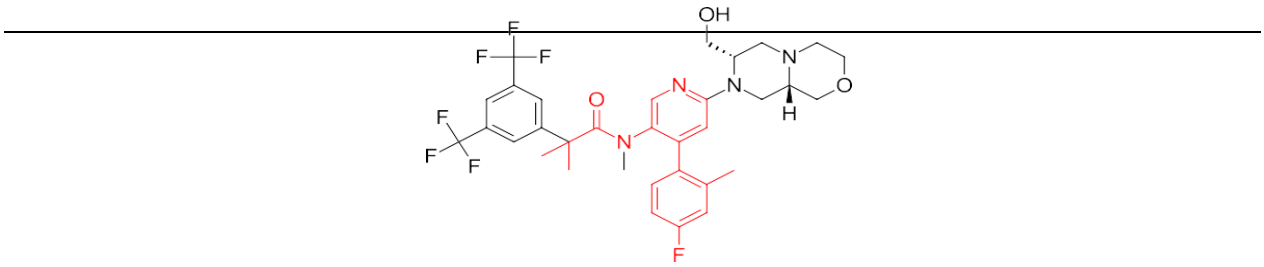
Overall, **elinzanetant** is predicted to be equivocal for the endpoints of liver damage and cholestasis, positive for bile duct disorders and gall bladder disorders, and negative for liver enzyme abnormalities. By contrast, **fezolinetant** is predicted or reported to be positive for the endpoints of liver damage, liver enzymes, and gall bladder and negative for cholestasis and bile duct disorders. Notably, the individual model predictions for **elinzanetant** for the liver damage and liver enzyme abnormalities endpoints are generally more negative than for **fezolinetant**, while for the endpoints of cholestasis and bile duct disorders the predictions are generally more positive. However, it is difficult to draw any conclusions about relative hepatotoxicity risk for **elinzanetant** compared to **fezolinetant** because their respective structures have limited similarity and, with the exception of the fluorobenzene alert, most significant structurally alerting features identified between the two drugs were different.

It is noted that **elinzanetant** and **fezolinetant** are predicted to be negative and positive, respectively, for liver enzyme abnormalities by the CU model despite identifying a similar structural alert corresponding to the bridging bonds between two aryl groups. During expert review of the predictions it was determined that the alerts are weighted differently for each molecule because of the dissimilar ring types between the two structures (pyridine-benzene in **elinzanetant**; thadiazole-triazole in **fezolinetant**). Therefore, the (Q)SAR predictions do not support the conclusion that clinical observations of elevated liver enzymes reported for **fezolinetant** should also be expected for **elinzanetant**.

While it is not possible to determine whether **elinzanetant** will present the same hepatic adverse event profile as **fezolinetant** based on chemical structure, a survey of other structurally similar analogs outside of the (Q)SAR model training sets identified a more structurally relevant drug, netupitant, that may serve as a comparator to **elinzanetant**. Netupitant is also an NK1 receptor antagonist and shares most of its substructural features with **elinzanetant**, including the *bis*(trifluoromethyl)benzene, dimethyl acetamide, pyridine, and piperazine groups (**Figure 1**). Netupitant does not have any drug-induced liver toxicity effects listed in the FDA drug label for the combination anti-emetic drug product, Akynzeo (FDA, 2018).

Figure 1: Structural Comparison of Elinzanetant and Netupitant.





Hepatobiliary Effect (Q)SAR Predictions for Elinzanetant [1]

Software	Liver Damage	Liver Enzyme Abnormalities	Cholestasis	Bile Duct Disorders	Gall Bladder Disorders
DX	NSA				
LMA	NC	NC	NC	NC	N/A
CU	Eqv	-	+	+	+
Overall Expert Prediction	**Eqv**	**-**	**Eqv**	**+**	**+**

[1] + = positive; - = negative; Eqv = equivocal; NC = test chemical features are not adequately represented in the model training data set, leading to a no call; NSA = no structural alerts are identified by *DX* (*DX* cannot differentiate between a negative call and the inability to make a call because of no coverage); N/A = no prediction available; structural alerts highlighted in red.

Elinzanetant is predicted to be equivocal for the endpoints of liver damage due primarily to the presence of the fluorobenzene substructural alert, with weaker contributing alerts from the bis-trifluoromethyl groups for the liver damage endpoint or the tertiary aryl amine for the cholestasis endpoint. For the cholestasis endpoint, the positive prediction from CU was downgraded due to dismissal of alerts corresponding to the primary alcohol on the piperazine ring, as this alert was found to be present in a different local chemical environment in most training set analogs. **Elinzanetant** is predicted to be positive for the endpoints of bile duct disorders and gall bladder disorders due to a combination of alerts corresponding to the fluorobenzene, dimethyl acetamide, and pyridine substructures. A lack of significant structural alerts led to a negative prediction for the liver enzyme abnormalities endpoint.

No expert rule-based alerts were identified for any endpoint by DX. In addition, while LMA did identify some alerts for several endpoints that were taken into consideration, no predictions could be made due to a lack of globally similar analogs in the model training set.

Hepatobiliary Effect (Q)SAR Predictions for Fezolinetant [2]

(b) (4)



References

FDA (2018). Drug label: AKYNZEO (netupitant and palonosetron), capsules for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210493s000lbl.pdf (accessed 12/18/2024).

FDA (2023). Drug label: VEOZAH (fezolinetant), tablets for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216578s000lbl.pdf (accessed 12/18/2024).

Neal-Perry, G. et al. (2023) Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause A Randomized Controlled Trial. *Obstetrics & Gynecology*, 141(4): 737-747. DOI: 10.1097/AOG.0000000000005114.

NIDDK (2024). Fezolinetant. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases, updated Oct 2024. https://www.ncbi.nlm.nih.gov/books/NBK608428/ (accessed 12/18/2024).

To: **Pratistha Tamrakar and Edna Albuquerque (CDER/OND/ORDPURM/DPTRDPURM)**
cc: **Andrea Benedict (CDER/OND/ORDPURM/DPTRDPURM)**
From: **Jahan Cooper and Naomi Kruhlak (CDER/OTS/OCP/DARS: Computational Toxicology Consultation Service)**
Re: **NDA 219469 – ICH M7 Bacterial Mutagenicity (Q)SAR Analysis of Elinzanetant Impurities**
Date: **February 28, 2025**

Summary

Seven impurities of the drug substance elinzanetant (API) from NDA 219469 were evaluated by the CDER/OTS/OCP/DARS Computational Toxicology Consultation Service for bacterial mutagenicity using (Q)SAR models. Three software programs were used: Derek Nexus 6.4.1 (DX), Leadscope Model Applier 2023.0.3-3 Bacterial Mut v2 model (LMA), and CASE Ultra 1.9.2.1 GT1_BMUT model 1.9.2.0 (CU). All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion. The (Q)SAR assessment of mutagenic potential for the compounds is consistent with recommendations described in the ICH M7(R2) guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). Overall, all seven impurities were predicted to be negative for bacterial mutagenicity.

No.	Chemical Name	Bacterial Mutagenicity Expert Prediction[1]
1	Compound (b) (4)	-
2	Compound	-
3	Compound	-
4	Compound	-
5	Compound	-
6	Compound	-
7	Compound	-

[1] - = negative.

Agency's (Q)SAR Predictions

No	Chemical Name	Structure	Bacterial Mutagenicity Predictions[2]				Comments
			DX	LMA	CU	Overall Expert	
1	**Compound** (b) (4)	(b) (4)	-	-	-	-	**Compound** (b) (4) is predicted to be negative for bacterial mutagenicity.
2	**Compound** (b) (4)		-	-	-	-	**Compound** (b) (4) is predicted to be negative for bacterial mutagenicity.
3	**Compound** (b) (4)		-	-	-	-	**Compound** (b) (4) is predicted to be negative for bacterial mutagenicity.

Reference ID: 5623053

4	**Compound** (b) (4)	(b) (4)	-	-	-	-	**Compound** (b) (4) is predicted to be negative for bacterial mutagenicity.
5	**Compound** (b) (4)		-	-	-	-	**Compound** (b) (4) is predicted to be negative for bacterial mutagenicity.
6	**Compound** (b) (4)		-	-	-	-	**Compound** (b) (4) is predicted to be negative for bacterial mutagenicity.
7	**Compound** (b) (4)		-	-	-	-	**Compound** (b) (4) is predicted to be negative for bacterial mutagenicity.

[2] - = negative.

Reference ID: 5623053

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/s/

PRATISTHA TAMRAKAR
07/11/2025 12:13:44 PM
Dr. Sarah Lee, Dr. Edna De Fatima Albuquerque and Dr. Pratistha Tamrakar jointly reviewed and authored this primary nonclinical review for NDA 219469

ANDREA BENEDICT
07/11/2025 12:39:54 PM
I concur with the review and recommendations as presented in this document

KIMBERLY P HATFIELD
07/11/2025 01:29:01 PM
I concur with the review and recommendations outlined in this review.

Office of Clinical Pharmacology
Division of Pharmacometrics (DPM)
Driving Study Review

NDA Number	219469
Brand Name	LYNKUET
Generic Name	Elinzanetant
Dosage Form and Strength	60 mg capsules
Route of Administration	Oral
Proposed Indication	Treatment of moderate to severe vasomotor symptoms associated with menopause
Applicant	Bayer HealthCare Pharmaceuticals Inc
OCP/DPM Review Team	Vishnu D Sharma, PhD; Atul Bhattaram, PhD
OCP/DPM Final Signatory	Hao Zhu, PhD

Reference ID: 5555516

Does elinzanetant have a potential to impact the next-day driving ability?

Findings on primary and secondary endpoints in the driving study suggest that next-day driving performance is impaired in some subjects taking single and repeat dose of elinzanetant 120 mg and 240 mg. The label should mention that there is a potential for next-day residual effects in some patients taking elinzanetant 120 mg.

Recommendations for the label are provided below:

HIGHLIGHTS
WARNINGS AND PRECAUTIONS----------
CNS Depressant Effects and Daytime Impairment: (b) (4) (b) (4) (5.1)

5 WARNINGS AND PRECAUTIONS
5.1 CNS Depressant Effects and Daytime Impairment
(b) (4) advise patients about the potential for (b) (4) somnolence. (b) (4) (b) (4)

(b) (4)

Ability to Operate Vehicles or Machinery
Driving performance was assessed at 9 hours after bedtime administration of LYNKUET 120 mg and 240 mg (two times the recommended dose) in a randomized, double-blind, placebo-and active-controlled, four-period crossover study in 64 healthy women (mean age 52.1 years) using a computer-based driving simulation. 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 established in a population with blood alcohol concentration of 0.05%. Although the mean SDLP did not reach the threshold for driving impairment after administration of LYNKUET 120 or 240 mg, driving ability was impaired in some subjects taking LYNKUET 120 or 240 mg.

(b) (4)

Background

The next-day driving ability following single dose and multiple doses (120 mg, 240 mg) of elinzanetant, administered at bedtime, was evaluated in healthy women by assessment of the mean standard deviation of the lateral position (SDLP) using driving simulator.

Study design

Figure 1 shows the design features of the driving study.

This study was conducted in a single center based on randomized, double-blind, placebo- and active controlled, 4-fold crossover design with oral administration of multiple doses (over 5 subsequent days) of elinzanetant 120 mg, elinzanetant 240 mg, placebo, or zopiclone 7.5 mg (on Days 1 and 5 only) per treatment period.

The 120 mg/day dose is the intended therapeutic dose. An additional dose of 240 mg/day was selected as supratherapeutic dose based on the following reasons. This dose leads to approximately twice the exposure of the therapeutic dose. The drug exposure of the 240 mg covers a potential maximum exposure increase of elinzanetant that could occur when elinzanetant is administered together with a weak CYP3A4 inhibitor as co-medication. The predicted steady state plasma concentrations have been investigated in healthy participants, where single elinzanetant doses of up to 600 mg were found to be safe and well tolerated.

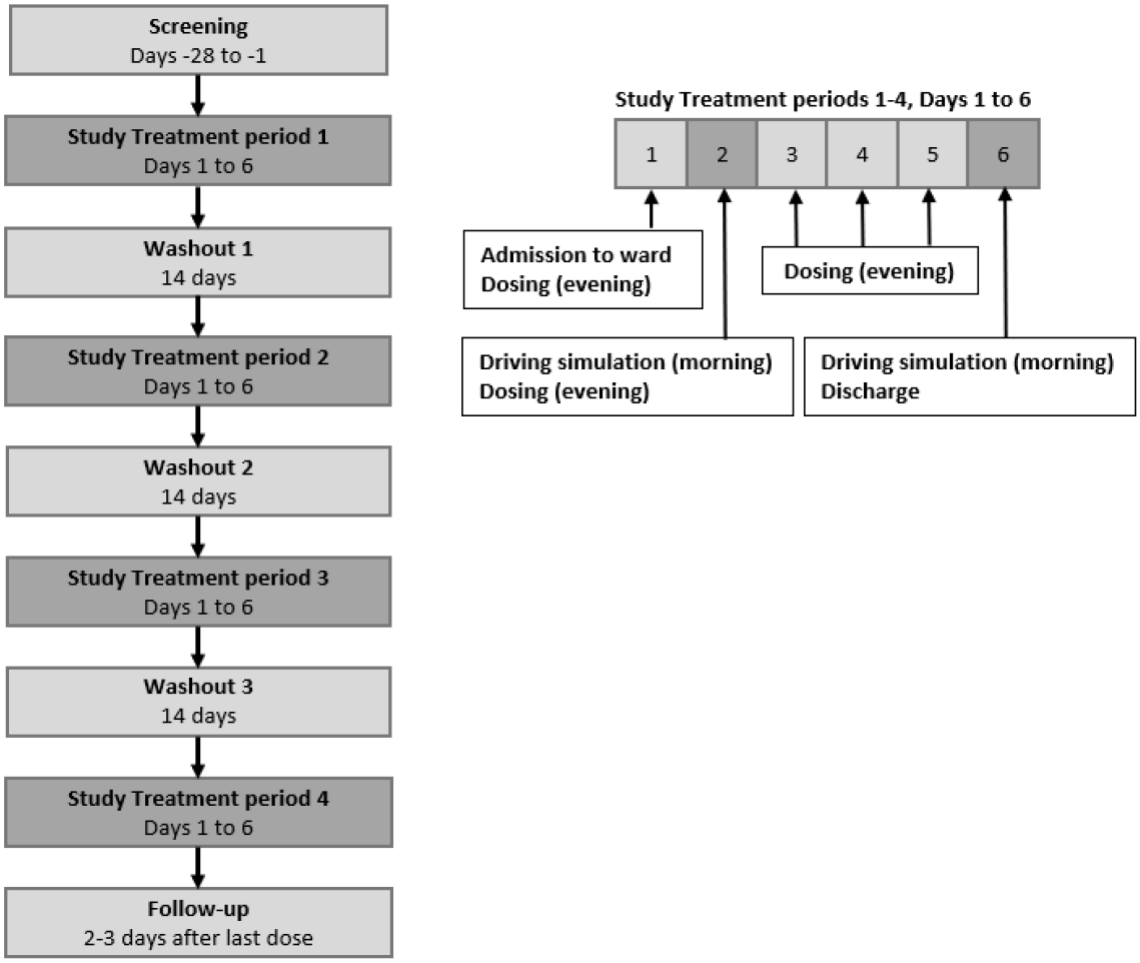
Study duration of 5 days was chosen since steady state concentrations would be achieved after 5 days of once daily dosing. Accumulation was expected to be modest (< 2-fold) after multiple dosing. After 14 days less than 20% receptor NK-1 occupancy was anticipated. This interval was deemed sufficient to exclude carry-over of pharmacodynamic effects of elinzanetant. NK-1 receptor antagonism is considered as the underlying mechanism of observed somnolence and fatigue during elinzanetant treatment. Hence, each treatment period was separated by a 7- to 14-day washout period.

Study interventions were administered in the evening via oral administration together with 240 mL of non-carbonated water at room temperature. Driving simulator assessments were performed the next morning, approximately 9-10 hours after dosing. This timing was chosen to reflect the recommended intake time of elinzanetant according to the intended label and to investigate potential residual driving impairment and cognitive effects which might pose a risk for patients. Blood samples for PK analysis were collected pre-dose on Days 1 and 6- and 8.5-hours post-dose on Days 2 and 6. The relationship between elinzanetant plasma concentrations and driving performance was evaluated.

Simulated driving performance was measured using SDLP in the CRCDS-MiniSim™ 9-10h after dosing. Additional measures of simulated driving performance in the CRCDS-MiniSim™ included Lane Exceedance, Excessive Speed Count, Average Speed and Speed Deviation, Excessive Ay, Total Collisions, and Divided Attention. Somnolence was measured using the KSS score.

Reference ID: 5555516

Figure 1: Overview of Study Design



Source: Figure 1 on page 17 in 22653-report-body.pdf

Study Endpoints

Primary Endpoint

- Standard Deviation of Lateral Position (SDLP) after a single dose and after multiple doses

Secondary Endpoints

- Lane Exceedance, including Number, Maximum Duration, and Area of Exceedance
- Excessive Speed Count
- Average Speed and Speed Deviation
- Excessive Ay (cornering speed threshold exceeded)
- Total Collisions

Reference ID: 5555516

- Divided Attention: Correct Responses; Omission Errors; Commission Errors; Reaction Time; Standard Deviation of Reaction Time
- CogScreen® Symbol Digit Coding Test
- KSS Score
- Participant's self-reported Readiness to Drive
- Self-report of motivation and appraisal of driving performance using VAS
- Number of participants with TEAEs and severity of TEAEs

Pharmacokinetic/Pharmacodynamic Endpoint

- Relationship between plasma concentration of elinzanetant and SDLP or other driving or cognition endpoints

Analysis methodology

SDLP data was analyzed using a mixed model with fixed effects for sequence, period, and treatment, with repeated periods for participants. Noninferiority testing was applied, with a noninferiority margin (NIM) of 4.4 cm. Various comparisons are listed below:

- Noninferiority of clinical dose (120 mg) vs placebo with respect to SDLP mean at day 2.
- Noninferiority of clinical dose (120 mg) vs placebo with respect to SDLP mean at day 6.
- Noninferiority of high dose (240 mg) vs placebo with respect to SDLP mean at day 2.
- Noninferiority of high dose (240 mg) vs placebo with respect to SDLP mean at day 6.

Each test was performed with a significance level of 2.5% one sided. No adjustment to alpha levels was made for either the comparison of zopiclone to placebo, or for secondary endpoints or analyses. All tests comparing zopiclone to placebo are only used to assess assay sensitivity.

Pharmacokinetic/Pharmacodynamic Analysis: Summaries of the correlation of elinzanetant plasma concentrations and SLDP difference from placebo (SDLP change) were determined. Also, the relationship between next-day residual concentrations of elinzanetant and SDLP difference from placebo after single and repeat dose was quantified using a linear regression model. The mean and 95% CI of the intercepts and slopes were calculated.

Results

Assay Sensitivity

Zopiclone separated from placebo demonstrating assay sensitivity on both Day 2 (**Table 1).** The upper limit of 95%CI exceeded 4.4cm threshold on Day 2.

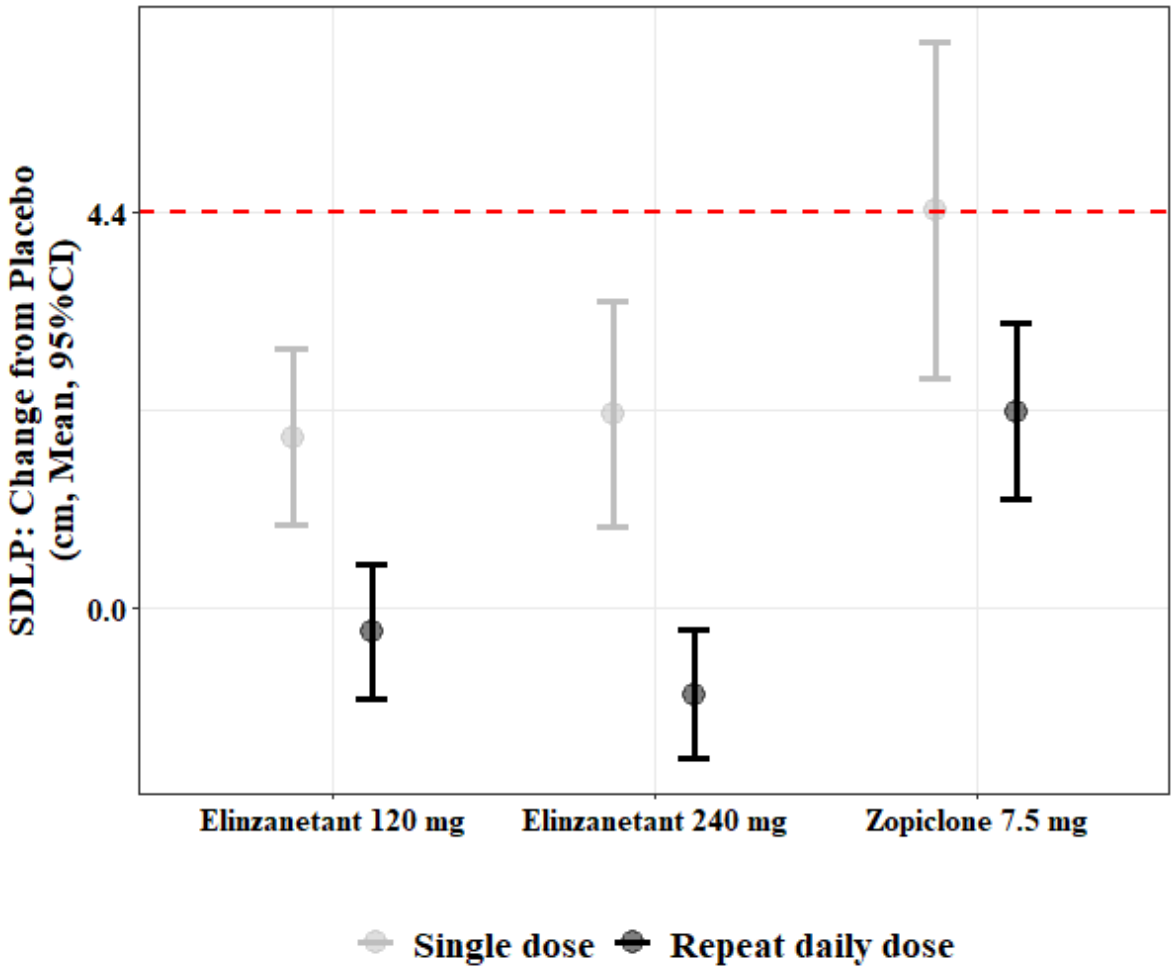
Analysis for primary endpoint

For elinzanetant 120 mg, the upper limits of the 95% CIs of the SDLP differences from placebo on Day 2 (3.028 cm) and on Day 6 (0.183 cm) did not exceed the pre-established noninferiority margin (NIM) of 4.4 cm (**Figure 2**).

For elinzanetant 240 mg, the upper limits of the 95% CIs of the SDLP differences from placebo on Day 2 (3.116 cm) and on Day 6 (-0.211 cm) did not exceed the pre-established NIM of 4.4 cm. The effect on driving impairment is lower on Day 6 compared to Day 2 likely due to the development of tolerance (**Figure 2, Table 1**).

Reference ID: 5555516

Figure 2: Mean Estimates of Placebo-Corrected Next-Day Morning SDLP [cm, 95% CI] After Single Dose and Repeated Doses. Shown as Red Line is the Noninferiority Margin of 4.4 cm.



Source: adsl.xpt, adft.xpt, Reviewer's analysis.

Reference ID: 5555516

Table 1: Summary of Standard Deviation of Lateral Position (cm) on Day 2 and 6 (Full Analysis Set)

Day 2

Statistics	Treatment			
	Elinzanetant 120 mg (N = 61)	Elinzanetant 240 mg (N = 64)	Zopiclone 7.5 mg (N = 62)	Placebo (N = 61)
N	61	63	62	61
Mean (SD)	31.706 (6.208)	32.185 (7.229)	34.238 (9.429)	29.783 (5.441)
Median	30.891	30.830	32.519	30.011
Min, Max	22.05, 50.25	21.42, 55.13	23.86, 78.87	19.34, 45.02
LSMeans [1]	32.079	32.166	34.443	30.260
p-value for period [1]				0.0003
p-value for sequence [1]				0.8123

	Elinzanetant 120 mg vs Placebo	Elinzanetant 240 mg vs Placebo	Zopiclone 7.5 mg vs Placebo
Difference in LSMeans, Treatment - Placebo [1]	1.819	1.906	4.183
95% CI [1]	(0.610, 3.028)	(0.696, 3.116)	(2.710, 5.657)
p-value [2]	0.0034	0.0022	<0.0001
Non-inferiority p-value [3]	<0.0001	<0.0001	0.3854

CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; N = number of participants; SD = standard deviation.
[1] Mixed effects model with fixed effects for sequence, period, and treatment, with repeated observations for participants for each of the driving time points, an unstructured covariance structure and Kenward-Roger degrees of freedom. Estimated differences were first treatment label listed minus second treatment label.
[2] P-value tested null hypothesis that difference in LS means = 0 versus alternative hypothesis that difference in LS means ≠ 0.
[3] Non-inferiority p-value tested null hypothesis that difference in LS Means ≥4.4 vs. alternative hypothesis that difference in LS Means <4.4

Day 6

Statistics	Treatment			
	Elinzanetant 120 mg (N = 61)	Elinzanetant 240 mg (N = 64)	Zopiclone 7.5 mg (N = 62)	Placebo (N = 61)
N	60	63	62	61
Mean (SD)	29.138 (4.821)	28.748 (4.649)	31.713 (5.420)	29.455 (4.440)
Median	29.453	28.954	31.010	29.750
Min, Max	18.09, 42.76	20.20, 43.58	22.50, 49.87	20.16, 39.70
LSMeans [1]	29.121	28.733	31.944	29.703
p-value for period [1]				<0.0001
p-value for sequence [1]				0.9931

	Elinzanetant 120 mg vs Placebo	Elinzanetant 240 mg vs Placebo	Zopiclone 7.5 mg vs Placebo
Difference in LSMeans, Treatment -Placebo [1]	-0.582	-0.970	2.241
95% CI [1]	(-1.346, 0.183)	(-1.730, -0.211)	(1.463, 3.019)
p-value [2]	0.1348	0.0126	<0.0001
Non-inferiority p-value [3]	<0.0001	<0.0001	<0.0001

CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; N = number of participants; SD = standard deviation.
[1] Mixed effects model with fixed effects for sequence, period, and treatment, with repeated observations for participants for each of the driving time points, an unstructured covariance structure and Kenward-Roger degrees of freedom. Estimated differences were first treatment label listed minus second treatment label.
[2] P-value tested null hypothesis that difference in LS means = 0 versus alternative hypothesis that difference in LS means ≠ 0.
[3] Non-inferiority p-value tested null hypothesis that difference in LS Means ≥4.4 vs. alternative hypothesis that difference in LS Means <4.4

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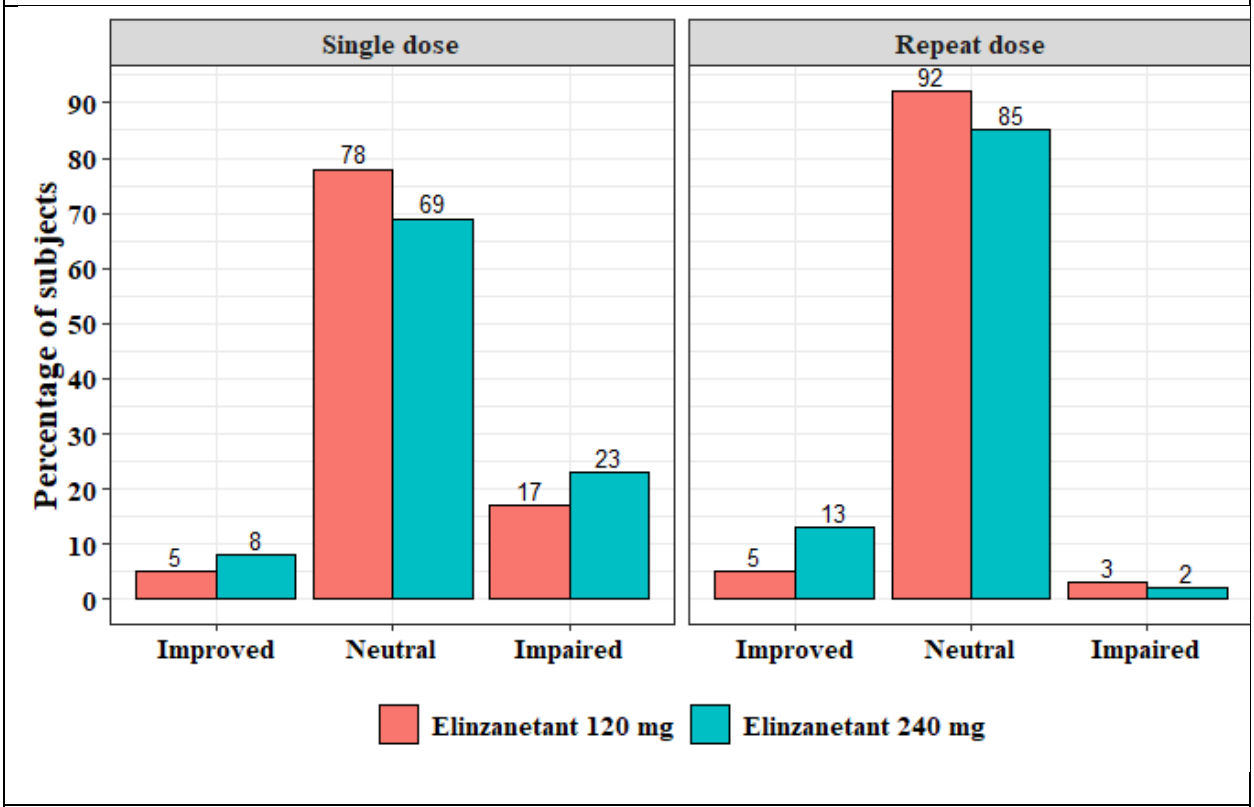
Source: Table 16, 17 on page 65, 66 in 22653-report-body.pdf

Reference ID: 5555516

Figure 3 showed the proportion of subjects with improved (SDLP < - 4.4 cm), neutral (SDLP ≥ -4.4 and SDLP < 4.4 cm), and impaired (SDLP ≥ 4.4 cm) SDLP changes after single dose and repeat dosing. Analysis of the distribution of within-subject differences in SDLP from placebo on Day 2 by treatment showed that 17% of participants treated with elinzanetant 120 mg exceeded the 4.4 cm threshold. Similarly, on Day 2, 23% of participants treated with elinzanetant 240 mg exceeded the 4.4 cm threshold.

Analysis of the distribution of within-subject differences in SDLP from placebo on Day 6 by treatment showed that 3% of participants treated with elinzanetant 120 mg exceeded the 4.4 cm threshold. For elinzanetant 240 mg, 2% of participants exceeded the 4.4 cm threshold on Day 6.

Figure 3. Proportion of Improved (SDLP < - 4.4 cm), Neutral (SDLP ≥ - 4.4 and SDLP < 4.4 cm), and Impaired (SDLP ≥ 4.4 cm) Subjects After Single and Repeat Doses of 120 or 240 mg.



Source: Reviewer's analysis

Analysis for Secondary Endpoints

The initial dose of both elinzanetant 120 mg and elinzanetant 240 mg also showed a statistically significant effect on number of lane exceedances; for elinzanetant 240 mg, it also appeared to affect excessive cornering speed compared to placebo. After the initial dose of both elinzanetant

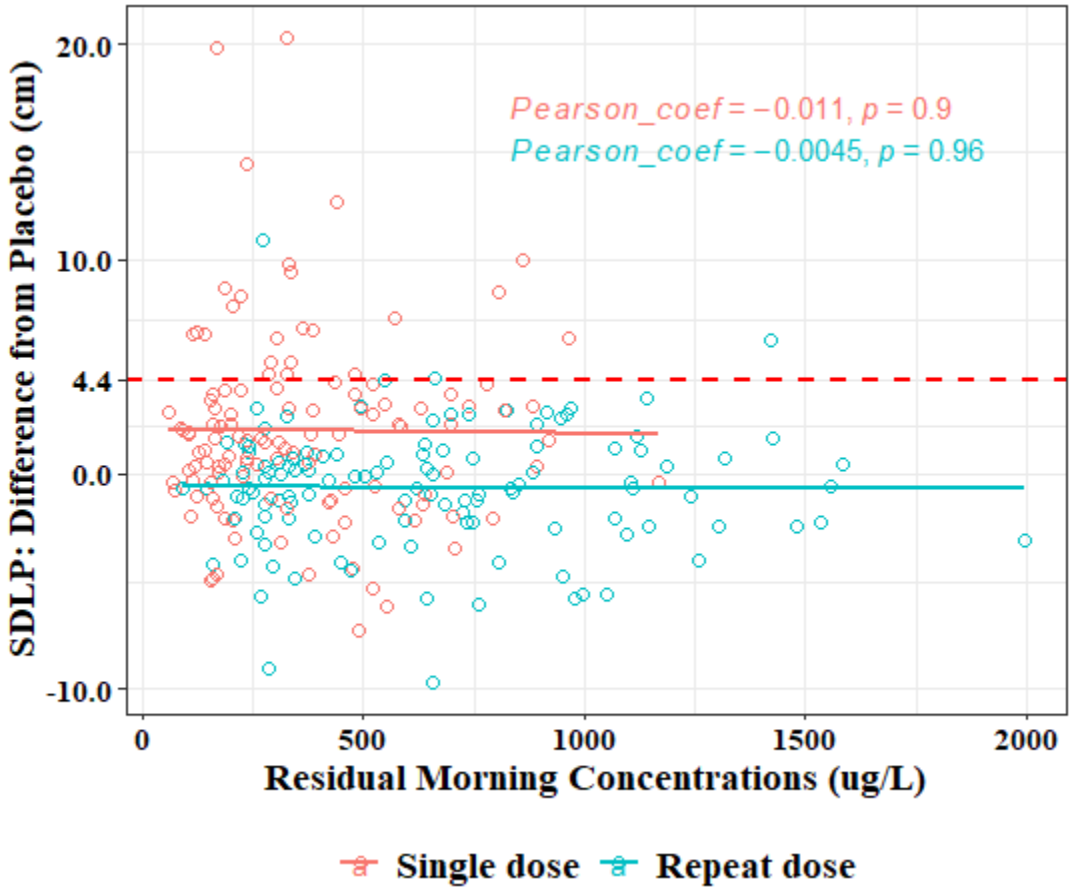
Reference ID: 5555516

120 mg and elinzanetant 240 mg, participants reported statistically significantly higher subjective sleepiness, decreased motivation to drive, and lower self-appraisal of their driving performance compared to placebo. Two participants (3.3%) receiving elinzanetant 120 mg and 4 participants (6.6%) receiving elinzanetant 240 mg reported not feeling ready to drive.

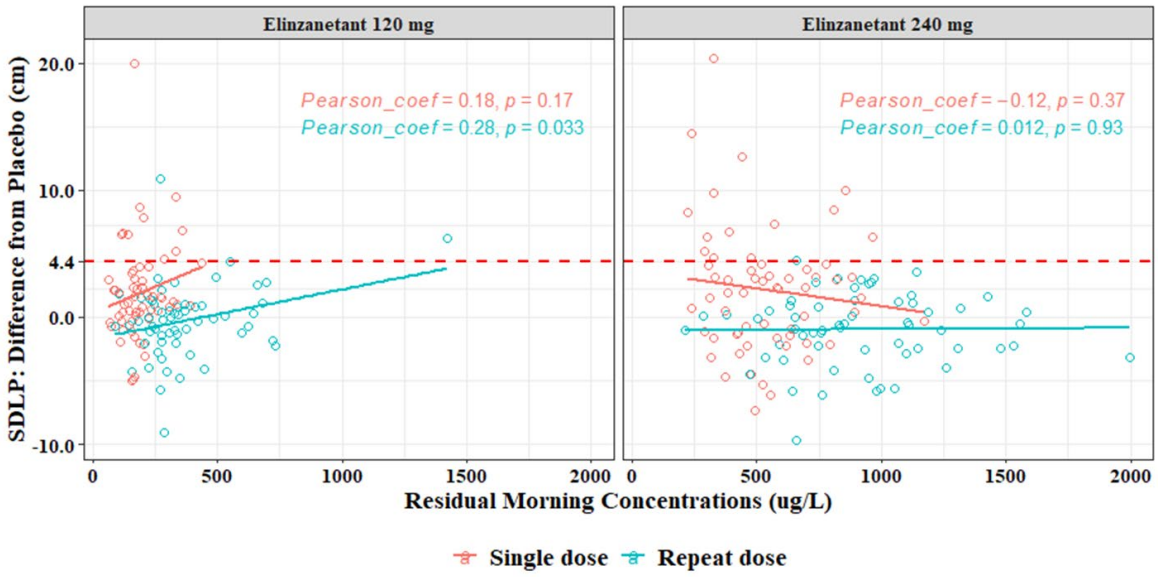
Pharmacokinetic/Pharmacodynamic Analysis

Figure 4 shows the findings of linear regression analysis of the relationship between next-day residual concentrations of elinzanetant and SDLP change from placebo. The 95% CI of the slope includes zero indicating lack of statistically significant relationship between elinzanetant exposure and SDLP change (**Table 2**).

Figure 4. Relationship Between Next-Day Residual Concentrations of Elinzanetant and SDLP Change



Reference ID: 5555516



Source: FDA OCP Reviewer's analysis

Table 2. Intercept and Slope Estimates Based on Linear Regression of Next-Day Residual Concentration and Change in SDLP (Placebo-Corrected)

	Intercept (cm)		Slope (cm per ug/mL)	
	Mean	**95% CI**	**Mean**	**95% CI**
Single dose	2.1024	0.6093, 3.5955	-0.0002	-0.0037, 0.0032
Repeat dose	-0.5995	-1.6168, 0.4179	-0.00003	-0.0014, 0.0013

Conclusion

Findings on primary and secondary endpoints in the driving study suggest that next-day driving performance is impaired in some subjects taking single and repeat dose of elinzanetant 120 mg and 240 mg. The label should mention that there is a potential for next-day residual effects in some patients taking elinzanetant 120 mg.

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	219469
Supporting document/s:	SDN 0001
Applicant's letter date:	July 26, 2024
CDER stamp date:	July 26, 2024
Product:	Elinzanetant
Indication:	Moderate to severe vasomotor symptoms associated with menopause
Applicant:	Bayer Healthcare Pharmaceuticals Inc
Clinical Review Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Pharm/Tox Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM)
Reviewers:	Edna De Fatima Albuquerque, PhD Pratistha Tamrakar, PhD Sarah Lee, PhD
Supervisor/Team Leader:	Andrea Benedict, PhD
Division Director:	Christina Chang, MD
Project Manager:	Samantha Bell

Template Version: September 1, 2010

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APPENDIX 56

Reference ID: 5523839

Executive Carcinogenicity Assessment Committee Cover Sheet for Final Carcinogenicity Study Reports

P/T Reviewer(s):	Edna Albuquerque, PhD (Rat Study Review) Pratistha Tamrakar, PhD (Mouse Study Review) Sarah Lee, PhD
Supervisor/TL:	Andrea Benedict, PhD
Pharm/Tox Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (DPT-RPURM)
Clinical Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Sponsor/Applicant:	Bayer Healthcare Pharmaceuticals Inc.
Drug Name(s):	Elinzanetant; BAY 3427080; NT-814; 7486; GSK 1144814A
CAS#:	929046-33-3 (Elinzanetant free base)
Indication(s):	Moderate to severe vasomotor symptoms associated with menopause.

Pharmacological/Chemical Classification: Neurokinin (NK) 1 and NK3 receptor antagonist

- Elinzanetant, an NK1/NK3 receptor antagonist, is being proposed for the treatment of moderate to severe vasomotor symptoms associated with menopause under IND 129492 / (b) (4) (b) (4)

Mutagenic/Genotoxic (y/n/equivocal/na; assay): No.
Elinzanetant tosylate at concentrations up to 1,500 µg/plate (in terms of free base) did not generate positive mutagenicity signals in AMES assays in the presence or absence of metabolic activation with an S9 mix. It also generated no genotoxic/clastogenic signal in: (i) the mouse lymphoma L5178Y $TK^{+/-}$ assay in the presence or absence of S9 mix, and (ii) the micronucleus assay of bone marrow erythroblasts from rats treated with oral doses up to 2,000 mg/kg/day for 2 days.

Rat Carcinogenicity Study: Study No. T105128-7

Study Duration (weeks):	104 weeks
Study site:	(b) (4)
Carcinogenicity Study Report Date:	April 19, 2024
Date of first dose:	May 03, 2022
Rat Strain:	Sprague-Dawley
Age:	8 weeks (113 to 184 g)
Route:	Oral gavage (twice daily [BID], inter-dose interval: 6 h ± 30 min)

Vehicle: 1.0% (w/v) carboxymethylcellulose (400 cps at 2%) in water treated by reverse osmosis

Dosing Comments: *[e.g., dose adjustments, early termination]*

- Rats were not fasted for dosing, unless fasted for other study procedures.
- Due to ocular observations (opaque eyes), Animal R0051 (Group 1, carcinogenicity), Animals R0620 and R0660 (Group 4, carcinogenicity), and Animal R0907 (Group 5, toxicokinetic) were replaced on treatment day 17 with a rat of similar body weight from the group of possible replacement animals.

Doses and numbers of animals

Table 1 summarizes the experimental groups in the study.

Table 1. Summary of General Characteristics of the Experimental Groups in the Rat Carcinogenicity Study [Adapted from the Applicant's Study Report].

Group	Subgroup	Dose Levels	Dose (mg/kg), BID	Numbers of Rats
1	1.1 [Carcinogenicity]	Control	0	100
	1.2 [Toxicokinetics]			3
2	2.1 [Carcinogenicity]	Low	3.5	100
	2.2 [Toxicokinetics]			9
3	3.1 [Carcinogenicity]	Intermediate Low	10	100
	3.2 [Toxicokinetics]			9
4	4.1 [Carcinogenicity]	Intermediate High	30	100
	4.2 [Toxicokinetics]			9
5	5.1 [Carcinogenicity]	High	40	100
	5.2 [Toxicokinetics]			9

Dosing volume = 5 mL/kg/dose (10 mL/kg/day). Concentrations of the test solutions used to dose rats: 0.7 mg/mL (group 2), 2 mg/mL (group 3), 6 mg/mL (group 4), and 8 mg/mL (group 5).

Basis for Doses Selected

Per the recommendations of the Executive Carcinogenicity Assessment Committee (Exec CAC), a high dose of 60 mg/kg/day (30 mg/kg BID) was selected to provide an AUC > 25-fold higher than the AUC generated by the maximal recommended human dose (MRHD). The mid- and low-dose were selected based on adequate spacing of AUCs.

Because elinzanetant is being developed for the clinical indication of moderate to severe vasomotor symptoms in postmenopausal women, the Exec CAC also suggested that the carcinogenicity study could be conducted only in female rats.

Prior FDA Exec CAC Dose Concurrence? Yes; October 19, 2020.

In the minutes issued by the Exec CAC following the SPA under IND 129492, the committee noted that, if the clinical dose changed such that the exposure ratio would no longer be at least 25-fold at the high dose, the carcinogenicity study would likely be inadequate to inform risk assessment. As summarized in Table 1, the Applicant used

the Exec CAC-recommended doses of elinzanetant and added a higher dose of 40 mg/kg, BID (for a total daily dose of 80 mg/kg), which provides 33-fold the proposed clinical exposure based on AUC.

Rat Carcinogenicity Conclusion: Positive

Rat Tumor Findings (details):

The FDA statistical reviewer Feng Zhou, MS, Division of Biometrics VI, reviewed the Applicant-submitted tumor data. The reviewer labeled experimental groups 1, 2, 3, 4, and 5 as VC (Vehicle Control; aqueous solution of 1% methylcellulose (viscosity 400 cP), LD (Low Dose), LM (Low-Mid Dose), MD (Mid Dose), and HD (High Dose), respectively. The analysis included all the data from all groups to identify statistically significant dose-response relationships and pairwise comparisons between each test article-treated group and the control group. Dose-response relationships were considered statistically significant at $p < 0.005$ and $p < 0.025$ for a common tumor and a rare tumor, respectively. Pairwise comparisons were considered statistically significant at $p < 0.01$ and $p < 0.05$ for a common tumor and a rare tumor, respectively.

As summarized in Table 2, the FDA statistical reviewer identified the following statistically significant dose-response relationships and pairwise comparisons:

- **Malignant lymphoma in the hematolymphoid system [Common tumor]**
  - Dose-response relationship p trend = 0.0002
  - ↑ Tumor incidence in the HD compared to the VC group (p = 0.0087)
- **Malignant endometrial adenocarcinoma [Common tumor] in uterus**
  - Dose-response relationship p trend < 0.00001
  - ↑ Tumor incidence in the MD and HD compared to VC (p = 0.0006 and 0.00001, respectively)
- **Combined malignant and benign endometrial tumors [Common tumors] in uterus**
  - Dose-response relationship p trend < 0.00001
  - ↑ Tumor incidence in the MD and HD compared to VC (p = 0.0006 and 0.00001, respectively)
- **Combined malignant and benign endometrial tumors [Common tumors] and malignant squamous cell carcinoma [Rare tumor] in uterus**
  - Dose-response relationship p trend < 0.00001
  - ↑ Tumor incidence in the MD and HD compared to VC (p = 0.0003 and 0.00001, respectively)

The FDA statistician identified a statistically significant dose-response relationship for malignant squamous cell carcinoma, a rare tumor, in the uterus (p trend < 0.0206). However, in the pairwise comparisons, the incidence of this carcinoma did not differ significantly between test article-treated and VC groups (Table 2).

Neither the FDA statistical reviewer nor the Applicant identified other statistically significant neoplasms in female rats.

Table 2. Tumor Types with Statistically Significant Dose-Response Relationships and Pairwise Comparisons in Elinzanetant-Treated Rats [from FDA Statistical Reviewer Report in Appendix 1].

Organ name	Tumor name	0 mg/kg/day Control (VC) p - Trend	7 mg/kg/day Low dose (LD) p - C vs. LD	20 mg/kg/day Low-mid dose (LM) p - C vs. LM	60 mg/kg/day Mid dose (MD) p - C vs. MD	80 mg/kg/day High dose (HD) p - C vs. HD
Hematolymphoid System	M-Lymphoma	1/100 (72) 0.0020 *	3/100 (67) 0.2831	3/100 (71) 0.3046	6/100 (71) 0.0557	9/100 (72) 0.0087 **
Uterus	M-Adenocarcinoma, Endometrium	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	22/100 (75) 0.00001 **
	M-Carcinoma, Squamous Cell	0/100 (72) 0.0206 *	0/100 (66) NC	1/100 (71) 0.4965	1/100 (69) 0.4894	3/100 (70) 0.1172
	C_Endometrium (B+M)	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	23/100 (75) 0.00001 **
	C_Endometrium (B+M)/ Carcinoma, Squamous Cell	2/100 (72) 0.00001 *	3/100 (67) 0.4658	6/100 (71) 0.1330	16/100 (72) 0.0003 **	25/100 (75) 0.00001 **

Note: X/ZZ (YY): X=number of tumor-bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. **The p-values marked with an asterisk * indicate statistically significant dose-response relationships at p < 0.005 and p < 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparisons at p < 0.01 and p < 0.05 for a common tumor and a rare tumor, respectively.**

Systemic Exposures

The low mid-dose of elinzanetant (20 mg/kg/day) was the highest dose not associated with carcinogenic signals in female rats, and the mid-dose of elinzanetant (60 mg/kg/day) was the lowest dose associated with carcinogenic signals in female rats. The area-under-the curve 0→24 h ($AUC_{0\text{-}24h}$) generated by each dose on treatment day 358 was 64000 µg•h/L and 252000 µg•h/L, respectively.

Based on statistical modeling of pharmacokinetic data from female VMS patients, the geometric value of the steady-state $AUC_{0\text{-}24h}$ generated by the MRHD of elinzanetant (120 mg) is 8572 µg•h/L (Clinical Report B002427, Table 21.3.1, Pg 521). Therefore, as shown in Table 3, based on AUCs, the exposure margins provided by the highest noncarcinogenic dose and the lowest carcinogenic dose in rats to the MRHD are approximately 7.5x and 29.4x, respectively.

According to the clinical study CPMX 50130 in which human subjects were given an oral dose of radiolabeled elinzanetant, BAY3462933 (M30/34) was identified as the predominant metabolite of the parent drug in humans. M30/34 accounted for approximately 11% of the total radioactivity recovered from the plasma of elinzanetant-treated subjects. Two other metabolites, BAY3462932 (M27) and BAY3462934 (M18/21), accounted for approximately 6% and 5.5% of the total radioactivity recovered from the plasma of the study subjects.

In the rat carcinogenicity study, the Sponsor assessed systemic exposures of the elinzanetant-treated rats to BAY3462932 (M27), BAY3462933 (M30/34), and BAY3462934 (M18/21). Table 3 summarizes the exposure margins (estimated based on AUCs) for each metabolite at the highest noncarcinogenic dose and the lowest carcinogenic dose in rats to the MRHD. While the carcinogenicity study generated adequate clinical exposure margins for the parent drug and its predominant metabolite in humans (M30/34), it provided very low exposure margins to the other two main metabolites (M27 and M18/21).

Table 3. Toxicokinetic Parameters for Elinzanetant and Its Metabolites in Female Rats and Clinical Exposure Margins Estimated on the Basis of AUCs [Reviewer-Generated Table].

		Rat dose: 20 mg/kg/day		Rat dose: 60 mg/kg/day	
	$AUC_{0\text{-}24h}$ (µg•h/L) at MRHD[a]	$AUC_{0\text{-}24h}$ (µg•h/L)	Exposure Margins	$AUC_{0\text{-}24h}$ (µg•h/L)	Exposure Margins
Elinzanetant	8572.0	64000	7.5x	252000	29.4x
M27	2496.3	550	0.2x	2020	0.8x
M30/34	4570.1	17000	3.7x	32100	7.0x
M18/21	2326.3	119	0.05x	237	0.1x

[a]$AUC_{0\text{-}24h}$ values are from the clinical study number CPM50130 (report number B002427).

Rat Study Comments:

Survival

The survival analyses conducted by the FDA statistical reviewer and by the Applicant revealed no statistically significant dose-response relationship for mortality. The survival rates in the VC, LD, LM, MD, or HD groups at the time all rats were terminated on Week 104 were 44%, 39%, 38%, 42%, and 37%, respectively.

Elinzanetant-Related In-Life Findings

Treatment of female rats with elinzanetant resulted in a dose-dependent reduction of body weight gain. At week 104, female rats in the LD, LM, MD, and HD groups weighed ~9%, 9%, 17%, and 19% less than rats in the VC group.

In a functional observation battery, central nervous system (CNS)-related safety signals of clinical relevance were also observed at doses ≥60 mg/kg/day, unless otherwise noted in the list below. These CNS-related safety signals, including convulsions, were also observed in the pivotal 13-week oral repeat-dose toxicity study in rats (Study No. RH17GJ).

- Increased incidence and severity of whole-body convulsions. Convulsion was related to “undetermined” death in several animals at the MD and HD groups.
- Increased incidence of hunched posture.
- Decreased general activity.
- Increased sensitivity to touch.
- Increased salivation.

- Irregular respiration (at ≥7 mg/kg/day).

Elinzanetant-Related Non-Neoplastic Histopathological Findings

The following non-neoplastic histopathological findings were observed at doses ≥60 mg/kg/day, unless otherwise noted:

- Uterus: Squamous cell metaplasia.
- Ovaries: Absence of corpora lutea and increased incidence of sex cord stromal hyperplasia and granulosa cell hyperplasia.
- Vagina: Decreased mucification.
- Mesenteric lymph node: Increased macrophage infiltrates (at ≥7 mg/kg/day).
- Liver: Biliary hyperplasia, biliary cysts, and multinucleated hepatocytes that correlated with increased liver weight.
- Adrenal glands: Hyperplasia or hypertrophy of the zona fasciculata, cystic degeneration, and hypertrophy of the zona glomerulosa in the adrenal cortex that correlated with increased adrenal weight.
- Parotid salivary gland, lacrimal glands, and pancreas: Atrophy.

Elinzanetant-Associated Reduction of Incidence of Common Spontaneous Tumors in the Mammary, Thyroid, and Pituitary Glands

Compared to female rats treated with vehicle, female rats treated with elinzanetant doses ≥60 mg/kg/day presented with reduced occurrence of: (i) hyperplasia in the mammary gland, (ii) benign thyroid C-cell adenomas, and (iii) adenomas in the pars distalis of the thyroid gland. Although the Applicant reported that these findings did not reach statistical significance, they could be related to the ability of the metabolite M30/34 to inhibit ERα and/or the ability of elinzanetant to decrease the activity of the hypothalamic-pituitary-gonad axis via inhibition of NK1/NK3 receptors in hypothalamic KNDy neurons leading to decreased estradiol-promoted cellular proliferation in estrogen-sensitive organs such as mammary, thyroid, and pituitary glands.

Mouse Carcinogenicity Study: Study No. B003184

Study Duration (weeks): 26 weeks
Study site: (b) (4)
Carcinogenicity Study Report Date: May 25, 2021
Date of first dose: January 24, 2019 (males)
January 25, 2019 (females)
Mouse Strain: Tg.rasH2
Route: Oral gavage
Vehicle: 1% w/v methylcellulose (MC) solution
Dosing Comments: None.

Doses and numbers of animals:

Group		Dose Levels (mg/kg/day) ^		No. of Animals	
		Males	Females	Main Study /sex/group	TK /sex/group
1	Vehicle*	0	0	25	3
2	Low	10	10	25	18
3	Mid	30	20	25	18
4	High	85	70	25	18
5	Positive Control**	75	75	10	10

* 1% aqueous methylcellulose
**N-methyl-N-nitrosourea (MNU); single intraperitoneal dose on Day 1 of the dosing phase
^ doses were administered BID (twice daily) @ 5,15, 42.5 mg/kg/dose for males and 5, 10, 30 mg/kg/dose for females. The second dose was administered 6 hours (± 15 minutes) after the first daily dose in Groups 1 through 4.

Basis for Doses Selected: MTD

Prior FDA ExecCAC Dose Concurrence? Yes, under IND 129462, December 6, 2022. The study was conducted at the recommended doses.

Mouse Carcinogenicity Conclusion: Negative

Mouse Tumor Findings (details):
The tumor data were analyzed by the FDA statistical reviewer,. Feng Zhou, MS, Division of Biometrics VI, for dose response relationships across the vehicle control group, and low, mid, and high dose groups, and pairwise comparisons of each of the three treated groups against the vehicle control group. Two separate analyses were conducted, one in male mice and one in female mice.

No tumor types with a statistically significant dose response relationship in tumor incidences were observed in male or female mice with increased elinzanetant dose when the positive control group was excluded. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in elinzanetant treated groups, when compared to the vehicle control group in either male or female mice when the positive control group was excluded.

Margins of exposure compared to human exposure [Total] and human exposure [unbound] at 120 mg/day:

Elinzanetant:

- The high-dose level of 85 mg/kg/day elinzanetant, in the male mouse has a corresponding $AUC_{0\text{-}24h}$ of 23900 ng•h/mL (Week 26), representing a Multiple of Exposure (MoE) margin of 2.8X MRHD of 120 mg/day based on $AUC_{0\text{-}24h}$ of 8572 ng•h/mL [from clinical study B002427].
- The high-dose level of 70 mg/kg/day elinzanetant in the female mouse has a corresponding $AUC_{0\text{-}24h}$ of 17500 ng•h/mL (Week 26), representing an MoE margin of 2.0X MRHD of 120 mg/day based on $AUC_{0\text{-}24h}$ of 8572 ng•h/mL [from clinical study B002427].

Metabolites:
Similarly for the metabolites of interest M27, M30/34 and M18/21, the exposure margins at NOAEL (high dose) were calculated. These metabolites exhibit high affinity and activity at the human NK1 and NK3 receptors that are similar to the affinity and activity of elinzanetant in in vitro binding and cellular functional assays. The fraction unbound values for human and mouse were derived from in-vitro plasma protein binding studies PH-42081 and PH-42138 and used to calculate unbound exposure for Elinzanetant and the metabolites, as well as the MoE. These are summarized in the table below:

Table 4. Systemic Exposure in Mice and Margins of Exposure for the MRHD (120 mg/day).

NOAEL/High dose [mg/kg]*	Sex	Total exposure $AUC_{0\text{-}24h}$ [µg•h/L]	MoE [total]#	Unbound exposure $AUC_{0\text{-}24h}$ [µg•h/L]##	MoE [unbound] ###
Elinzanetant					
85	M	23900	2.8 x	550	21 x
70	F	17500	2.0 x	464	18 x
M27					
85	M	936	0.4 x	11.51	6.6 x
70	F	647	0.3 x	12.94	7.5 x
M30/34					
85	M	7220	1.6 x	48.37	2.1 x
70	F	7000	1.5 x	81.9	3.5 x
M18/21					
85	M	266	0.1 x	7.71	3.3 x
70	F	270	0.1 x	7.56	3.3 x

F= female; M=male; NOAEL= No Observed Adverse Effect Level; $AUC_{0\text{-}24h}$: area under the curve over the last 24-h dosing interval; MoE= margins of exposure (when compared to the human plasma levels at 120 mg/day).

* bid=The daily dose was administered to the animals in 2 doses.

\# Based on $AUC_{0\text{-}24h}$ of 8572 ng•h/mL (Elinzanetant), 2496 ng•h/mL (M27), 4570 ng•h/mL (M30/34), 2326 ng•h/mL (M18/21), obtained from clinical study B002427.

\## fu (fraction unbound) mouse = 2.30/2.65% (M/F) for Elinzanetant, 1.23/2.0% for M27(M/F), 0.67/1.17% for M30/34(M/F), 2.9/2.8% (M/F) for M18/21 (based on in-vitro plasma protein binding studies PH-42081 and PH-42138).

\### Based on $AUC_{0\text{-}24h}$ of 25.9 ng•h/mL (Elinzanetant), 1.74 ng•h/mL (M27), 22.85 ng•h/mL (M30/34), 2.32 ng•h/mL (M18/21) calculated using fu (fraction unbound) human = approximately 0.3% for Elinzanetant, 0.07% for M27, 0.5% for M30/34, 0.1% for M18/21 (based on in-vitro plasma protein binding studies PH-42081 and PH-42138).

Reference ID: 5523839

<u>Reviewer comment</u>: MOE is higher when considering the unbound fraction based on in-vitro plasma binding.

Mouse Study Comments:
Elinzanetant did not affect the overall survival rate or adverse clinical signs up to the high dose of 85 mg/kg/day in males and 70 mg/kg/day in females. The survival rates were 88%, 92%, 96% and 92% for males, and 88%, 100%, 100% and 92% for females, in the dose groups 0 (vehicle), 10, 30 and 85 mg/kg/day for males and dose groups 0 (vehicle), 10, 20 and 70 mg/kg/day for females, respectively. No elinzanetant-related changes in body weight, body weight gain, or food consumption were observed over the course of the 26-week study.

No non-neoplastic findings related to elinzanetant were identified.

<u>Questions to the Exec CAC:</u>

1. In a clinical PK study, the Applicant identified M30/34 as the predominant metabolite in humans (accounting for ~11% of the total radioactivity recovered from the plasma of [3H]elinzanetant-treated human subjects). The Applicant identified two other metabolites, M27 and M18/21, each of which accounted for ~6% and 5.5%, respectively, of the total radioactivity recovered from the plasma of the same study subjects. While the rat study provides reasonable multiples of exposure for the primary metabolite M30/34, it provides very low multiples of exposure for M27 and M18/21. Given that neither metabolite exceeds 10% of the metabolite profile in humans, would we consider the rat carcinogenicity study adequate to inform the carcinogenic potential of elinzanetant?

2. In the mouse study, the Applicant took into account the percent (%) of protein unbound fraction to estimate multiples of exposure. The % unbound fraction was derived from an in-vitro study, as summarized in Table 4. Would this approach be acceptable?

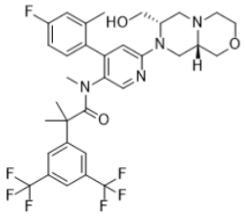
Post eCAC meeting notes:

1. The Exec CAC agreed metabolite coverage in rat carcinogenicity study is adequate.
2. The Exec CAC noted that MOEs based on AUC is not used for Tg.RAS mouse carcinogenicity studies, hence expression of the MOE based on either bound or unbound fraction is not relevant.

Reference ID: 5523839

Nonclinical Summary

Drug Information+

Type of Product:	Drug (Soft oral capsule)
Code/ Generic Name:	BAY 3427080, NT-814, GSK1144814A, elinzanetant
Chemical Name (optional):	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]-3-pyridinyl}-N,2-dimethylpropanamide
CAS#:	929046-33-3
Structure or Biochemical Description:	
Molecular Formula/ Molecular Weight:	$C_{33}H_{35}F_7N_4O_3$ / 668.66 g/mol
Proposed 505(b)(2): If Yes, Listed Drug:	No

Clinical Information

First in human:	N
Proposed Doses/ Duration/ Route of Administration:	• Three phase 3, double-blind, randomized, placebo-controlled, multicenter studies have been completed to investigate the effectiveness and safety of elinzanetant for the treatment of postmenopausal women with vasomotor symptoms. ○ Tested dose: 120 mg/d ○ Treatment durations: ▪ Clinical Study 21651: 26 weeks ▪ Clinical Study 21652: 26 weeks ▪ Clinical Study 21810: 52 weeks
Patient Population:	Postmenopausal women
Sponsor's Maximum Recommended Human Dose/ Target AUC or C_{max}:	120 mg/day $AUC_{0\text{-}24h}$: 8572 µg•h/L C_{max}: 1423 µg/L (Clinical Report B002427, Table 21.3.1, Pg 521)

Pharmacology/ Toxicology Summary

Pharmacology (primary & MoA)

Key Findings:
Elinzanetant is a dual NK-1 and NK-3 receptor (NK-1R and NK-3R) antagonist and displays high affinity for human NK-1 receptors [pKi values of 8.71 – 10.15 (mean pKi of 9.43)] and NK-3 receptors [pKi values of 8.03 – 8.8 (mean pKi of 8.42)], leading to an ~10-fold lower affinity of elinzanetant towards human NK3 receptors compared to human NK1 receptors. Strong antagonism at human NK-1R and NK-3R, with calculated pKB values of 9.02 - 9.1 (human NK-1 receptor) and 8.17 - 8.5 (human NK-3 receptor) was demonstrated for elinzanetant in functional in-vitro assays.

- Based on radioligand binding displacement assays, elinzanetant has relatively higher selectivity to NK-1R and NK-3R subtypes than the NK-2R subtype of different species, including humans, baboons, gerbils, guinea pigs, and rats.
    - Rat NK receptors are generally less sensitive to elinzanetant than the human receptors.
- Based on in-vitro functional assays, elinzanetant acts as an insurmountable antagonist at NK1 and NK3 receptors.

Mechanism of Action: NK receptors are Gq protein coupled receptors expressed by KNDy neurons in the infundibular nucleus of the thalamus in humans. KNDy neurons synapse onto neurons in the vasomotor center in the hypothalamic median preoptic nucleus and onto GnRH-expressing neurons in the infundibular nucleus and the preoptic nucleus. NK receptor activation in KNDy neurons stimulates vasomotor responses. It also stimulates the release of GnRH that stimulates the anterior pituitary gland to secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH) that, in turn, can increase secretion of sex hormones from the gonads.

In the context of vasomotor symptoms in postmenopausal women, NK-3R antagonists are thought to act by inhibiting the activity of KNDy neurons, thereby suppressing the activation of the vasomotor center.

Metabolites:
The principal metabolites of interest (M27, M30/34 and M18/21), which accounted for 6%, 11% and 5.5% respectively of total radioactivity in a human clinical study (# CPMX 50130), each showed high affinity and antagonistic activity at the human NK-1R and NK-3R similar to the affinity and activity of elinzanetant at human NK-1R and NK-3R. The binding affinity and functional antagonism of elinzanetant and its metabolites at human NK-1R and NK-3R are noted in Table 5.

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Table 5. Binding Affinity and Functional Inhibition Potency for Elinzanetant and Its Metabolites at Human NK-1R and NK-3R Ectopically Expressed in Cell Lines [Extracted from eCTD Section 2.6.2. Pharmacology Written Summary].

Compound	Binding assay [pK_i]	Functional assay [pK_B]
Elinzanetant		
NK-1R	8.71 – 10.15	9.02 – 9.1
NK-3R	8.03 - 8.8	8.17 – 8.5
Metabolite M18/21		
NK-1R	9.62	9.80
NK-3R	7.89	8.64
Metabolite M22§		
NK-1R	8.96	9.89
NK-3R	8.38	8.77
Metabolite M27		
NK-1R	8.96	9.89
NK-3R	7.96	8.52
Metabolite M30/34		
NK-1R	8.77	9.42
NK-3R	8.30	7.96

pK_B: -log of K_B, pK_i: -log of K_i; NK: neurokinin; R: receptor.
§ M22 is not a principal human metabolite (b) (4)

Pharmacokinetics

Key Findings:

In rat, following an oral dose, clearance was low and plasma elimination terminal half-life of the unchanged compound was long with 6.3 and 7.8 h in male and female rat.

Elinzanetant was brain penetrant in the rat and monkey with brain to blood ratios of 0.1 to 0.2 and 0.6, respectively.

Plasma Protein Binding: The plasma protein binding of elinzanetant was high in male and female human plasma, in female SD rat plasma, and in female Cynomolgus monkey plasma and resulted in a low fraction unbound (fu) of less than 1%. The protein binding in female and male CD-1 mouse plasma and in male SD rat plasma was noted to be lower, with fu values of approximately 2-3%. Similar plasma protein binding profiles were identified for the main human metabolites, M27, M30/34, and M18/21, as shown in Tables 6 through 9.

Table 6. Binding of elinzanetant to plasma proteins of selected species (in vitro) as well as blood to plasma concentration ratio.

Species / Matrix	Concentration [µg-eq/L]	f_u[a] [%]
Human (m)	711 - 6739	0.272
Human (f)	706 - 6268	0.332
CD-1 mouse (m)	982 - 10735	2.30
CD-1 mouse (f)	1005 - 10891	2.65
Sprague Dawley rat (m)	989 - 10679	1.91
Sprague Dawley rat (f)	976- 10734	0.843

a = fraction of free (unbound) drug in plasma, b = at a concentration of 10000 µg/L,
c = not applicable
Source: Module 4.2.2.3 PH-42081; Module 4.2.2.2. R-13621

Note: Truncated from the Applicant's submission (2.6.4 Pharmacokinetics Written Summary)

Table 7. Binding of M27 to plasma proteins of selected species (in vitro).

Species / Matrix	Concentration [µg-eq/L]	f_u[a] [%]
Human (m)	298 to 18204	0.0679
Human (f)	201 to 19374	0.0689
CD-1 mouse (m)	247 to 17229	1.23
CD-1 mouse (f)	208 to 18762	2.00
SD rat (m)	265 to 19000	1.44
SD rat (f)	201 to 19143	1.25

a = fraction of free (unbound) drug in plasma
Source: Module 4.2.2.3 PH-42138

Note: Truncated from the Applicant's submission (2.6.4 Pharmacokinetics Written Summary)

Table 8. Binding of M30/34 to plasma proteins of selected species (in vitro).

Species / Matrix	Concentration [µg-eq/L]	f_u[a] [%]
Human (m)	181 to 17514	0.475
Human (f)	169 to 14843	0.514
CD-1 mouse (m)	196 to 1537	0.699
CD-1 mouse (f)	171 to 16886	1.17
SD rat (m)	242 to 14024	0.661
SD rat (f)	165 to 11879	0.510

a = fraction of free (unbound) drug in plasma
Source: Module 4.2.2.3 PH-42138

Note: Truncated from the Applicant's submission (2.6.4 Pharmacokinetics Written Summary)

Table 9. Binding of M18/21 to plasma proteins of selected species (in vitro).

Species / Matrix	Concentration [µg-eq/L]	f_u[a] [%]
Human (m)	467 to 19768	0.181 to 0.322
Human (f)	371 to 19502	0.140 to 0.302
CD-1 mouse (m)	355 to 25667	2.99
CD-1 mouse (f)	202 to 21786	2.84
SD rat (m)	346 to 26371	2.37
SD rat (f)	385 to 26257	2.51

a = fraction of free (unbound) drug in plasma
Source: Module 4.2.2.3 PH-42138

Note: Truncated from the Applicant's submission (2.6.4 Pharmacokinetics Written Summary)

Metabolites: According to the clinical study CPMX 50130 in which human subjects were given an oral dose of radiolabeled elinzanetant, M30/34 was identified as the predominant metabolite of the parent drug in humans, accounting for ~11% of the total radioactivity measured in the plasma of [^{3}H]elinzanetant-treated subjects. The other two main metabolites, M27 and M18/21, accounted for <10% of the total radioactivity measured in plasma from the study subjects [Table 10].

Table 10. Relative Exposures to Elinzanetant and Its Metabolites in Human Subjects After a Single Oral Dose of [3H]Elinzanetant [Reviewer-Generated Table with Data from Clinical Study 21664].

	[3H] AUCs (µg•h/L)	Relative Exposure (% Calculated)
Total (Measured)	21700	NA
M27	1320	6.1
M30/34	2450	11.3
M18/21	1200	5.5
Elinzanetant	6620	30.5

Genotoxicity

Key Findings:
A full battery of genotoxicity studies including an AMES test, an in-vitro mouse lymphoma L5178Y cell assay, and an in-vivo rat micronucleus assay did not reveal any evidence of a genotoxic potential of elinzanetant.

Carcinogenicity

Key Findings:
104-week carcinogenicity study in female Sprague Dawley rat (Study T105128-7):

- Oral treatment of female rats with elinzanetant doses ranging from 7 to 80 mg/kg/day compared to vehicle for 104 weeks reduced their body weight gain but had no effect on their survival.
- Neoplastic Histopathology:
    - Elinzanetant caused statistically significant increases in the incidence of malignant adenocarcinoma of the uterus and malignant lymphoma in the hematolymphoid system.
    - Elinzanetant also caused statistically significant increases in the incidence of combined uterine adenocarcinoma and squamous cell carcinoma.
    - The oral dose of 20 mg/kg/day was the highest test dose not associated with carcinogenic signals in female rats. Based on AUCs, the clinical exposure margins provided by the highest noncarcinogenic dose to the MRHD is ~7.5x for elinzanetant and ~0.2x, 3.7x, and 0.05x for the metabolites M27, M30/34, and M18/21, respectively.
    - The oral dose of 60 mg/kg/day was the lowest test dose associated with carcinogenic signals in female rats. Based on AUCs, the clinical exposure margin provided by this dose to the MRHD is ~29.4x for elinzanetant and ~0.8x, 7.0x, and 0.1x for the metabolites M27, M30/34, and M18/21, respectively.
- Elinzanetant-related, non-neoplastic findings included:
    - Squamous cell metaplasia in the uterus (≥60 mg/kg/day).
    - Biliary hyperplasia, biliary cysts, and multinucleated hepatocytes that correlated with increased liver weight. Biliary hyperplasia and increased incidence of biliary cysts correlated with the increased bilirubin concentration (≥60 mg/kg/day).
    - Epithelial hyperplasia (≥7 mg/kg/day) and decreased lymphocyte counts (≥20 mg/kg/day) in the thymus that correlated with decreased thymus weight.
    - Absence of corpora lutea, sex cord stromal hyperplasia, and granulosa cell hyperplasia in the ovaries (≥60 mg/kg/day).
    - Increased macrophage infiltrates in the mesenteric lymph node (≥7 mg/kg/day).
    - Hyperplasia or hypertrophy of the zona fasciculata, cystic degeneration, and hypertrophy of the zona glomerulosa in the adrenal cortex that correlated with increased adrenal weight (≥60 mg/kg/day).

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  - Decreased incidence of vaginal mucification (≥20 mg/kg/day).
  - Decreased incidence of thyroid C-cell hyperplasia (≥60 mg/kg/day).
  - Atrophy/lobular atrophy in the parotid salivary gland, lacrimal glands, and pancreas (≥60 mg/kg/day).
- In-life clinical observations of animals treated with elinzanetant revealed the following central nervous system-related findings:
  - Increased incidence of whole-body convulsions (≥60 mg/kg/day).
  - Increased incidence of hunched posture (≥60 mg/kg/day).
  - Decreased general activity (≥60 mg/kg/day).
  - Increased sensitivity to touch (≥60 mg/kg/day).
  - Increased salivation (≥60 mg/kg/day).
  - Irregular respiration (≥7 mg/kg/day).

26-Week Carcinogenicity study in male and female transgenic mice (Study No. 8375970)

Oral treatment with elinzanetant doses ranging from 10 to 85 mg/kg/day in males and 10 to 70 mg/kg/day in females compared to vehicle for 26 weeks resulted in no statistically significant neoplastic or non-neoplastic findings.

Nonclinical Assessment and Recommendation

Under NDA 219469, Bayer Healthcare Pharmaceuticals, Inc., is developing elinzanetant, an NK-1R/NK-3R antagonist, for the clinical indication of treatment of moderate-to-severe vasomotor symptoms associated with menopause.

The Applicant has conducted a 2-year carcinogenicity study in female rats treated by oral gavage with elinzanetant doses ranging from 7 to 80 mg/kg/day. They have also conducted a 26-week carcinogenicity study in transgenic mice treated by oral gavage with doses ranging from 10 to 85 mg/kg/day for male mice and 10 to 70 mg/kg/day for female mice.

The data analysis by the FDA statistical reviewer and the Applicant led to the conclusions that: (i) in transgenic male and female mice, elinzanetant did not induce statistically significant neoplastic or non-neoplastic findings, and (ii) elinzanetant was carcinogenic in female rats.

In female rats, elinzanetant significantly increased the incidence of malignant lymphoma in the hematolymphoid system and malignant endometrial adenocarcinoma. The dose response-relationships for elinzanetant-induced increased incidence of these common tumors were statistically significant at $p < 0.005$, and pairwise comparisons were significant between rats treated with elinzanetant doses ≥60 mg/kg/day and vehicle control ($p < 0.01$). The highest noncarcinogenic dose was 20 mg/kg/day.

Elinzanetant significantly increased the incidence of combined malignant and benign endometrial tumors and malignant squamous cell carcinoma in uterus. The effects were

statistically significant with respect to the dose-response relationships and pairwise group comparisons with VC at doses ≥60 mg/kg/day.

Although the dose-response relationship for the rare malignant squamous cell carcinoma in the uterus was statistically significant (p trend < 0.025), pairwise comparisons indicated that the incidence of this carcinoma alone did not differ significantly between elinzanetant- and vehicle-treated female rats.

In-life central nervous system-related safety signals of clinical relevance were observed during the functional observation battery recorded during the treatment of the female rats with elinzanetant. These signals included: (i) whole-body convulsions at doses ≥60 mg/kg/day, and (ii) increased incidence of hunched posture, decreased general activity, increased sensitivity to touch, and increased salivation at doses ≥60 mg/kg/day.

The following non-neoplastic findings were also observed at doses ≥60 mg/kg/day, unless otherwise noted in the: (i) liver: biliary hyperplasia, biliary cysts, and multinucleated hepatocytes that correlated with increased liver weight and increased serum bilirubin levels; (ii) uterus: squamous cell metaplasia; (ii) ovaries: absence of corpora lutea and increased incidence of sex cord stromal hyperplasia and granulosa cell hyperplasia; (iv) vagina: decreased mucification; (v) mesenteric lymph node: increased macrophage infiltrates (at ≥7 mg/kg/day); (v) adrenal glands: hyperplasia or hypertrophy of the zona fasciculata, cystic degeneration, and hypertrophy of the zona glomerulosa in the adrenal cortex that correlated with increased adrenal weight; and (vii) parotid salivary gland, lacrimal glands, and pancreas: atrophy.

Although not discussed in the Applicant's report, the main metabolites of elinzanetant – BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 346934 (M18/21) – inhibit [^{3}H]progesterone binding to PR-B with Kis of 1.08 µM, 0.96 µM, and 1.35 µM, respectively. Elinzanetant does not interact with PR-B. Considering that, in female rats treated with the elinzanetant dose of 60 mg/kg/day, C_{max} and $AUC_{0\text{-}24h}$ of BAY 3462933 (M30/34) were 2.09 µM and 46.8 µM•h, respectively, on treatment day 358, it is possible that inhibition of PR-B by BAY 3462933 (M30/34) contributes to the increased incidence of endometrial cancers in rats treated with elinzanetant doses ≥60 mg/kg/day.

At 10 µM, BAY 3462933 (M30/34) has been reported to inhibit by ~60% and ~55% radioligand binding to ERα ectopically expressed in Sf9 cells and to $GABA_A$ receptors in rat brain membranes, respectively. BAY 3462933 (M30/34)-induced inhibition of ERα activity could contribute to the reduced incidence of tumors and hyperplasia in estradiol-sensitive organs (such as the mammary, pituitary, and thyroid glands) in elinzanetant-treated female rats. BAY 3462933 (M30/34)-induced inhibition of PR-B and $GABA_A$ receptors could also contribute to the proconvulsant effects of elinzanetant in female rats.

Based on trend and pairwise comparisons, the FDA statistical reviewer and the Applicant concluded that, in female rats, the highest noncarcinogenic dose was 20 mg/kg/day (which provide a clinical exposure margin of ~7.5x) and the lowest

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carcinogenic dose was 60 mg/kg/day (which provides a clinical exposure margin of ~29.4x).

While the carcinogenicity study generated adequate clinical exposure margins for the parent drug and its primary metabolite (M30/34) in rats, it provided very low exposure margins to the other two main metabolites (M27 and M18/21). Based on AUCs, the clinical exposure margins provided by the rat doses of 20 mg/kg/day and 60 mg/kg/day to the MRHD were, respectively: (i) 3.7x and 7.0x for M30/34, respectively, (ii) 0.2x and 0.8x for M27, and (iii) 0.05x and 0.1x for M18/21.

Exposure Margins Based on Pivotal Carcinogenicity Studies

2-year carcinogenicity study				Clinical Exposure Margins [= $AUC_{rat\ dose} \div AUC_{MRHD}$]
Species	Analyte	Elinzanetant Dose (mg/kg/day)	$AUC_{0\text{-}24h}$ (µg•h/L) Day 358	MRHD: 120 mg/day $AUC_{0\text{-}24h}$: 8572 µg•h/L for Elinzanetant 2496.3 µg•h/L for M27 4570.1 µg•h/L for M30/34 2326.3 µg•h/L for M18/21
Rat	Elinzanetant [Parent Drug]	7	17600	2.1x
		20	**64000**	**7.5x**
		60	252000	29.4x
		80	280000	32.7x
	M27 [Metabolite]	**20**	**550**	**0.2x**
		60	2020	0.8x
	M30/34 [Metabolite]	**20**	**17000**	**3.7x**
		60	32100	7.0x
	M18/21 [Metabolite]	**20**	**119**	**0.05x**
		60	237	0.1x

Data in **bold blue font** are for the highest test dose determined to be noncarcinogenic.
$AUC_{0\text{-}24h}$: Area-under-the-curve of plasma concentrations for the different analytes vs time. $AUC_{0\text{-}24h}$ for the MRHD is from Clinical Report B002427.
MRHD: Maximum Recommended Human Dose.

1 Background

1.1 Regulatory History

Under NDA 219469, the Applicant, Bayer Healthcare Pharmaceuticals, Inc., is developing elinzanetant, an NK1/NK3 receptor antagonist, for the clinical indication of treatment of moderate-to-severe vasomotor symptoms associated with menopause. Clinical and nonclinical studies to support the advanced development of elinzanetant were conducted under IND 129492.

On August 14, 2020, the Applicant submitted to IND 129492 a request for a Rat Carcinogenicity Study Special Protocol Assessment (SPA). After being initially rejected due to lack of a signed full report of the nonclinical repeat-dose toxicity study used to support the proposed dose selection for the carcinogenic study, the study protocol for the rat carcinogenic study was resubmitted on September 4, 2020 [IND 129492, SDN 34, SN 0033]. The SPA Agreement for the Rat Carcinogenicity Study from the Division and the FDA's Exec CAC was provided to the Sponsor on October 19, 2020.

On October 24, 2022, the Applicant submitted to IND 129492 an SPA for a mouse TgRasH2 carcinogenicity study. The SPA Agreement for the Mouse Carcinogenicity Study from the Division and the FDA's Exec CAC was provided to the Sponsor on December 8, 2022. The Applicant opened the NDA on July 26, 2024, and submitted the results of the rat carcinogenic study T105128-7 to both the NDA and the IND.

1.2 Relevant INDs, NDAs, BLAs or DMFs

IND 129492. Drug: Elinzanetant; Sponsor: Bayer Healthcare Pharmaceuticals, Inc.; Indication: Treatment of moderate-to-severe vasomotor symptoms associated with menopause; IND Submission Date: February 04, 2016.

1.3 Previous Reviews Referenced

Application	Reviewer	Date in DARRTS	Notes
IND 129492	Frederic Moulin, DVM, PhD	10/19/2020	SPA Rat Carcinogenicity Study Review
	Leslie McKinney, PhD	12/13/2022	SPA Mouse Carcinogenic Study Review
	Leslie McKinney, PhD	03/01/2023	Review of Sponsor's Question for Early Termination of Rat Carcinogenicity Study
	Leslie McKinney, PhD	10/16/2024	Close-out memo [Studies to be reviewed under the NDA]

1.4 Clinical Information

Previous Clinical Experience

The Applicant has completed three phase 3 double-blind, randomized, placebo-controlled studies to assess the effectiveness, safety, and pharmacokinetic profile of elinzanetant (120 mg/day; oral softgel capsules). The Sponsor is currently seeking

marketing approval under NDA 219469 for this drug product for the indication of treatment of moderate-to-severe vasomotor symptoms associated with menopause.

2 Supplemental Drug Information

2.1 Drug Formulation

Table 11 shows the drug product composition. The excipients are not novel for the oral route of administration and are considered adequately qualified.

Table 11. Drug Product Composition.

	Amount (mg)/capsule
Elinzanetant	60.0
All-rac-α-tocopherol	(b) (4)
Caprylocaproyl macrogoglycerides	
Glyceryl monocaprylocaprate	
Glyceryl monooleate	
Polysorbate 80	

2.2 Comments on Novel Excipients

There are no novel excipients.

2.3 Proposed Clinical Population and Dosing Regimen

The recommended dose of elinzanetant is 120 mg per day (two 60 mg soft gel capsules) taken once daily at bedtime in the general population of individuals with moderate to severe VMS associated with menopause.

3 Studies Submitted

3.1 Studies Reviewed

Study Number	Study Title
T105128-7	A 104-Week Twice Daily Oral Gavage Toxicokinetic and Carcinogenicity Study with NT-814 (BAY3427080) in Sprague Dawley Rats
T105265-9	A 26-Week Carcinogenicity and Toxicokinetic Study of BAY 3427080 (NT-814) When Administered Twice Daily via Oral Gavage to Transgenic Mice

4 Carcinogenicity

4.1 Study Title+: A 104-Week Twice Daily Oral Gavage Toxicokinetic and Carcinogenicity Study with NT-814 (BAY3427080) in Sprague Dawley Rats

Study no.:	T105128-7
Study report location:	NDA 219469, SDN 6 [SN 0006]
Study initiation date:	May 2, 2021
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Elinzanetant (free base). Batch: 7486-P54/20-002, Purity: 100.7%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	The FDA's Exec CAC recommended the doses of 0 (vehicle), 7, 20, and 60 mg/kg/day, by oral gavage, for female rats. The clinical exposure margin based on AUCs was the basis for the recommendation of the highest dose. The lower doses were selected for adequate dose spacing. The Exec CAC agreement fax was sent to the Sponsor on October 19, 2020. In addition to testing the Exec CAC-recommended doses, the Applicant added a higher dose to the study (80 mg/kg/day).

Reviewer Carcinogenicity Conclusion (negative/ positive)
Positive

Key Study Findings
Long-term carcinogenicity studies were conducted in rats dosed orally with elinzanetant for 104 weeks. Female rats were dosed at 0, 7, 20, 60, and 80 mg/kg/day. In female rats, elinzanetant was found to be carcinogenic at doses ≥60 mg/kg, which generated systemic exposures (AUC_{0-24h}) ≥29.4-fold higher than the human systemic exposure at the MRHD of 120 mg/day.

Adequacy of Carcinogenicity Study

- Adequate multiples of the clinical exposure were achieved in the carcinogenicity study in rats (29.4x and 32.8x for the mid-dose and the high-dose groups, respectively).

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- Survival to scheduled necropsy was greater than 40% in all groups (with >20 rats surviving until terminal sacrifice at Week 104), without a clear dose-related mortality.
- Body weight gain was reduced dose dependently in female rats treated with elinzanetant.
    - At terminal sacrifice, body weights of female rats in the LD, LM, MD, and HD groups were approximately ~9%, 9%, 17%, and 19% lower than those of female rats in the VC group.
    - The reduced body weight gain was not due to reduced feed consumption.

Appropriateness of Test Models

The carcinogenicity study in rats appears appropriate because:

- Animals received treatment through the entire duration of the study (104 weeks).
- Although the study was restricted to female rats, the drug is being develop for a clinical indication in women.
- The rat strain (Sprague-Dawley) was the same as that used in the repeat-dose toxicity study that served as the basis for the selection of test doses.

Evaluation of Tumor Findings

- The FDA statistical reviewer Feng Zhou reported:
    - Statistically significant increase in the incidence of malignant lymphoma in the hematolymphoid system and the incidence of malignant endometrial adenocarcinoma at the dose-response relationship level with significant pairwise comparisons between doses ≥60 mg/kg/day and VC.
    - Statistically significant increase of combined malignant and benign endometrial tumors and combined endometrial tumors (malignant and benign) and malignant squamous cell carcinoma in uterus at the dose-response relationship level with significant pairwise comparisons between doses ≥60 mg/kg/day and VC.
    - Statistically significant increase of the incidence of rare malignant squamous cell carcinoma in the uterus at the level of the dose-response relationship but not at the level of pairwise comparisons.
    - No other statistically significant or toxicologically relevant neoplastic lesions.
- The findings of the FDA statistician aligned with those described in the Applicant's report.
- The highest test dose found to be noncarcinogenic was 20 mg/kg/day and the lowest dose found to be carcinogenic was 60 mg/kg/day; these doses generated $AUC_{0\text{-}24h}$s of 64000 µg•h/L and 252000 µg•h/L (Day 358), which provide 7.5-fold and 29.4-fold multiples of clinical exposures to the MRHD.

Methods

Doses:	0 (vehicle), 7 mg/kg/day (LD), 20 mg/kg/day (LM), 60 mg/kg/day (MD), 80 mg/kg/day (HD)
Frequency of dosing:	Twice daily

Number/Sex/Group:	• Main Study: 100 females/group
	• Satellite (Toxicokinetics):
	  ○ Vehicle: 3 females
	  ○ Elinzanetant: 9 females/group

Dose volume:	5 mL/kg/dose (10 mL/kg/day)
Formulation/Vehicle:	1.0% (w/v) carboxymethylcellulose (400 cps at 2%) in water treated by reverse osmosis
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	SPRAGUE-DAWLEY
Age:	8 weeks at the initiation of dosing
Comment on Study Design and Conduct:	• Animals were not fasted for dosing, unless fasted for other study procedures. • Due to ocular observations (opaque eyes), Animal R0051 (Group 1, carcinogenicity), Animals R0620 and R0660 (Group 4, carcinogenicity), and Animal R0907 (Group 5, toxicokinetic) were replaced on Day 17 of the dosing phase with an animal of a similar body weight from the group of possible replacement animals.
Dosing Comments (Dose Adjustments or Early Termination):	There were no dosing adjustments, and the study lasted through treatment week 104
Dosing Solution Analysis:	Concentrations of the test article were verified in samples collected from vehicle control and test item formulations prepared for administration on treatment days 1, 85, 176, 267, 358, 449, 540, 631, 694, and 722. On day 267, the formulation containing 6 mg/mL (used to deliver the dose of 60 mg/kg/day) failed to meet acceptance criteria (76.8 and 75.4% of the theoretical for primary and backup samples, respectively). On day 722, the formulation containing 0.7 mg/mL (used to deliver the dose of 7 mg/kg/day) also failed to meet acceptance criteria (79.8 and 79.6% of the theoretical for primary and backup samples, respectively). According to the Applicant, these variations had minimal impact on the ability to assess the

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carcinogenicity potential of NT-814, because the highest dose met the acceptance criteria throughout the study.

All other formulations were within 15% (suspensions) of the target concentrations (ranging from 90.1 to 104.8% of the theoretical). The test item was not detected in any vehicle control formulation.

FDA Statistical Analysis of Tumor Findings: *A separate statistical review of survival and tumor was conducted by the FDA statistical reviewer Feng Zhou from the Division of Biometrics VI. The statistical review appears in Appendix 1 and is referenced in the sections below.*

Observations and Results

Mortality

Rats were observed twice daily for morbidity and mortality.

As described in the Dr. McKinney's Review of Sponsor's Question for Early Termination of Rat Carcinogenicity Study, on February 21, 2023, the Sponsor had requested to terminate the carcinogenicity study early (b) (4) because the number of animals per dose group was progressively decreasing towards 50%. The Division did not concur with the Sponsor's request and recommended setting the criteria for early termination of the study at 20 and 15 surviving animals for the control the elinzanetant groups, respectively. The study proceeded, and all groups remained viable with >20 rats/group surviving until the terminal sacrifice at Week 104.

For the carcinogenicity main study animals, numbers (%) of deaths that occurred prior to termination of the group at Week 104 were 56 (56%), 61 (61%), 62 (62%), 58 (58%), or 63 (63%) in the VC, LD, ML, MD, or HD groups, respectively (Table 12).

Table 12. Group Mortality Incidence [Excerpted from the Applicant's Report].

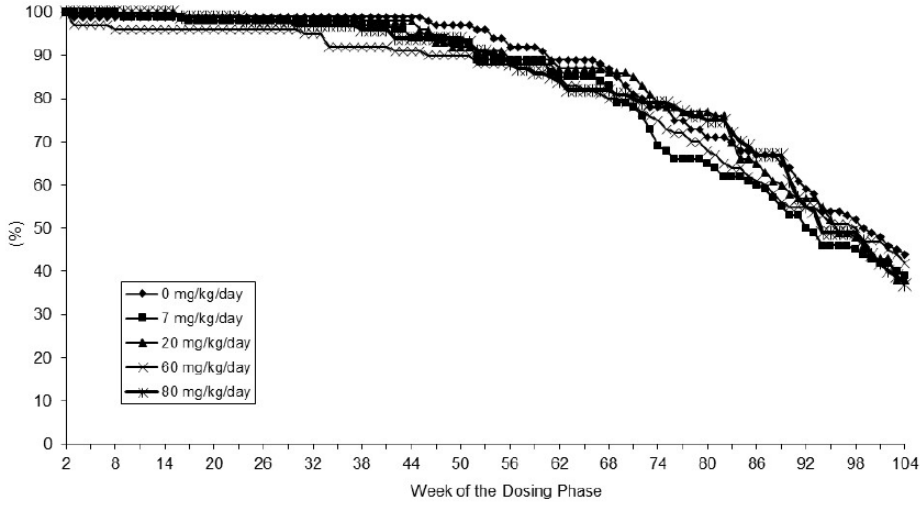
Sex	Females				
Dose Level (mg/kg/day)	0	7	20	60	80
Total number of animals on study	100	100	100	100	100
Total number of decedent animals	56	61	62	58	63
Total number at terminal sacrifice	44	39	38	42	37

The Applicant's statistical analysis indicated that survival in elinzanetant- and vehicle-treated rats did not differ significantly. The FDA statistical reviewer, Feng Zhou, agreed with the Applicant that there was no elinzanetant-related effect on animal survival in the female rats (see Appendix 1). Additionally, per the FDA statistical reviewer and the Applicant's report, there were no differences in the intercurrent mortality between elinzanetant- and vehicle-treated rats, with most deaths occurring after approximately Week 53 for all groups (Table 13 and Figure 1).

Table 13. Intercurrent Mortality Rate in Female Rats [Excerpted from Feng Zhou's Statistical Report].

	Vehicle Control		Low Dose		Mid-low		Mid Dose		High Dose	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	4	4.00	12	12.00	9	9.00	12	12.00	11	11.00
53 - 78	23	27.00	23	35.00	14	23.00	18	30.00	15	26.00
79 - 96	19	46.00	20	55.00	28	51.00	19	49.00	27	53.00
97 - 104	9	55.00	6	61.00	11	62.00	8	57.00	10	63.00
Accidental Death	1	1.00					1	1.00		
Terminal sacrifice	44	44.00	39	39.00	38	38.00	42	42.00	37	37.00
Total	100		100		100		100		100	

Figure 1. Kaplan-Meier Survival Functions for Female Rats [Excerpted from Feng Zhou's Report].



Causes of Early Morbidity and Mortality: Causes of early morbidity and mortality are presented in Table 14.

Common causes of death/moribund condition for female rats at an unscheduled time included mammary gland neoplasms and pituitary adenoma of the pars distalis, particularly in the VC, LD, and ML dose groups (Table 14). These are representative of common, spontaneously occurring, age-related findings in laboratory rats.

Causes of early deaths among female rats that received elinzanetant doses ≥60 mg/kg/day included: (i) an increased incidence of malignant lymphoma and uterine neoplasms, and (ii) an increased incidence of an "undetermined" cause of death, largely related to clinical observations of convulsions. Due to lack of microscopic correlates in the brain, the Applicant refers to convulsions-associated deaths as deaths of "undetermined cause".

It was also noted that in the MD and HD groups, the incidence of mammary gland neoplasms-associated deaths decreased.

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Table 14. Causes of early mortality and morbidity [Excerpted from the Applicant's Report].

	Females				
Dose Level (mg/kg/day)	0[a]	7	20	60	80
Number of Animals/Group	100	100	100	100	100
Mortality[b]	56	61	62	58	63
Death Comment					
Neoplasm, hematolymphoid	1	3	3	6	8
Neoplasm, pituitary	7	5	8	3	1
Neoplasm, mammary gland	33	38	35	2	9
Neoplasm/hyperplasia, uterus	2	3	5	12	19
Undetermined	7	2	10	27	14

a Vehicle control item.
b Total number of animals found dead or sacrificed at an unscheduled interval.

Clinical Signs

Clinical signs were checked once daily and detailed clinical examinations were performed once weekly.

As summarized in Table 15, elinzanetant-induced clinical signs in female rats included:

- Increased incidence of whole-body convulsions (≥60 mg/kg/day)
- Increased incidence of hunched posture (≥60 mg/kg/day)
- Decreased general activity (≥60 mg/kg/day)
- Increased sensitivity to touch (≥60 mg/kg/day)
- Irregular/audible/fast respiration (≥7 mg/kg/day)
- Increased salivation (≥60 mg/kg/day)

Table 15. Incidence of Clinical Signs per Treatment Group [Reviewer-Generated Table Using Data from the Applicant's Report].

	VC	LD	LM	MD	HD
Number of Rats	**101**	**100**	**100**	**102**	**100**
Involuntary movements					
Convulsions, whole body <1 minute	7	7	9	27	26
Convulsions, whole body >1 minute	2	0	5	11	9
All convulsions (# associated deaths)	8 (1)	7 (1)	9 (5)	30 (20)	28 (11)
Hunched posture	7	6	2	13	10
Decreased activity	3	5	4	10	16
Increased sensitivity to touch	4	6	2	18	12
Respiration					
Irregular	1	4	3	8	10
Audible	1	1	2	3	4
Fast	1	2	2	6	4
Excessive salivation					
Clear	1	2	2	8	5
Colorless	0	0	0	0	3

VC = vehicle control; LD = 7 mg/kg/day; LM = 20 mg/kg/day; MD = 60 mg/kg/day; HD = 80 mg/kg/day

Reviewer's Comment on Biological Plausibility of Elinzanetant-Induced Convulsions

Considering the current knowledge that NK1 and NK3 receptor activation increases neuronal excitability,[1,2] it is unlikely that elinzanetant-induced inhibition of NK1/NK3 receptors would lead to the development of convulsions.

The Applicant has reported that, at 10 µM, the elinzanetant metabolite BAY 3462933 (M30/34) inhibits by ~55% [^{3}H]tert-butylbicycloorthobenzoate ([^{3}H]TBOB) binding to gamma-amino butyric acid type A ($GABA_A$) receptors in Wistar rat brain membrane preparations (R-14018). Since $GABA_A$ receptor antagonists (e.g., picrotoxin and bicuculline) are well known for their proconvulsant effects,[3] BAY 3462933 (M30/34)-induced inhibition of $GABA_A$ receptors may contribute to the proconvulsant effects of elinzanetant in rats. It is also possible that BAY 3462933 (M30/34)-induced PR-B inhibition contributes to the proconvulsant properties of elinzanetant because progesterone receptor antagonists and null mutations of the genes that encode progesterone receptors A and B reportedly suppress the anticonvulsant effects of progesterone.[4,5]

Ophthalmological examinations performed on main study animals in Weeks 7, 26, 52, and 100 revealed no elinzanetant-related abnormal ophthalmological findings.

Body Weights

Body weight was recorded at least once before treatment, once daily between treatment days 1 and 15, once weekly thereafter until treatment day 134, once every four weeks after day 134 followed by once every two weeks starting on day 246 until the end of treatment.

Treatment with elinzanetant dose dependently reduced the body weight gain of female rats (Figure 2). The reduction in body weight gain was not due to a reduction in food consumption, which was not significantly different between treatment groups.

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1 Stacey AE, Woodhall GL, Jones RS. Neurokinin-receptor-mediated depolarization of cortical neurons elicits an increase in glutamate release at excitatory synapses. Eur J Neurosci. 2002 Nov;16(10):1896-906. doi: 10.1046/j.1460-9568.2002.02266.x. PMID: 12453053.

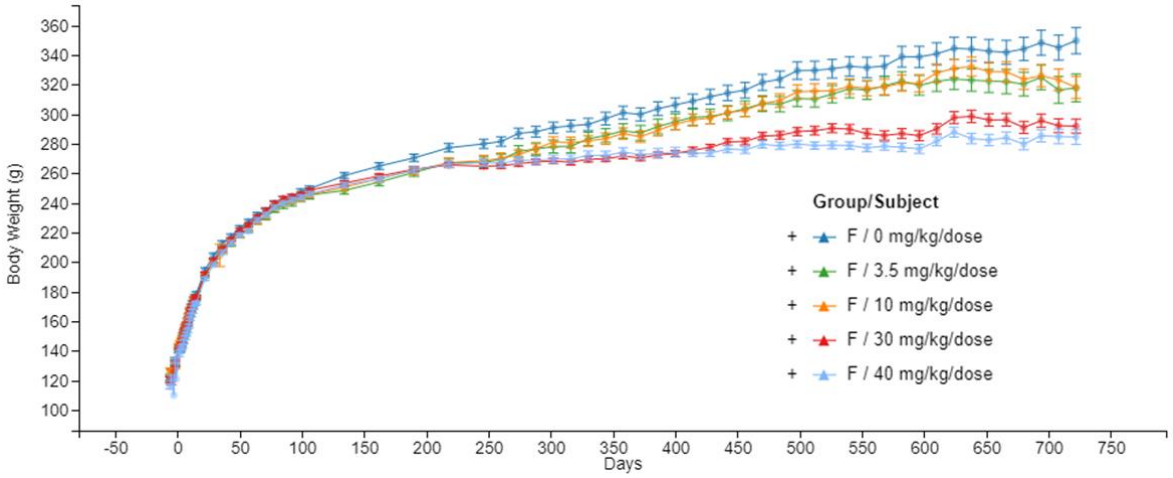
2 Gallopin T, Geoffroy H, Rossier J, Lambolez B. Cortical sources of CRF, NKB, and CCK and their effects on pyramidal cells in the neocortex. Cereb Cortex. 2006 Oct;16(10):1440-52. doi: 10.1093/cercor/bhj081. Epub 2005 Dec 7. PMID: 16339088.

3 Sigel E, Steinmann ME. Structure, function, and modulation of GABA(A) receptors. J Biol Chem. 2012 Nov 23;287(48):40224-31. doi: 10.1074/jbc.R112.386664. Epub 2012 Oct 4. PMID: 23038269; PMCID: PMC3504738.

4 Lonsdale D, Nylen K, McIntyre Burnham W. The anticonvulsant effects of progesterone and its metabolites on amygdala-kindled seizures in male rats. Brain Res. 2006 Jul 26;1101(1):110-6. doi: 10.1016/j.brainres.2006.05.005. Epub 2006 Jun 19. PMID: 16784731.

5 Shiono S, Sun H, Batabyal T, Labuz A, Williamson J, Kapur J, Joshi S. Limbic progesterone receptor activity enhances neuronal excitability and seizures. Epilepsia. 2021 Aug;62(8):1946-1959. doi: 10.1111/epi.16970. Epub 2021 Jun 24. PMID: 34164810; PMCID: PMC8349834.

Figure 2. Mean Body Weight [Reviewer-Generated Figure].



Hematology

Blood samples for hematology, coagulation, and clinical chemistry were collected from fasted carcinogenicity animals via a jugular vein once during treatment weeks 26, 52, and 102, and on the day of unscheduled or terminal sacrifice.

Among early sacrifice animals, moderately to markedly higher white blood cell count was noted in a few animals, due to the presence of immature hematopoietic cells, likely reflecting hematopoietic neoplasia. Levels of fibrinogen were also significantly increased dose dependently by elinzanetant throughout the dosing period (Table 16). No other consistent alterations in hematological parameters were attributed to the test article.

Table 16. Changes in Hematological Parameters in Female Rats Treated Orally with Elinzanetant [Reviewer-Generated Table].

Hematological Parameter	Group	VC	LD	LM	MD	HD
	Dose (mg/kg/day)	0†	7	20	60	80
Fibrinogen (mg/dL) [**Week 26**]	Mean	138	134	137	149*	151*
	% Ctrl (G1)	–	*-3%*	*0%*	*7.9%*	*9.4%*
Fibrinogen (mg/dL) [**Week 52**]	Mean	144	147	140	156	166*
	% Ctrl (G1)	–	*2%*	*-3%*	*8.3%*	*15.3%*
Fibrinogen (mg/dL) [**Week 104**]	Mean	147	141	161	163	197*
	% Ctrl (G1)	–	*-4.1%*	*9.5%*	*10.9%*	*34.0%*

%Ctrl (G1): % change from the mean of vehicle control (VC) group; *p<0.05 vs VC group by Anova and Dunnett post-hoc.

Clinical Chemistry

Elinzanetant-related changes in clinical chemistry parameters observed during treatment at Week 104 are summarized in Table 17.

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Table 17. Changes in Clinical Chemistry Parameters Measured on Week 104 in Female Rats Treated Orally with Elinzanetant [Reviewer-Generated Table].

Clinical Chemistry (Week 104)	Group	VC	LD	LM	MD	HD
	Dose (mg/kg/day)	0	7	20	60	80
Glucose (mg/dL)	Mean	87	89	92	105*	103*
	% Ctrl (G1)	–	*2%*	*5%*	*21%*	*18%*
Albumin (g/dL)	Mean	5.1	5.2	5.0	5.0	4.6*
	% Ctrl (G1)	–	*2%*	*-2%*	*-2%*	*-10%*
Globulin (g/dL)	Mean	2.1	2.2	2.5*	2.5*	2.9*
	% Ctrl (G1)	–	*5%*	*14%*	*14%*	*38%*
Albumin:Globulin	Mean	2.5	2.5	2.1*	2.0*	1.7*
	% Ctrl (G1)	–	*0%*	*-16%*	*-20%*	*-32%*
Cholesterol (mg/dL)	Mean	187	180	189	235*	272*
	% Ctrl (G1)	–	*-4%*	*1%*	*26%*	*45%*
Bilirubin (mg/dL)	Mean	<0.1	0.2	0.3	0.3	0.3
	% Ctrl (G1)	–	*NA*	*NA*	*NA*	*NA*

%Ctrl (G1): % change from the mean of vehicle control (VC) group; *p<0.05 vs VC group by Anova and Dunnett post-hoc.

In short, elinzanetant dose dependently increased serum glucose, globulin, cholesterol, and bilirubin levels and reduced serum albumin levels and the ratio albumin to globulin. The increased bilirubin levels correlated with increased severity/incidence of biliary cysts or biliary hyperplasia observed microscopically in the liver (see below).

Gross Pathology

A complete macroscopic examination was performed on all main study animals sacrificed at the end of the treatment period, prematurely sacrificed, or found dead.

Organ Weights

Absolute and relative organ weights that were dose dependently affected by elinzanetant are summarized in Table 18.

Table 18. Summary of NT-814-Related Organ Weight Differences Compared with Concurrent Controls at Terminal Necropsy [Excerpted from Applicant's Report].

		NT-814				
	Sex	Females				
	Dose Level (mg/kg/day)	0	7	20	60	80
	Terminal body weight (g)	329	298*	298	272*	261*
	% difference	-	91*	91	83*	80*
Adrenal						
	Absolute Weight (g)	0.0661	99	112	119*	118*
	Body Weight Ratio (%)	0.0209	109	118	139*	144*
	Brain Weight Ratio (%)	3.5666	102	115	121*	120*
Liver						
	Absolute Weight (g)	7.6753	93	96	93	120*
	Body Weight Ratio (%)	2.3596	103	95	129*	150*
	Brain Weight Ratio (%)	412.9613	95	99	109	122*
Pituitary						
	Absolute Weight (g)	0.0305	81	151	71*	66*
	Body Weight Ratio (%)	0.0096	88	174	84	80
	Brain Weight Ratio (%)	1.6402	84	61	72*	67*
Thymus						
	Absolute Weight (g)	0.1586	84	77	61*	63*
	Body Weight Ratio (%)	0.0478	91	85	75*	79*
	Brain Weight Ratio (%)	8.5091	87	79	62*	64*
Uterus/Cervix						
	Absolute Weight (g)	0.9956	98	107	105	135
	Body Weight Ratio (%)	0.3144	109	117	123*	164*
	Brain Weight Ratio (%)	53.9173	101	110	106	134

* = Statistically significant difference (absolute or relative) compared with respective control mean value ($p \leq 0.5$).
Note: Values for absolute weight and ratio of organ weights (relative to body or brain) for test item-treated groups are expressed as a percentage increase/decrease relative to the control.

Macroscopic Findings

Liver: Increases in liver and uterine weights seen at elinzanetant doses ≥60 mg/kg/day were accompanied by increases in the incidence of biliary cysts and uterine masses, respectively (Table 19).

Table 19. Macroscopic Findings in the Liver and Uterus of Female Rats at Necropsy [Table Excerpted from Applicant's Report].

		NT-814				
	Sex	Females				
	Dose Level (mg/kg/day)	0	7	20	60	80
	Number Examined	100	100	100	100	100
Liver						
	Cysts	7	5	3	13	13
Uterus						
	Mass	3	3	2	9	11

Histopathology

Peer-Review Conducted: Yes. The peer-review statement signed by the study pathologist, (b) (4), (b) (6), and the external peer-review pathologist, (b) (4), (b) (6), states that "*the external peer-review of histopathologic findings has been conducted and that consensus was achieved on the histopathologic evaluation and reporting.*"

Per the study report, "*the peer review was conducted by an expert Peer Review Pathologist located at a facility not in compliance with current regulatory GLP requirements. The Peer Review Pathologist followed Sponsor standard operating procedures (SOPs) and ensured that slides were stored properly, and records related to the chain of custody of the slides and any records or raw data (if applicable) were provided to the Study Director for archival*."

Historical Control Provided for Tumor Incidence: Per the study report, "*historical control data used for pathology interpretation referenced were generated by a non-validated software, and not GLP compliant*."

Neoplastic Findings

FDA Statistical Analysis of Tumor Findings

The FDA statistical reviewer Feng Zhou conducted an independent review of the Applicant's report data (for details regarding the method and data analysis, refer to the FDA Statistical Review of Feng Zhou in Appendix 1).

In short, the statistical reviewer used the Poly-k method described in Bailer and Portier (1988) and Bieler and Williams (1993) to analyze the tumor data from the five test groups (VC, LD, LM, MD, and HD) to identify statistically significant dose-response relationships and pairwise comparisons between test article groups and the VC group.

To adjust for the effect of multiple testing, the statistical reviewer used the methodologies described in the *Draft Guidance: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals* (2001), available at https://www.fda.gov/media/72296/download. Per the Guidance, criteria for identification of statistically significant effects in 2-year carcinogenicity studies with 50 rats/group were as follows:

- Dose-response relationships were considered statistically significant at $\alpha = 0.025$ for rare tumors (i.e., tumors with a background rate of ≤1%) and $\alpha = 0.005$ for common tumors.
- Pairwise comparisons between each test article group and control were considered statistically significant at $\alpha = 0.05$ for rare tumors and $\alpha = 0.01$ for common tumors.

Summary of the FDA Statistical Reviewer's Neoplastic Findings in Female Rats

Uterus

The FDA statistical reviewer identified statistically significant positive dose-response relationships for elinzanetant-related neoplastic findings in the female rat uterus, with an increase in the incidence of malignant endometrial adenocarcinomas (a common tumor) and of combined benign and malignant endometrial cancers (common tumors) and malignant endometrial squamous cell carcinoma (a rare tumor) (trend; p-values < 0.0001). The incidence of these tumors was higher in female rats treated with the oral elinzanetant doses of 60 mg/kg/day and 80 mg/kg/day compared to concurrent vehicle control (pairwise; p-values < 0.006) (Table 2). Both findings meet the recommended

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criteria of statistical significance for common tumors (p-trend < 0.005; p-pairwise < 0.01).

Lymphoma in Hematolymphoid System

The FDA statistical reviewer also identified statistically significant positive dose-response relationships for elinzanetant-related neoplastic findings in the female rat hematolymphoid system, with an increase in the incidence of malignant lymphoma (a common tumor) (trend; p-value = 0.002). The incidence of this tumor was significantly higher in female rats treated with the oral elinzanetant doses of 60 mg/kg/day and 80 mg/kg/day compared to concurrent vehicle control (pairwise; p-value = 0.0087) (Table 2; page 7). Both findings meet the recommended criteria of statistical significance for common tumors (p-trend < 0.005; p-pairwise < 0.01).

See Table 2 on page 7 of this review for the FDA statistical reviewer's table of significant neoplastic findings. No other statistically significant tumor findings were identified by the FDA statistical reviewer-conducted analysis of tumor findings for female rats.

Summary of the Applicant's Neoplastic Findings in Female Rats

The Applicant also reported that elinzanetant-related increased neoplastic/proliferative microscopic findings were noted in the uterus and hematolymphoid system. However, as shown in Table 20, they only provided the unadjusted p-values and interpreted increased incidence of tumors to be statistically significant even when p-trend met the criteria for significance but p-pairwise did not.

Table 20. Elinzanetant-Related Carcinogenic Signals Reported by the Applicant [Excerpted from the Applicant's Report].

Tissue and Lesion	Rare or Common	Test	Unadjusted p-value	FDA Interpretation
Hematolymphoid System	Common	Trend	0.0024 (P)	Significant (p<0.005)
M-Lymphoma		G5 v Control	0.0091 (P)	Significant (p<0.01)
Liver	Common	Trend	0.0490 (P)	Not significant (p≥0.005)
B-Adenoma, hepatocellular/ M-Hepatocellular carcinoma				
Skin/Subcutis	Rare	Trend	0.0336 (P)	Not significant (p≥0.025)
B-Fibroma/ M-Fibrosarcoma				
Uterus	Common	Trend	<0.0001 (P)	Significant (p<0.005)
M-Adenocarcinoma, endometrium		G4 v Control	0.0006 (P)	Significant (p<0.01)
		G5 v Control	<0.0001 (P)	Significant (p<0.01)
Uterus	Rare	Trend	0.0232 (P)	Significant (p<0.025)
M-Carcinoma, squamous cell				
Uterus	Common	Trend	<0.0001 (P)	Significant (p<0.005)
B-Adenoma, endometrium/		G4 v Control	0.0006 (P)	Significant (p<0.01)
M-Adenocarcinoma, endometrium		G5 v Control	<0.0001 (P)	Significant (p<0.01)
Uterus	Common	Trend	<0.0001 (P)	Significant (p<0.005)
B-Adenoma, endometrium/		G4 v Control	0.0003 (P)	Significant (p<0.01)
M-Adenocarcinoma, endometrium/ M-Carcinoma, squamous cell		G5 v Control	<0.0001 (P)	Significant (p<0.01)

P = Peto

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No other statistically significant tumor findings were reported in the Applicant's statistical analysis of tumor findings for female rats.

Considering the observed neoplastic findings in the uterus and the hematolymphoid system, the Applicant concluded that oral elinzanetant doses ≥60 mg/kg/day were carcinogenic to female rats. The dose level of 20 mg/kg/day was considered to be not carcinogenic.

Reviewer's Comments

1. ***Based on the FDA statistical reviewer's and the Applicant's data analyses, uterine tumors (malignant adenocarcinomas and for the combination of malignant and benign uterine tumors and malignant squamous cell carcinoma) and malignant lymphoma in the hematolymphoid system were considered positive tumor findings due to statistical significance by both trend and pairwise comparison.***
2. ***The inhibition of PR-B receptors by the elinzanetant metabolite M30/34 provides a mechanistic basis to support that these tumors are indeed elinzanetant-treatment related (See Biological Plausibility section below). This reviewer agrees that the tumor findings in the uterus and the hematolymphoid system are due to the elinzanetant treatment.***

3. ***Biological Plausibility of Elinzanetant-Related Carcinogenic Signals in Rats***
   According to the results of binding studies in the nonclinical reports R-14017, R-14018, and R-14019, the main elinzanetant metabolites – BAY 3462932 (M27), BAY 3462933 (M30/34), and BAY 346934 (M18/21) – inhibit [^{3}H]progesterone binding to the progesterone receptor B isoform (PR-B) ectopically expressed in human T-47D cells with Kis of approximately 1.08 µM, 0.96 µM, and 1.35 µM, respectively. Elinzanetant itself does not interact with PR-B.

   BAY 3462933 (M30/34) is the most abundant metabolite of elinzanetant in rats and humans. The toxicokinetic assessments conducted as part of the carcinogenicity study in rats revealed that C_{max} and AUC_{0-24h} of BAY 3462933 (M30/34) in rats treated with the elinzanetant dose of 60 mg/kg/day were 1430 µg/L (~2.1 µM, considering that the molecular weight attributed to the metabolite is ~685.3) and 32100 µg•h/L (~46.8 µM•h), respectively, on treatment day 358. These concentrations would be sufficient to inhibit by >50% the activity of PR-Bs.

   Since progesterone-induced PR-B activation is known to suppress proliferation of epithelial and stromal cells in the endometrium[6] and loss of PR-B has been associated with development of invasive endometrial

[6] Yang S, Thiel KW, Leslie KK. Progesterone: the ultimate endometrial tumor suppressor. Trends Endocrinol Metab. 2011 Apr;22(4):145-52. doi: 10.1016/j.tem.2011.01.005. Epub 2011 Feb 25. PMID: 21353793; PMCID: PMC4062362.

cancer in humans,[7] it is possible that PR-B inhibition by BAY 3462933 (M30/34) in the endometrium contributes to the increased incidence of endometrial cancer in rats treated with elinzanetant doses ≥60 mg/kg/day.

Although less is known about the role of PR-B receptors in lymphomas, it has been reported that progesterone can suppress the proliferation of T- and B-lymphoma cell lines.[8] If the antiproliferative effects of progesterone on lymphoma cells are mediated by PR-B signaling, BAY 3462933 (M30/34)-induced PR-B inhibition could also contribute to the increased incidence of malignant lymphoma in the hematolymphoid system of elinzanetant-treated female rats.

Elinzanetant-Associated Reduction of Incidence of Common Spontaneous Tumors in the Mammary, Thyroid, and Pituitary Glands

Compared to concurrent vehicle control female rats, the groups of female rats treated with elinzanetant doses ≥60 mg/kg/day presented with lower incidence of: (i) malignant adenocarcinoma, benign adenoma, benign fibroadenoma, and physiological and atypical hyperplasia in the mammary glands, (ii) adenomas in the pars distalis of the pituitary glands, and (iii) benign C-cell adenomas in the thyroid glands (Table 21). However, the magnitude of the effects did not reach statistical significance.

[7] Hanekamp EE, Gielen SC, Smid-Koopman E, Kühne LC, de Ruiter PE, Chadha-Ajwani S, Brinkmann AO, Grootegoed JA, Burger CW, Huikeshoven FJ, Blok LJ. Consequences of loss of progesterone receptor expression in development of invasive endometrial cancer. Clin Cancer Res. 2003 Sep 15;9(11):4190-9. PMID: 14519645.

[8] Seki T, Suzuki R, Ohshima S, Manabe Y, Onoue S, Hoshino Y, Yasuda A, Ito R, Kawada H, Ishimoto H, Shiina T, Kametani Y. Liposome-encapsulated progesterone efficiently suppresses B-lineage cell proliferation. Biochem Biophys Rep. 2024 Apr 11;38:101710. doi: 10.1016/j.bbrep.2024.101710. PMID: 38638674; PMCID: PMC11024493.

Table 21. Incidence and Severity of Neoplastic/Proliferative Findings in the Mammary, Pituitary, and Thyroid Glands of Female Rats [Adapted from the Applicant's Report].

Sex	Females				
Dose Level (mg/kg/day)	0	7	20	60	80
Number Examined	99	100	98	98	93
Mammary Gland					
M-Adenocarcinoma	9	9	6	0	0
B-Adenoma	4	1	0	0	0
B-Fibroadenoma	45	49	43	9	15
Hyperplasia, physiologic					
Total Incidence	20	16	14	2	1
Minimal	7	0	6	1	0
Slight	13	16	7	1	1
Moderate	0	0	1	0	0
Hyperplasia, atypical					
Total Incidence	3	1	2	0	0
Minimal	2	1	2	0	0
Slight	1	0	0	0	0
Number Examined	99	100	100	100	100
Pituitary Gland					
B-Adenoma, pars distalis	26	18	29	10	6
Number Examined	100	100	99	99	98
Thyroid Gland					
B-Adenoma, C-cell	15	16	7	3	0
Hyperplasia, C-cell					

B- = Benign; M- = Malignant.

Reviewer's Comment on Biological Plausibility of Apparent Reduction of Incidence of Histopathological Signals of Benign and Malignant Neoplasm in the Mammary Glands, Pituitary, and Thyroid Glands in Rats

According to a nonclinical pharmacological study, BAY 3462933 (M30/34) at 10 µM inhibited by ~60% binding of [^{3}H]estradiol to human estrogen receptor α (ERα) ectopically expressed in Sf9 cells (R-14018).

There are several reports that ERα activation can promote hyperplasia and tumor development in the mammary, thyroid, and pituitary glands.[9,10,11] Therefore, in rats treated with elinzanetant doses ≥60 mg/kg/day, BAY 3462933 (M30/34)-induced inhibition of ERα could contribute to the reduced incidence of: (i) mammary gland neoplasms and hyperplasia, (ii) pituitary adenomas, and (iii) thyroid C-cell adenomas.

9 Shull JD, Dennison KL, Chack AC, Trentham-Dietz A. Rat models of 17β-estradiol-induced mammary cancer reveal novel insights into breast cancer etiology and prevention. Physiol Genomics. 2018 Mar 1;50(3):215-234. doi: 10.1152/physiolgenomics.00105.2017. Epub 2018 Jan 26. PMID: 29373076; PMCID: PMC5899232.

10 Derwahl M, Nicula D. Estrogen and its role in thyroid cancer. Endocr Relat Cancer. 2014 Oct;21(5):T273-83. doi: 10.1530/ERC-14-0053. Epub 2014 Jul 22. PMID: 25052473.

11 Osamura RY. Pituitary Tumors Induced by Estrogen, Rat. In: Jones, T.C., Capen, C.C., Mohr, U. (eds) Endocrine System. Monographs on Pathology of Laboratory Animals. 1996. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-60996-1_9.

NK1/NK3 receptors are expressed in hypothalamic KNDy (Kisspeptin/Neurokinin B [NKB]/Dynorphin) neurons, and activation of these receptors in KNDy neurons increases the activity of gonadotropin-releasing hormone (GnRH)-expressing neurons that, in turn, stimulates the anterior pituitary gland to release gonadotrophins that induce the release of sex hormones from the gonads. Elinzanetant-induced inhibition of NK1/NK3 receptors may lead to a reduction of estradiol levels that could contribute to the apparent reduction of tumors and hyperplasia in estradiol-sensitive organs, including the mammary, pituitary, and thyroid glands.

Non-Neoplastic Findings

Adrenal gland: The increased absolute and relative weights of adrenal glands in rats treated with elinzanetant doses ≥60 mg/kg/day correlated with hyperplasia or hypertrophy of the zona fasciculata and/or the occurrence of adrenal cystic degeneration (Table 22).

Table 22. Microscopic Findings in the Adrenal Cortex of Female Rats at Necropsy [Table Excerpted from Applicant's Report].

	NT-814				
Sex	Females				
Dose Level (mg/kg/day)	0	7	20	60	80
Number Examined	100	100	100	99	99
Adrenal Cortex					
Hyperplasia, focal, zona fasciculata					
Total Incidence	5	6	8	16	13
Minimal	4	5	7	14	9
Slight	1	0	1	2	4
Moderate	0	1	0	0	0
Hypertrophy, zona fasciculata					
Total Incidence	15	15	21	27	20
Minimal	8	6	10	13	7
Slight	7	9	8	12	9
Moderate	0	0	3	2	4
Degeneration, cystic					
Total Incidence	21	27	28	45	41
Minimal	17	21	19	32	28
Slight	3	6	7	11	12
Moderate	1	0	2	2	1

Thymus: The decrease in thymus weights correlated with decreased lymphocytes in females treated with elinzanetant doses ≥60 mg/kg/day (Table 23).

Table 23. Microscopic Findings in the Thymus of Female Rats at Necropsy [Table Excerpted from Applicant's Report].

Sex	NT-814				
	Females				
Dose Level (mg/kg/day)	0	7	20	60	80
Number Examined	92	94	97	93	95
Thymus					
Hyperplasia, epithelium					
Total Incidence	58	70	75	74	76
Minimal	45	60	59	42	43
Slight	13	10	16	32	32
Moderate	0	0	0	0	1
Lymphocytes, decreased					
Total Incidence	55	51	59	62	69
Minimal	18	14	16	9	10
Slight	19	16	18	25	17
Moderate	16	20	20	22	16
Marked	2	1	5	6	26

Ovaries: Elinzanetant at doses ≥60 mg/kg/day increased the incidence of corpora lutea absence and hyperplasia of sex cord stromal/granulosa cells (Table 24).

Table 24. Microscopic Findings in the Ovaries of Female Rats at Necropsy [Table Excerpted from Applicant's Report].

Sex	NT-814				
	Females				
Dose Level (mg/kg/day)	0	7	20	60	80
Number Examined	100	100	100	99	100
Ovary					
Absence, corpora lutea					
Total Incidence	68	69	75	92	87
Hyperplasia, granulosa cell					
Total Incidence	0	0	0	1	3
Slight	0	0	0	1	2
Moderate	0	0	0	0	1
Hyperplasia, sex cord stromal cell, mixed					
Total incidence	5	7	6	10	12
Minimal	5	4	4	9	10
Slight	0	3	2	1	2

Mesenteric Lymph Node: Elinzanetant increased the incidence and severity of macrophage infiltrates in the mesenteric lymph node (Table 25).

Reference ID: 5523839

Table 25. Microscopic Findings in the Mesenteric Lymph Node of Female Rats at Necropsy [Table Excerpted from Applicant's Report].

	NT-814				
Sex	Females				
Dose Level (mg/kg/day)	0	7	20	60	80
Number Examined	100	100	100	100	100
Mesenteric Lymph Node					
Infiltrate, macrophage					
Total Incidence	34	41	42	66	70
Minimal	31	35	32	43	33
Slight	3	6	10	23	37

Vagina: Elinzanetant dose dependently reduced vaginal mucification (Table 26).

Table 26. Microscopic Findings in the Vagina of Female Rats at Necropsy [Table Excerpted from Applicant's Report].

	NT-814				
Sex	Females				
Dose Level (mg/kg/day)	0	7	20	60	80
Vagina					
Number Examined	99	97	100	99	99
Mucification, epithelium					
Total incidence	20	16	12	2	2
Minimal	2	2	3	0	1
Slight	17	13	8	2	1
Moderate	1	1	1	0	0

Toxicokinetics

Blood samples for TK analysis were collected on treatment days 1, 176, 358, and 694 from the satellite animals at different time points after treatment on each day. The TK parameters of day 694 are only rough estimates because of the sampling scheme and are not used to estimate clinical exposure margins.

On all test days, systemic exposures to the parent compound elinzanetant and its metabolites BAY3462932 (M27), BAY3462933 (M30/34), and BAY3462934 (M18/21) increased as the oral gavage dose of the parent compound increased from 7 to 80 mg/kg/day (Table 27). The metabolites BAY3462932 and BAY3462933 were quantifiable in blood from animals treated with all doses of elinzanetant on days 1, 176, 358, and 694. Metabolite BAY3462934 was quantifiable in blood from animals treated with elinzanetant doses ≥20 mg/kg/day on days 1, 176, 358, and 694 and in blood from animals treated with the low dose of 7 mg/kg/day on days 176, 358, and 694.

As shown in Table 27, exposures to the metabolites were markedly lower than the exposure to the unchanged parent drug. In agreement with previous pharmacokinetic studies, metabolite BAY3462933 (M30/34) is the most prevalent in elinzanetant-treated rats (as it is in humans treated with elinzanetant).

Reference ID: 5523839

Table 27. Toxicokinetic Parameters of Elinzanetant on Treatment Day 358 Following Oral Administration to Female Rats [Reviewer-Generated Table].

		Elinzanetant Doses			
		7 mg/kg/day	20 mg/kg/day	60 mg/kg/day	80 mg/kg/day
Elinzanetant	C_{max} (µg/L)	1020	3980	12500	14100
	AUC_{0-12h} (µg•h/L)	9970	36200	132000	143000
	AUC_{0-24h} (µg•h/L)	17600	64000	252000	280000
BAY 3462932 (M27)	C_{max} (µg/L)	8.2	29.4	96.5	144
	AUC_{0-12h} (µg•h/L)	67.7	285	990	1380
	AUC_{0-24h} (µg•h/L)	117	550	2020	2960
BAY 3462933 (M30/34)	C_{max} (µg/L)	456	794	1430	1680
	AUC_{0-12h} (µg•h/L)	4070	8490	15600	18400
	AUC_{0-24h} (µg•h/L)	7700	17000	32100	38000
BAY 3462934 (M18/21)	C_{max} (µg/L)	2.9	6.35	11.6	17.3
	AUC_{0-12h} (µg•h/L)	30.3	59.1	113	160
	AUC_{0-24h} (µg•h/L)	53.1	119	237	348

While the carcinogenicity study generated adequate clinical exposure margins for the parent drug and its predominant metabolite in humans (M30/34), it provided very low exposure margins to the other two main metabolites (M27 and M18/21) (Table 28).

Table 28. Clinical Exposure Margins to Elinzanetant and Its Metabolites Estimated on the Basis of AUCs [Reviewer-Generated Table].

		Rat dose: 20 mg/kg/day		Rat dose: 60 mg/kg/day	
	AUC_{0-24h} (µg•h/L) at MRHD[a]	AUC_{0-24h} (µg•h/L)	Exposure Margins	AUC_{0-24h} (µg•h/L)	Exposure Margins
Elinzanetant	8572.0	64000	7.5x	252000	29.4x
M27	2496.3	550	0.2x	2020	0.8x
M30/34	4570.1	17000	3.7x	32100	7.0x
M18/21	2326.3	119	0.05x	237	0.1x

[a]AUC_{0-24h} values are from the clinical study number CPM50130 (report number B002427).

4.2 Study title: A 26-Week Carcinogenicity and Toxicokinetic Study of BAY 3427080 (NT-814) When Administered Twice Daily via Oral Gavage to Transgenic Mice

Study no.:	B003184 [Bayer study ID T105265-9]
Study report location:	NDA 219469, SDN 6 [SN 0006]
Conducting laboratory and location:	(b) (4)
Date of study initiation:	01/09/2023
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	180621 (99.62%)
CAC concurrence:	Protocol: 12-06-2022 Final study: TBD

Key Study Findings
There were no statistically significant neoplastic findings related to elinzanetant (BAY 3427080).

No BAY 3427080-related non-neoplastic lesions were observed.

Adequacy of Carcinogenicity Study
The Division considers the transgenic mouse study an adequate assessment of carcinogenic potential because the high dose of BAY 3427080 was based on MTD and doses recommended by the Exec CAC were utilized. A single intraperitoneal dose of N-methyl-N-nitrosourea (MNU) at 75 mg/kg/day was used as a positive control.

The decrease in survival and occurrence of MNU-related findings of neoplasia (such as malignant lymphomas in the hematolymphoid system, squamous cell papilloma and/or adenoma in the nonglandular stomach and skin/subcutis) were consistent with the published literature for the rasH2 transgenic mice administered MNU, validating the model for this study.

Tables 7A and 7B (pages 72-73) in the appended statistical report summarize the findings of the analysis conducted by the FDA statistical reviewer for tumor rates and p-values for dose-response relationship trends and for pairwise comparisons between vehicle control mice and elinzanetant-treated mice or positive control mice.

Appropriateness of Test Models
Yes.

Evaluation of Tumor Findings
Negative.

Reference ID: 5523839

Methods

Doses:	0 (1% w/v MC: vehicle control) 10, 30, and 85 mg/kg/day (males) 10, 20, 70 mg/kg/day (females) N-methyl-N-nitrosourea (MNU) 75 mg/kg/day (positive control) Elinzanetant batch no# 7486-P54/20-002 (purity 100.7%)
Frequency of dosing:	BID (twice daily, 6 hr apart)
Dose volume:	5 mL/kg/dose for treatment groups; 10 mL/kg for positive control
Route of administration:	Oral gavage
Formulation/Vehicle:	1% w/v methylcellulose solution
Basis of dose selection:	MTD. Sponsor conducted study at the doses that were recommended by the Exec CAC committee. The Exec CAC protocol minutes can be found appended in DARRTS review dated 12/13/2022 under IND 129462
Species/Strain:	Tg.rasH2
Number/Sex/Group:	25/sex/group
Age:	7 to 8 weeks of age
Animal housing:	Up to 3 animals/cage
Paradigm for dietary restriction:	Allowed free access to pelleted diet and tap water
Dual control employed:	Yes
Interim sacrifice:	No
Satellite groups:	Yes, TK animals.
Deviation from study protocol:	No effect on the study findings.

Study design

		Dose Level[b]				Dose Concentration[b]		Number of Animals	
Group[a]	Subgroup	Males (mg/kg/dose)	Females (mg/kg/dose)	Males (mg/kg/day)[c]	Females (mg/kg/day)[c]	Males (mg/mL)	Females (mg/mL)	Males	Females
1 (Control)	1 (Carcinogenicity)	0	0	0	0	0	0	25	25
	2 (Toxicokinetic)	0	0	0	0	0	0	3	3
2 (Low)	1 (Carcinogenicity)	5	5	10	10	1.0	1.0	25	25
	2 (Toxicokinetic)	5	5	10	10	1.0	1.0	18	18
3 (Intermediate)	1 (Carcinogenicity)	15	10	30	20	3.0	2.0	25	25
	2 (Toxicokinetic)	15	10	30	20	3.0	2.0	18	18
4 (High)	1 (Carcinogenicity)	42.5	35	85	70	8.5	7.0	25	25
	2 (Toxicokinetic)	42.5	35	85	70	8.5	7.0	18	18
5 (Positive Control)[d]	1 (Carcinogenicity)	75	75	75	75	7.5	7.5	10	10

a Group 1 was administered vehicle control item only.
b Animals in Groups 1 through 4 were dosed at a volume of 5 mL/kg/dose (10 mL/kg/day). Animals in Group 5 were dosed at 10 mL/kg.
c The second daily dose was administered 6 hours (± 15 minutes) after the first daily dose for animals in Groups 1 through 4.
d Group 5 was dosed with one intraperitoneal dose of N-methyl-N-nitrosourea (MNU) on Day 1 of the dosing phase. These animals were included as positive controls to ensure animals supplied appropriately expressed oncogenes and responded to carcinogenic insult.

Observations and Results

Mortality

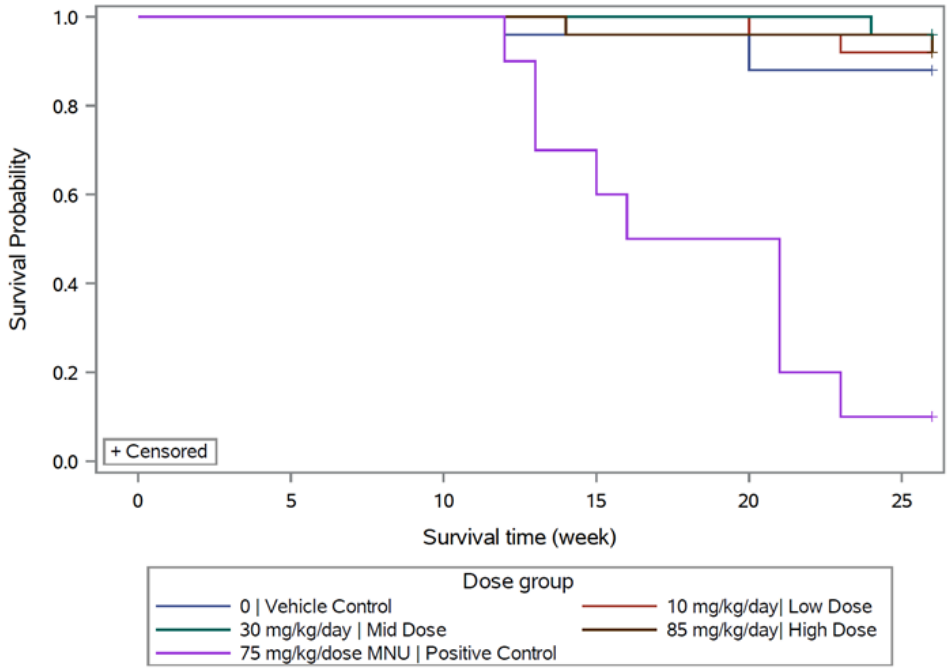
There were no test article-related changes in survival rate.

Reference ID: 5523839

- **FDA Statistical reviewer, Feng Zhou, agreed with the Applicant's survival analysis that there was no treatment related effect on survival.**
- The numbers (percent) of death that occurred prior to termination of the group were 3 (12%), 2 (8%), 1 (4%), 2 (8%), or 9 (90%) in male mice and 3 (12%), 0, 0, 2 (8%), or 8 (80%) in female mice in the vehicle control (VC), low dose (LD), mid dose (MD), high dose (HD) or positive control (PC) groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males or females when data of the PC group were excluded. The mortality rates for the PC group were statistically significantly higher than that for the VC group for both male and female mice.

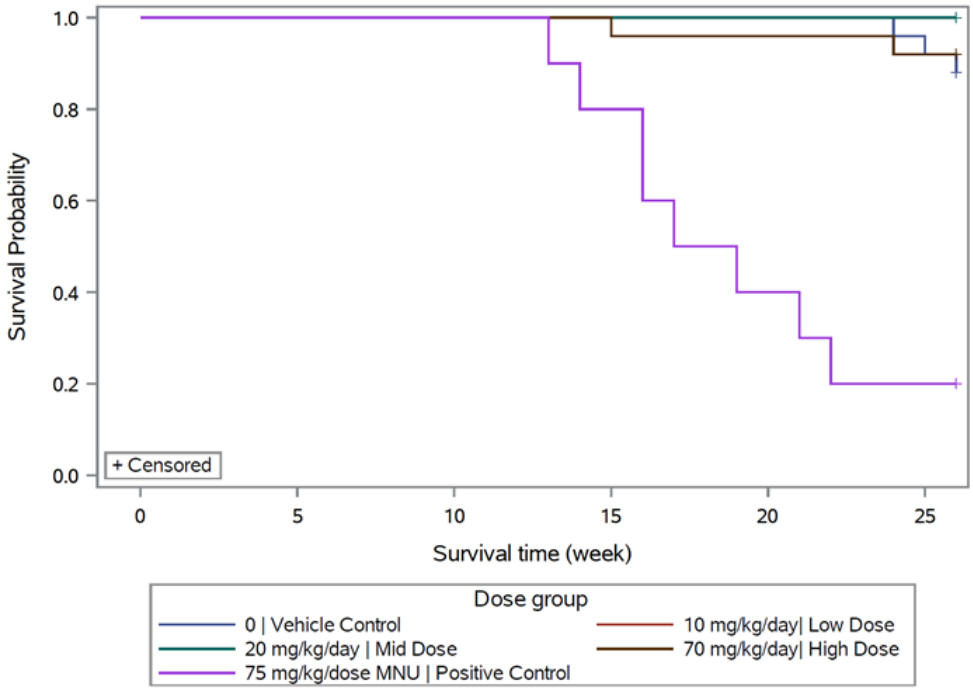
The Kaplan-Meier curves for survival rates of all treatment groups are shown below. The figures below are extracted from the statistical review by FDA Statistical reviewer, Feng Zhou.

Figure 3. Kaplan-Meier Adjusted Survival Data (Male Mice).



[Extracted from FDA's stat review]

Figure 4. Kaplan-Meier Adjusted Survival Data (Female Mice).



[Extracted from FDA's stat review]

- There were no differences in the intercurrent mortality rate between treated and control groups in both male and female mice.

Early deaths were considered not BAY 3427080-related and did not increase the number of deaths attributable to specific neoplasms or non-neoplastic lesions. Unscheduled necropsy included 3 M and 3F in vehicle control, 2 M at LD, 1 M at MD, 1 M at HD and 2F at HD.

Table *29*. Summary Incidence and Cause of Early Death/Moribund Condition.

Animal Number	Group	Sex	Dose Level (mg/kg/day)	Day of Necropsy	Cause of Death/Moribund Condition
M0009[a]	1	M	0	134	Undetermined
M0014[a]	1	M	0	82	Undetermined
M0025[a]	1	M	0	137	Undetermined
M0120	2	M	10	160	Hemangiosarcoma
M0122	2	M	10	138	Undetermined
M0205	3	M	30	168	Hemangiosarcoma
M0312	4	M	85	181	Hemangiosarcoma
M0503[a]	1	F	0	169	Undetermined
M0507[a]	1	F	0	176	Undetermined
M0508[a]	1	F	0	168	Carcinoma, Lung
M0812	4	F	70	102	Papilloma, Squamous Cell
M0820	4	F	70	168	Hemangiosarcoma

F = Females; M = Males.
a Vehicle control.

[Extracted from the Study No. B003184 study report page 41.]

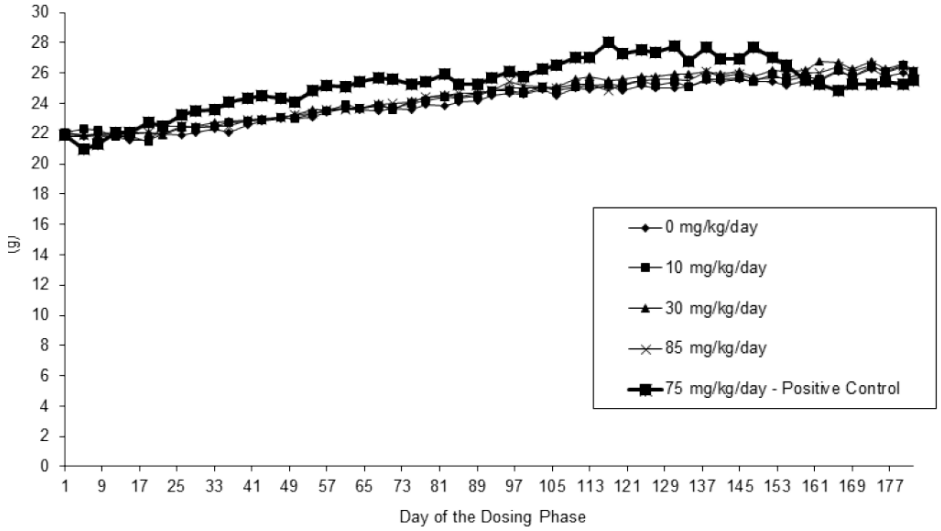
Clinical Signs

No BAY 3427080-related clinical observations were noted.

Body Weights

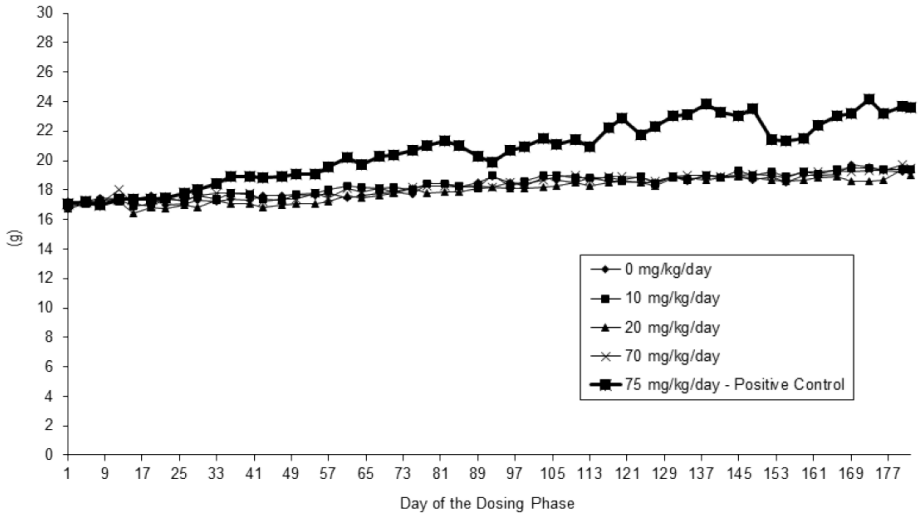
No test item-related effect on body weight or body weight gain were noted.

Figure *5*. Mean Body Weight (Males).



[Extracted from study no B003184 report page 58]

Figure *6*. Mean Body Weight (Females).

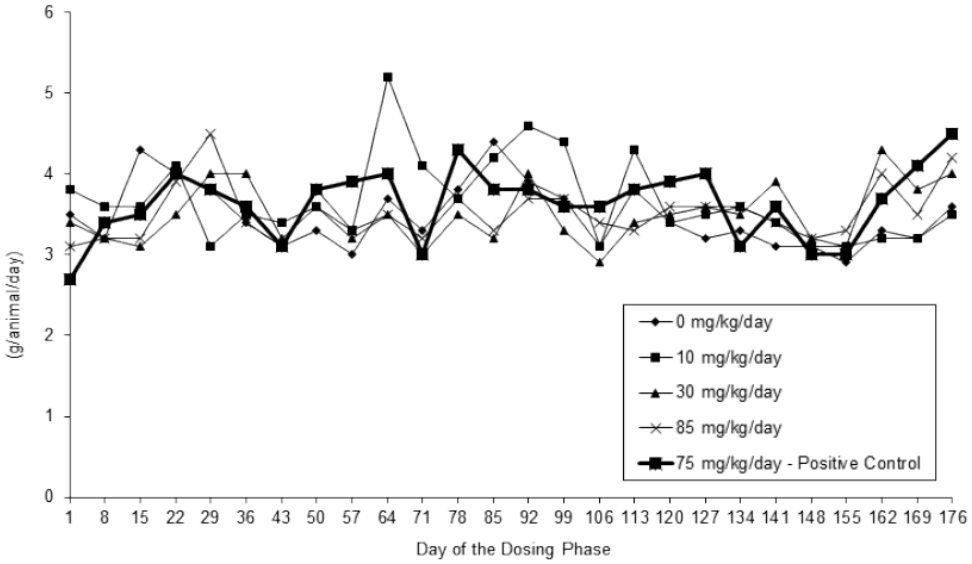


[Extracted from study no B003184 report page 59]

Feed Consumption

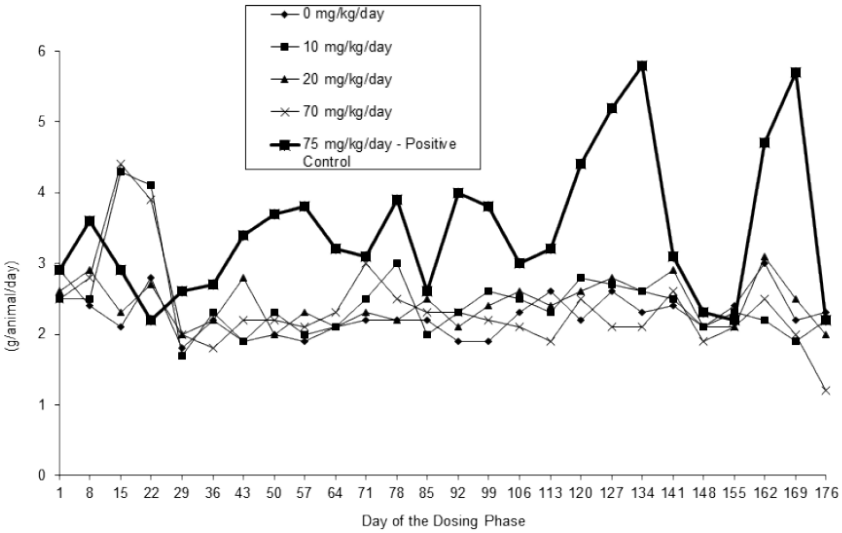
No test item-related effect on food consumption was noted.

Figure *7*. Mean food consumption (males).



[Extracted from the Study No. B003184 study report page 60]

Figure *8*. Mean Food Consumption (Females).



[Extracted from the Study No. B003184 study report page 61]

Gross Pathology
No test item-related effect

Histopathology

Peer Review
Yes.

Neoplastic Findings

- **FDA's statistical reviewer's findings**

There were no statistically significant positive dose response relationships among the BAY 3427080 treated groups and vehicle control group for male and female mice when data of the positive control group were excluded. There were also no tumor types with a statistically significant increase in tumor incidences in BAY 3427080 treated groups by the pairwise comparison test, when compared to the vehicle control group in either male or female mice.

- **Applicant's findings**

Overall, the Applicant determined that there were no neoplastic findings attributed to BAY 3427080 in this assay.

Reference ID: 5523839

Table 30. Incidence of Primary Neoplastic Findings - All Animals (Groups 1-4).

	BAY 3427080 (NT-814)							
Sex	Males				Females			
Dose Level (mg/kg/day)	0	10	30	85	0	10	20	70
Number of Animals	25	25	25	25	25	25	25	25
Vascular Neoplasms[a]								
M-Hemangiosarcoma	2	1	1	1	0	2	0	1
Lung								
B-Adenoma, bronchiolo-alveolar	2	2	1	2	1	1	1	0
M-Carcinoma, bronchiolo-alveolar	0	0	0	0	1	0	0	0
Liver								
B-Adenoma, hepatocellular	0	0	1	0	0	0	0	0
Stomach, Nonglandular								
M-Carcinoma, squamous cell	0	0	0	0	0	1	0	0
Skin/subcutis								
B-Papilloma, squamous cell	0	0	0	0	0	0	0	1
Harderian Gland								
B-Adenoma	0	0	0	0	0	0	1	0

B = Benign; M = Malignant.
a Present in multiple tissues, including the spleen, skin/subcutis, and testis.

[Extracted from the Study No. B003184 study report page 43]

However, the Applicant noted that there was a statistically significant increased incidence for the neoplastic finding of **squamous cell papilloma in the skin/subcutis [benign]** observed for females administered HD (70 mg/kg/day). The following table presents the statistically significant results:

Females

Tissue and Lesion	Rare or Common	Test	Unadjusted p-value	FDA Interpretation
Skin/Subcutis B-Papilloma, squamous cell	Rare	Trend	0.0473 (LR, W)	Significant (p<0.05)

LR = Log-Rank, W = Wilcoxon
[Extracted from the Study No. B003184 (statistical analysis contributory report) study report page 2436]

Results of Statistical Analysis of Neoplastic Lesions - Females

			Unadjusted Lifetime Incidence Rate			
	Group	Trend	1	2	3	4
Tissue and Lesion	Dose Level (mg/kg/day)	(1,2,3,4)	0	10	20	70
Skin/Subcutis						
B-Papilloma, squamous cell						
	No. Examined		25	25	25	25
	Fatal Tumors		0	0	0	1
	Incidental Tumors		0	0	0	0
	Total Tumors		0	0	0	1
	Log-Rank P-value (v1)	0.0473*	N/A	N/A	N/A	0.1587
	Wilcoxon P-value (v1)	0.0473*	N/A	N/A	N/A	0.1587

* = Significant at 5% level

Sponsor notes that this finding was considered not related to BAY 3427080 because it was a single papilloma in the perianal region limited to one female (Animal M0812) administered 70 mg/kg/day; no corresponding progression for other proliferative or neoplastic findings (e.g., epidermal hyperplasia or carcinoma, respectively) was noted in females or males (the latter of which were administered a higher dose of 85 mg/kg/day); and the tumor in this female was noted macroscopically at the perianal region, a typical site of chronic grooming (e.g., ano-urogenital region, ears, nose, etc.) for which cutaneous squamous cell papilloma is documented to occur spontaneously in transgenic mice (Mecklenburg, et al., 2013)[12].

> ***Reviewer Comment*: Based on the FDA Statistical reviewer's assessment, the neoplastic finding of squamous cell papilloma in the skin/subcutis [benign] observed in one female administered HD (70 mg/kg/day) was not statistically significant by trend or pairwise tests as compared to the concurrent vehicle control group.**

Non-Neoplastic
No non-neoplastic findings related to BAY 3427080 were identified.

The Applicant noted microscopic findings of minimal or slight myocyte degeneration/regeneration, sometimes accompanied by mononuclear and/or mixed cell infiltrates, in the biceps femoris muscle of almost all animals from all groups, including concurrent controls (vehicle and positive control groups), was consistent with the spontaneously occurring skeletal muscle myopathy reported for this transgenic mouse strain (Tsuchiya et al., 2002).[13]

Toxicokinetics
In the toxicokinetics analysis, the systemic exposure to BAY 3427080 and its major metabolites, M27, M30/34, M18/21, was demonstrated.

- In male mice, BAY 3427080 exposure increased moderately more than dose-proportionally from 10 to 30 mg/kg/day in terms of $AUC_{0\text{-}24h}$ and C_{max}, while from 30 to 85 mg/kg/day $AUC_{0\text{-}24h}$ and C_{max} increased about dose-proportionally.
- In female mice, BAY 3427080 exposure increased slightly more than dose-proportionally from 10 to 20 mg/kg/day in terms of $AUC_{0\text{-}24h}$ and markedly more than dose proportional for C_{max}; while from 20 to 70 mg/kg/day $AUC_{0\text{-}24h}$ and C_{max} increased moderately more than dose-proportional and about dose-proportional, respectively.

[12] Mecklenburg L, Kusewitt D, Kolly C, et al (2013) Proliferative and non-proliferative lesions of the rat and mouse integument. J Toxicol Pathol; 26(3 Suppl):27S-57S.
[13] Tsuchiya T, Kobayashi K, Sakairi T, et al (2002) Skeletal myopathy in transgenic mice carrying human prototype c-Ha-ras gene. Toxicol Pathol; 30(4):501-506.

Table *31*. Systemic Exposure Summary of BAY 3427080 [Elinzanetant/Parent Compound] on Day 182.

Day 182		Female	Female	Female	Male	Male	Male
Group		2F	3F	4F	2M	3M	4M
Dose	[mg/kg/day]	10	20	70	10	30	85
Parameter	Unit						
$AUC_{(0-9h)}$	µg*h/L	634	1790	7960	775	3200	11700
$AUC_{(0-9h),\ norm}$	kg*h/L	0.0634	0.0896	0.114	0.0775	0.107	0.137
$AUC_{(0-24h)}$	µg*h/L	1000	2980	17500	1330	7010	23900
$AUC_{(0-24h),\ norm}$	kg*h/L	0.1	0.149	0.251	0.133	0.234	0.281
t_{last}	h	24	24	24	24	24	24
C_{max}	µg/L	109	459	1410	125	561	1770
$C_{max,\ norm}$	kg/L	0.0109	0.0229	0.0201	0.0125	0.0187	0.0209
t_{max}	h	7	7	7	7	9	7
C_{last}	µg/L	6.75	39.9	320	14.9	86.8	408
$C(t_{int})/C_{max}$	%	6.2	8.7	22.7	11.9	15.5	23
$RA\text{-}AUC_{(0-9h)}$	%	85.2	114.7	115	95.9	63.9	79.6
$RA\text{-}AUC_{(0-24h)}$	%	73.5	111.2	124.1	91.1	75.2	86.3
$RA\text{-}C_{max}$	%	58.6	128.9	115.6	89.9	53.9	47.2
$R_{F/M}\ AUC_{(0-9h),\ norm}$		0.8	0.8	0.8			
$R_{F/M}\ AUC_{(0-24h),\ norm}$		0.8	0.6	0.9			
$R_{F/M}\ C_{max,\ norm}$		0.9	1.2	1.0			

[Extracted from the Study No. B003184 study report page 37]

Exposure of elinzanetant in women at once daily dose of 120 mg (study B002427, module 5.3.3.5) is:
C_{max} = 1423 µg/L and AUC_{0-24h} = **8572 µg•h/L** [total exposure]

Hence, for the highest dose in male mice, the MOE based on exposure (AUC) is **2.8-fold** (C_{max} of 1770 µg/L and AUC_{0-24h} of 23900 µg•h/L at the high dose of 85 mg/kg/day)

for the highest dose in female mice, the MOE based on exposure (AUC) is **2.0-fold** (C_{max} of 1410 µg/L and AUC_{0-24h} of 17500 µg•h/L at the high dose of 70 mg/kg/day).

Table 32. Systemic Exposure Summary of BAY 3462932 [Metabolite M 27] on Day 182.

Day 182		Female	Female	Female	Male	Male	Male
Group		2F	3F	4F	2M	3M	4M
Dose	[mg/kg/day]	10	20	70	10	30	85
Parameter	Unit						
$AUC_{(0-9h)}$	µg*h/L	n.c.	60.8	322	n.c.	82.7	501
$AUC_{(0-9h),\ norm}$	kg*h/L	n.c.	0.00296	0.00449	n.c.	0.00269	0.00575
$AUC_{(0-24h)}$	µg*h/L	n.c.	n.c.	647	n.c.	n.c.	936
$AUC_{(0-24h),\ norm}$	kg*h/L	n.c.	n.c.	0.00903	n.c.	n.c.	0.0108
t_{last}	h	7	9	24	7	9	24
C_{max}	µg/L	2.72	18.7	55.7	2.30	16.3	78.7
$C_{max,\ norm}$	kg/L	0.000267	0.000914	0.000777	0.000225	0.000530	0.000905
t_{max}	h	7	7	7	7	7	7
C_{last}	µg/L	2.72	3.91	7.57	2.3	13.3	10.1
$C(t_{int})/C_{max}$	%	n.c.	n.c.	13.6	n.c.	n.c.	12.8
$RA\text{-}AUC_{(0-9h)}$	%	n.c.	131.9	85.4	n.c.	61.3	107.1
$RA\text{-}AUC_{(0-24h)}$	%	n.c.	n.c.	89.7	n.c.	n.c.	104.9
$RA\text{-}C_{max}$	%	50	167	74.4	93.1	48.8	70.9
$MR\text{-}AUC_{(0-9h),norm}$ (BAY 3462932)	%	n.c.	3.3	3.9	n.c.	2.5	4.2
$MR\text{-}AUC_{(0-24h),norm}$ (BAY 3462932)	%	n.c.	n.c.	3.6	n.c.	n.c.	3.8
$MR\text{-}C_{max,\ norm}$ (BAY 3462932)	%	2.4	4.0	3.9	1.8	2.8	4.3
$R_{F/M}\ AUC_{(0-9h),\ norm}$		n.c.	1.1	0.8			
$R_{F/M}\ AUC_{(0-24h),\ norm}$		n.c.	n.c.	0.8			
$R_{F/M}\ C_{max,\ norm}$		1.2	1.7	0.9			

[Extracted from the Study No. B003184 study report page 38]

Exposure of **M27** in women at once daily dose of 120 mg (study B002427, module 5.3.3.5; Phase 3 popPK model) is:
C_{max} = 256 µg/L and AUC_{0-24h} = **2496 µg•h/L** [total exposure]

- Hence, for the highest dose in **male mice**, the MOE based on exposure (AUC) is **0.4-fold** (C_{max} of 79 µg/L and AUC_{0-24h} of 936 µg•h/L at the high dose of 85 mg/kg/day)

- for the highest dose in **female mice**, the MOE based on exposure (AUC) is **0.3-fold** (C_{max} of 56 µg/L and AUC_{0-24h} of 647 µg•h/L at the high dose of 70 mg/kg/day).

Table *33*. Systemic Exposure Summary of BAY 3462933 [metabolite M30/34] on Day 182.

Day 182		Female	Female	Female	Male	Male	Male
Group		2F	3F	4F	2M	3M	4M
Dose	[mg/kg/day]	10	20	70	10	30	85
Parameter	Unit						
$AUC_{(0\text{-}9h)}$	µg*h/L	501	1210	3120	517	1480	3520
$AUC_{(0\text{-}9h),\ norm}$	kg*h/L	0.0491	0.0590	0.0435	0.0507	0.0481	0.0405
$AUC_{(0\text{-}24h)}$	µg*h/L	766	1910	7000	833	2930	7220
$AUC_{(0\text{-}24h),\ norm}$	kg*h/L	0.0751	0.0931	0.0977	0.0817	0.0955	0.083
t_{last}	h	24	24	24	24	24	24
C_{max}	µg/L	85.9	265	517	73.6	247	508
$C_{max,\ norm}$	kg/L	0.00842	0.0129	0.00722	0.00721	0.00805	0.00584
t_{max}	h	7	7	9	7	9	7
C_{last}	µg/L	3.58	14.8	105	5.06	25.2	107
$C(t_{int})/C_{max}$	%	4.2	5.6	20.4	6.9	10.2	21.0
$RA\text{-}AUC_{(0\text{-}9h)}$	%	75.2	96.8	75.4	85.0	66.4	72.7
$RA\text{-}AUC_{(0\text{-}24h)}$	%	68.4	91.4	86.4	82.5	70.6	68.1
$RA\text{-}C_{max}$	%	62.7	116.7	81.8	79.1	68.4	73.6
$MR\text{-}AUC_{(0\text{-}9h),norm}$ (BAY 3462933)	%	77.4	65.8	38.2	65.4	45.0	29.6
$MR\text{-}AUC_{(0\text{-}24h),norm}$ (BAY 3462933)	%	75.1	62.5	38.9	61.4	40.8	29.5
$MR\text{-}C_{max,\ norm}$ (BAY 3462933)	%	77.2	56.3	35.9	57.7	43.0	27.9
$R_{F/M}\ AUC_{(0\text{-}9h),\ norm}$		1.0	1.2	1.1			
$R_{F/M}\ AUC_{(0\text{-}24h),\ norm}$		0.9	1.0	1.2			
$R_{F/M}\ C_{max,\ norm}$		1.2	1.6	1.2			

[Extracted from the Study No. B003184 study report page 39]

Exposure of **M30/34** in women at once daily dose of 120 mg (study B002427, module 5.3.3.5; Phase 3 popPK model) is:
C_{max} = 496 µg/L and $AUC_{0\text{-}24h}$ = **4570 µg•h/L** [total exposure]

- Hence, for the highest dose in **male mice**, the MOE based on exposure (AUC) is **1.6-fold** (C_{max} of 508 µg/L and $AUC_{0\text{-}24h}$ of 7220 µg•h/L at the high dose of 85 mg/kg/day)

- And for the highest dose in **female mice**, the MOE based on exposure (AUC) is **1.5-fold** (C_{max} of 517 µg/L and $AUC_{0\text{-}24h}$ of 7000 µg•h/L at the high dose of 70 mg/kg/day).

Table *34*. Systemic Exposure Summary of BAY 3462934 [Metabolite M18/21] on Day 182.

Day 182		Female	Female	Female	Male	Male	Male
Group		2F	3F	4F	2M	3M	4M
Dose	[mg/kg/day]	10	20	70	10	30	85
Parameter	Unit						
$AUC_{(0-9h)}$	µg*h/L	n.c.	46.6	126	n.c.	43.4	141
$AUC_{(0-9h),\ norm}$	kg*h/L	n.c.	0.00222	0.00172	n.c.	0.00138	0.00158
$AUC_{(0-24h)}$	µg*h/L	n.c.	n.c.	270	n.c.	n.c.	266
$AUC_{(0-24h),\ norm}$	kg*h/L	n.c.	n.c.	0.00368	n.c.	n.c.	0.00298
t_{last}	h	7	9	24	7	9	24
C_{max}	µg/L	2.81	11.5	20.1	1.30	6.97	23.1
$C_{max,\ norm}$	kg/L	0.000268	0.000549	0.000274	0.000124	0.000222	0.000259
t_{max}	h	1	7	9	3	1	1
C_{last}	µg/L	2.78	3.55	3.56	1.14	6.45	2.93
$C(t_{int})/C_{max}$	%	n.c.	n.c.	17.7	n.c.	n.c.	12.7
$RA\text{-}AUC_{(0-9h)}$	%	n.c.	120.7	58.1	n.c.	64.9	83.4
$RA\text{-}AUC_{(0-24h)}$	%	n.c.	n.c.	68.0	n.c.	n.c.	81.3
$RA\text{-}C_{max}$	%	58.3	150.5	56.6	64.7	52.4	84.6
$MR\text{-}AUC_{(0-9h),norm}$ (BAY 3462934)	%	n.c.	2.5	1.5	n.c.	1.3	1.2
$MR\text{-}AUC_{(0-24h),norm}$ (BAY 3462934)	%	n.c.	n.c.	1.5	n.c.	n.c.	1.1
$MR\text{-}C_{max,\ norm}$ (BAY 3462934)	%	2.5	2.4	1.4	1.0	1.2	1.2
$R_{F/M}\ AUC_{(0-9h),\ norm}$		n.c.	1.6	1.1			
$R_{F/M}\ AUC_{(0-24h),\ norm}$		2.0	n.c.	1.2			
$R_{F/M}\ C_{max,\ norm}$		2.2	2.5	1.1			

[Extracted from the Study No. B003184 study report page 40]

Exposure of **M18/21** in women at once daily dose of 120 mg (study B002427, module 5.3.3.5; Phase 3 popPK model) is:
C_{max} = 280 µg/L and AUC_{0-24h} = **2326 µg•h/L** [total exposure]

- Hence, for the highest dose in **male mice**, the MOE based on exposure (AUC) is **0.11-fold** (C_{max} of 23.1 µg/L and AUC_{0-24h} of 266 µg•h/L at the high dose of 85 mg/kg/day)

- And for the highest dose in **female mice**, the MOE based on exposure (AUC) is **0.11-fold** (C_{max} of 20.1 µg/L and AUC_{0-24h} of 270 µg•h/L at the high dose of 70 mg/kg/day).

Unbound fraction and MoE calculations:
The fraction unbound values for human and mouse was derived from the invitro plasma protein binding studies PH-42081 and PH-42138 and used to calculate unbound exposure for elinzanetant and the metabolites, as well as the MoE. These are summarized in the table below:

Table *35*. Systemic Exposure in Mice Carcinogenicity Study and Margins of Exposure Compared to Human Exposure at 120 mg/day [Reviewer-Generated Table]**.**

NOAEL/High dose [mg/kg]*	Sex		Total exposure $AUC_{0\text{-}24h}$ [µg•h/L]	MoE [total]#	Unbound exposure $AUC_{0\text{-}24h}$ [µg•h/L]##	MoE [unbound] ###
	Elinzanetant (BAY 3427080)					
85	M		23900	2.8 x	550	21 x
70	F		17500	2.0 x	464	18 x
	M27					
85	M		936	0.4 x	11.51	6.6 x
70	F		647	0.3 x	12.94	7.5 x
	M30/33					
85	M		7220	1.6 x	48.37	2.1 x
70	F		7000	1.5 x	81.9	3.5 x
	M18/21					
85	M		266	0.1 x	7.71	3.3 x
70	F		270	0.1 x	7.56	3.3 x

F= female; M=male; NOAEL= No Observed Adverse Effect Level; $AUC_{0\text{-}24h}$: area under the curve over the last 24-hour dosing interval; MoE= margins of exposure (when compared to the human plasma levels at 120 mg/day)

* Bid = The daily dose was administered to the animals in 2 doses

\# Based on $AUC_{0\text{-}24h}$ of 8572 ng•h/mL (Elinzanetant), 2496 ng•h/mL (M27), 4570 ng•h/mL (M30/33), 2326 ng•h/mL (M18/21), obtained from clinical study B002427.

fu (fraction unbound) mouse = 2.30/2.65% (M/F) for Elinzanetant, 1.23/2.0% for M27 (M/F), 0.67/1.17% for M30/34 (M/F), 2.9/2.8% (M/F) for M18/21 (based on invitro plasma protein binding studies PH-42081 and PH-42138).

Based on AUC0-24h of 25.9 ng•h/mL (Elinzanetant), 1.74 ng•h/mL (M27), 22.85 ng•h/mL (M30/33), 2.32 ng•h/mL (M18/21) calculated using fu (fraction unbound) human= approximately 0.3% for Elinzanetant, 0.07% for M27, 0.5% for M30/34, 0.1% for M18/21 (based on in-vitro plasma protein binding studies PH-42081 and PH-42138).

Dosing Solution Analysis

Homogeneity criteria was met. All formulations were within ±15% of the target concentrations (ranging from 86.7 to 102% of the theoretical), with a few minor exceptions:

Day 50:

- 1 mg/mL formulation [used in LD M and F] was 82.6 and 83.1% of the theoretical concentration.
- 2 mg/mL formulation [used in MD F] was 72.8 and 74.0% of the theoretical concentration.
- 3 mg/mL formulation [used in MD M] was 83.9 and 82.0%.

Day 182:

- 3 mg/mL formulation [used in MD M] was 84.2 and 82.5%

APPENDIX

Appendix 1: NDA 219469: FDA Statistical Review and Evaluation Carcinogenicity Studies by Feng Zhou, MS (CDER/OTS/Office of Biostatistics), dated December 12, 2024

Appendix 2: NDA 219469: Executive Carcinogenicity Assessment Committee (ECAC) Final Study Agreement, dated December 20, 2024

Appendix 3: IND 129492: Executive Carcinogenicity Assessment Committee (ECAC) SPA Agreement for mouse study, dated December 08, 2022

Appendix 4: IND 129492: Executive Carcinogenicity Assessment Committee (ECAC) SPA Agreement for rat study, dated October 19, 2020

APPENDIX 1

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA219469
Drug Name:	Elinzanetant (BAY 3427080, NT-814)
Indication(s):	The treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.
Applicant:	Bayer Healthcare Pharmaceuticals Inc. PO box 0915, 100 Bayer Blvd., Whippany, NJ 07981-0915, USA Laboratory: (b) (4) (b) (4)
Date(s):	Received 8/27/2024
Documents Reviewed:	Study t105128-7 (rats) and Study t105265-9 (mice) reports and the electronic tumor.xpt and SEND datasets were submitted on 7/26/2024 (via NDA 219469/S-0001).
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, MS
Concurring Reviewers:	Atiar Mohammad Rahman, PhD, Team Leader
Medical Division:	CDER/OND/ORPURM/DUOG/ Division of Urology, Obstetrics, and Gynecology
Nonclinical Team:	Prati Tamrakar, PhD; Andrea L. Benedict, PhD
Project Manager:	
Keywords:	Carcinogenicity, Dose response

Reference ID: 5523897

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Reference ID: 5223897

1 Summary

This review evaluates statistically the data of a 2-year oral carcinogenicity study in female Sprague-Dawley rats and a 26-weeks oral carcinogenicity study in male and female Hemizygous rasH2 Transgenic mice. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality).

Rat Study: One hundred female rats per group (100/group) were dosed by oral gavage with NT-814 twice daily for up to 104 weeks. The respective NT-814 doses in the vehicle control (VC), low (LD), mid-low (ML), mid-high (MH), and high (HD) groups were 0, 7, 20, 60, and 80 mg/kg/day. The vehicle control item was 1% aqueous methylcellulose.

The survival analyses didn't show any statistically significant dose response relationship in mortality. The female rats were terminated at Week 104. The respective survival rates in the VC, LD, ML, MH, or HD groups at the time they were terminated were 44%, 39%, 38%, 42%, and 37%.

The tumor analysis showed that a positive dose response was statistically significant in the common tumor incidences of malignant lymphoma in hematolymphoid system ($p=0.0020<0.005$). For this tumor type, the incidences rate of HD group was statistically significantly greater than that of the VC group ($p=0.0087<0.01$). A positive dose response was statistically significant in the common tumor incidences of malignant adenocarcinoma endometrium and the combined tumor incidences of benign and malignant endometrium, and malignant squamous cell in uterus ($Ps<0.00001 <0.005$). For these tumor types, the incidences rates of MH and HD groups were statistically significantly greater than that of the VC group ($Ps<0.006<0.01$). A positive dose response was statistically significant in the rare tumor incidences of malignant carcinoma squamous cell in uterus ($Ps<0.0206 <0.025$). For this tumor type, the incidence rate in any dosed group was not statistically significantly greater than that of the vehicle control group.

Table 1: Tumor Types with Statistically Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Controls in Female Rats

Organ name	Tumor name	0 mg/kg/day Control P - Trend	7 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid-Low (ML) P - C vs. ML	60 mg/kg/day Mid-High (MH) P - C vs. MH	80 mg/kg/day High (H) P - C vs. H
Hematolymphoid System	M-Lymphoma	1/100 (72) 0.0020 *	3/100 (67) 0.2831	3/100 (71) 0.3046	6/100 (71) 0.0557	9/100 (72) 0.0087 **
Uterus	M-Adenocarcinoma, Endometrium	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	22/100 (75) 0.00001**
	M-Carcinoma, Squamous Cell	0/100 (72) 0.0206 *	0/100 (66) NC	1/100 (71) 0.4965	1/100 (69) 0.4894	3/100 (70) 0.1172
	C-Endometrium/B+M	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	23/100 (75) 0.00001 **
	C-Endometrium/B+M /Carcinoma, squamous cell	2/100 (72) 0.00001 *	3/100 (67) 0.4658	6/100 (71) 0.1330	16/100 (72) 0.0003 **	25/100 (75) 0.00001 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

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Mouse Study: Twenty-five mice per sex per group (25/sex/group) were dosed by oral gavage with NT-814 for up to 26 weeks. The respective NT-814 doses in the vehicle control (VC), low (LD), mid (MD), high-dose (HD) groups were 0, 10, 30, 85 mg/kg/day for male mice and 0, 10, 20, 70 mg/kg/day female mice. Twenty mice of the positive control (PC) group (10/sex/group) were dosed with one intraperitoneal dose of N-methyl-N-nitrosourea on day 1 of the dosing phase.

Excluding the PC group, the survival analyses didn't show any statistically significant dose response relationship in mortality in males and females. The respective survival rates in the VC, LD, MD, HD, and PC groups at the time they were terminated were 88%, 92%, 96%, 92%, and 10% in males and 88%, 100%, 100%, 92%, and 20% in females. The mortality rates for the PC group were statistically significantly higher than that for the VC group for both male and female mice.

Excluding the PC group, the tumor analysis showed that there were no statistically significant positive dose response relationships in any tumor types among the NT-814 treated groups and the VC group for male and female mice.

Reference ID: 5223897

2 Background

The sponsor, Bayer Healthcare Pharmaceuticals, Inc., is submitting a New Drug Application (NDA) 219469 for Elinzanetant (BAY 3427080, NT814) capsule for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. The sponsor submitted two carcinogenicity study reports: Study t105128-7: "A 104-Week Twice Daily Oral Gavage Toxicokinetic and Carcinogenicity Study with NT-814 (BAY3427080) in Sprague Dawley Rats" and Study t105265-9: "A 26-Week Carcinogenicity and Toxicokinetic Study of BAY 3427080 (NT-814) When Administered Twice Daily via Oral Gavage to Transgenic Mice". Study reports and electronic tumor.xpt and SEND datasets were submitted on 7/26/2024 (via NDA 219469/S-0001.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the nonclinical team.

3 Rat Study- t105128-7

Study Report: **t105128-7-pre-clinical-study-report.pdf (statistical report on page 6700)**
SAS data: **Tumor.xpt**

The objective of this study was to evaluate the carcinogenic potential and toxicokinetics of NT-814 (also known as BAY3427080 and elinzanetant) when administered twice daily (6 hours ± 30 minutes) via oral gavage to female Sprague Dawley (Hsd:Sprague Dawley SD) rats for at least 104 weeks. Female rats were assigned to five groups, and doses were administered as indicated in the following table. Animals were dosed via oral gavage at a volume of 5 mL/kg/dose (10 mL/kg/day). The vehicle control item was 1% aqueous methylcellulose.

Group[a]	Subgroup	Dose Level[b] (mg/kg/dose)	Dose Level[b] (mg/kg/day)	Dose Concentration[b] (mg/mL/dose)	Number of Animals (Females)
1 (Control)	1 (Carcinogenicity)	0	0	0	100
	2 (Toxicokinetic)	0	0	0	3
2 (Low)	1 (Carcinogenicity)	3.5	7	0.7	100
	2 (Toxicokinetic)	3.5	7	0.7	9
3 (Intermediate - Low)	1 (Carcinogenicity)	10	20	2	100
	2 (Toxicokinetic)	10	20	2	9
4 (Intermediate - High)	1 (Carcinogenicity)	30	60	6	100
	2 (Toxicokinetic)	30	60	6	9
5 (High)	1 (Carcinogenicity)	40	80	8	100
	2 (Toxicokinetic)	40	80	8	9

a Group 1 were administered vehicle control only.
b Animals were dosed at a volume of 5 mL/kg/dose (10 mL/kg/day).

Assessment of carcinogenicity was based on anatomic pathology to include incidences of masses or tumors and possible effects on survival. Mortality, clinical observations, body weight, and food consumption were also monitored and evaluated.

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3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Tests to compare survival were performed, with a two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response (vehicle control and treated groups only) and for each treated group against vehicle control using Kaplan-Meier product-limit estimation curves, along with log-rank and Wilcoxon tests. These were performed using the LIFETEST procedure in SAS. The time to death or sacrifice (in weeks) was the dependent variable. The treatment group was included as the stratum. Animals with a death or sacrifice status recorded as a planned terminal sacrifice or an accidental death were censored in the analysis.

time to death (weeks) =integer part of ([day of death - 1] / 7) + 1).

Sponsor's concluded results: No NT-814-related effects on survival were noted.

3.1.2 Tumor Data Analysis

Only tumors from tissues listed in the protocol to be examined for all animals were analyzed. Statistical analysis was performed for each given tumor type. Tests to compare tumor incidence were performed, with a one-sided risk for increasing incidence with dose. Tests were performed for dose response (vehicle control and treated groups only) and for each treated group against vehicle control.

For tumors occurring in animals dying spontaneously or sacrificed in a moribund condition, the Pathologist classified the context of observation as one of the following:

1. Fatal: The tumor was a factor in the demise of the animal.
2. Non-fatal: The tumor was not a factor in the demise of the animal.
3. Uncertain

Tumors (palpable and non-palpable) were analyzed by the IARC asymptotic fixed interval-based prevalence test (Peto et al., 1980). The cut off points for the interval-based test were Weeks 0 to 52, 53 to 78, 79 to 92, 93 to before terminal sacrifice, and the terminal sacrifice. Fatal and non-fatal tumors were analyzed together, with a separate stratum for each. No tumors of uncertain context were noted. The test was implemented using PROC MULTTEST in the SAS system. In the case of sparse tables, the exact form of the test was used for that stratum. Otherwise, the asymptotic version of the test was used.

Animals were assigned to the terminal sacrifice stratum based on the death or sacrifice status recorded in the data and were not assigned based on their week of necropsy. Unadjusted P-values were reported for tumors. Indication of a possible treatment effect were assessed on the basis of rare or common tumor type, in line with the FDA guidelines (Food and Drug Administration Draft Guidance for Industry, 2001). The Study Pathologist determined whether a tumor type was rare or common.

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Site or tumor combinations were also statistically analyzed. The criteria for combination were based on Guidelines for combining neoplasms for evaluation of rodent carcinogenicity studies (McConnell et al., 1986) and as indicated by the Study Pathologist. Incidences of multiple-organ and combined neoplastic findings, such as hemangioma, fibrosarcoma, and endometrial stromal polyp, were counted by animal, not tissue type.

Sponsor's concluded results: NT-814-related neoplastic findings were noted in the uterus and hematolymphoid system. These findings included statistically significant increases in the incidences of uterine neoplasms (adenocarcinoma and squamous cell carcinoma) and an increased severity/incidence of cystic glandular hyperplasia of the endometrium with concomitant, but not statistically significant, endometrial hyperplasia with atypia in females administered ⩾60 mg/kg/day, which correlated with increased uterus/cervix weights. In addition, an increase in the incidence of malignant lymphoma was noted in females administered 60 or 80 mg/kg/day (statistically significant only for females administered 80 mg/kg/day). Decreased incidences (not statistically significant) of mammary neoplasms (fibroadenoma, adenoma, and/or adenocarcinoma), with a concurrent decrease in the occurrence of physiological hyperplasia and atypical hyperplasia in the mammary gland, and a decreased occurrence of pituitary and thyroid C-cell adenomas were noted in females administered ⩾60 mg/kg/day.

3.2 Reviewer's Analyses

3.2.1 Data Quality

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer analyzed the SAS data sets of this study received on 7/26/2024 via NDA219469/S-0001. The sponsor submitted tumor.xpt and SEND datasets. The data quality for both datasets were acceptable. The analyses in this review are based on the tumor.xpt datafile.

3.2.2 Survival Analysis

The survival distributions of rates in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions were tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A in the appendix. The intercurrent mortality data are given in Tables 1A in the appendix. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 3A in the appendix.

Reviewer's findings: The female rats were terminated at Week 104. This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 56 (56%), 61 (61%), 62 (62%), 58 (58%), or 63 (63%) rats in the VC, LD, ML, MH, or HD groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in the mortality of females.

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3.2.3 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The adjusted levels of significance for testing a positive dose response in the 2-year rat study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparisons in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group. The tumor incidences rates and the p-values of the tested tumor types are listed in Tables 5A in the appendix.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Female Rats

Organ name	Tumor name	0 mg/kg/day Control P - Trend	7 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid-Low (ML) P - C vs. ML	60 mg/kg/day Mid-High (MH) P - C vs. MH	80 mg/kg/day High (H) P - C vs. H
Hematolymphoid System	M-Lymphoma	1/100 (72) 0.0020 *	3/100 (67) 0.2831	3/100 (71) 0.3046	6/100 (71) 0.0557	9/100 (72) 0.0087 **
Pituitary	M-Carcinoma, Pars Distalis	0/99 (71) 0.0453	0/100 (66) NC	2/100 (71) 0.2482	1/100 (69) 0.4929	3/100 (71) 0.1223
Skin/Subcutis	C_Fibroma /Fibroadenoma	0/100 (72) 0.0328	0/100 (66) NC	0/100 (70) NC	1/100 (69) 0.4894	2/100 (71) 0.2448
Uterus	M-Adenocarcinoma, Endometrium	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	22/100 (75) 0.00001 **

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Organ name	Tumor name	0 mg/kg/day Control P - Trend	7 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid-Low (ML) P - C vs. ML	60 mg/kg/day Mid-High (MH) P - C vs. MH	80 mg/kg/day High (H) P - C vs. H
	M-Carcinoma,	0/100 (72)	0/100 (66)	1/100 (71)	1/100 (69)	3/100 (70)
	Squamous Cell	0.0206 *	NC	0.4965	0.4894	0.1172
	C_Endometrium/B+M	2/100 (72)	3/100 (67)	5/100 (71)	15/100 (71)	23/100 (75)
		0.00001 *	0.4658	0.2149	0.0006 **	0.00001 **
	C_Endometrium/B+M	2/100 (72)	3/100 (67)	6/100 (71)	16/100 (72)	25/100 (75)
	/Carcinoma,squamous cell	0.00001 *	0.4658	0.1330	0.0003 **	0.00001 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, the positive dose response was statistically significant in the common tumor incidence of malignant lymphoma in Hematolymphoid System ($p=0.0020<0.005$). For this tumor type, the incidences rate of HD group was statistically significantly greater than that of the VC group ($p=0.0087<0.01$).

The positive dose responses were statistically significant in the common tumor incidences of malignant adenocarcinoma endometrium and the combined tumor incidences of benign and malignant endometrium, and malignant squamous cell in uterus ($Ps<0.0001<0.005$). For these tumor types, the incidences rates of MH and HD groups were statistically significantly greater than that of the VC group ($Ps<0.006<0.01$).

A positive dose response was statistically significant in the rare tumor incidences of malignant carcinoma squamous cell in uterus ($Ps<0.0206<0.025$). For this tumor type, the incidence rate in any dosed group was not statistically significantly greater than that of the vehicle control group.

4 Mouse Study- t105265-9

Study Report: t105265-9-pre-clinical-study-report.pdf (statistical report on page 2431)
SAS data: Tumor.xpt

The purpose of this study was to evaluate the carcinogenic potential of the test item, NT-814 (also known as BAY3427080 and elinzanetant), when administered twice daily by oral gavage to 001178-T (hemizygous) RasH2 mice for at least 26. The respective NT-814 doses in the vehicle control (VC), low (LD), mid (MD), high-dose (HD), and positive control (PC) groups were displayed in following table:

Reference ID: 5223897

		Dose Level[b]				Dose Concentration[b]		Number of Animals	
Group[a]	Subgroup	Males (mg/kg/dose)	Females (mg/kg/dose)	Males (mg/kg/day)[c]	Females (mg/kg/day)[c]	Males (mg/mL)	Females (mg/mL)	Males	Females
1 (Control)	1 (Carcinogenicity)	0	0	0	0	0	0	25	25
	2 (Toxicokinetic)	0	0	0	0	0	0	3	3
2 (Low)	1 (Carcinogenicity)	5	5	10	10	1.0	1.0	25	25
	2 (Toxicokinetic)	5	5	10	10	1.0	1.0	18	18
3 (Intermediate)	1 (Carcinogenicity)	15	10	30	20	3.0	2.0	25	25
	2 (Toxicokinetic)	15	10	30	20	3.0	2.0	18	18
4 (High)	1 (Carcinogenicity)	42.5	35	85	70	8.5	7.0	25	25
	2 (Toxicokinetic)	42.5	35	85	70	8.5	7.0	18	18
5 (Positive Control)[d]	1 (Carcinogenicity)	75	75	75	75	7.5	7.5	10	10

a Group 1 was administered vehicle control item only.
b Animals in Groups 1 through 4 were dosed at a volume of 5 mL/kg/dose (10 mL/kg/day). Animals in Group 5 were dosed at 10 mL/kg.
c The second daily dose was administered 6 hours (± 15 minutes) after the first daily dose for animals in Groups 1 through 4.
d Group 5 was dosed with one intraperitoneal dose of N-methyl-N-nitrosourea (MNU) on Day 1 of the dosing phase. These animals were included as positive controls to ensure animals supplied appropriately expressed oncogenes and responded to carcinogenic insult.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

4.1 Sponsor's Analyses

4.1.1 Survival Analysis

The sponsor used the same survival analysis methods for the mouse study as they used in the rat study.

Sponsor's concluded results: NT-814 administered orally to mice for up to 26 weeks had no effect on survival.

4.1.2 Tumor Data Analysis

The sponsor used the same tumor data analysis methods for the mouse study as they used in the rat study.

Sponsor's findings: There were no neoplastic findings attributed to NT-814.

4.2 Reviewer's Analyses

4.2.1 Data Quality

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer analyzed the SAS data sets of this study received on 7/26/2024 via NDA219469/S-0001. The sponsor submitted tumor.xpt and SEND datasets. The data quality for both datasets were acceptable. The analyses in this review are based on the tumor.xpt datafile.

4.2.2 Survival Analysis

Reference ID: 5523897

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals are given in Tables 4A and 4B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 3 (12%), 2 (8%), 1 (4%), 2 (8%), or 9 (90%) in male mice and 3 (12%), 0, 0, 2 (8%), or 8 (80%) in female mice in the VC, LD, MD, HD or PC groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males or females when data of the PC group were excluded. The mortality rates for the PC group were statistically significantly higher than that for the VC group for both male and female mice.

4.2.3 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of the vehicle control group separately with each of the treated groups using the same method that was used for the rat study. The adjusted level of significance for testing a positive dose response in the 6-month mice study is 0.05 for both a common tumor and a rare tumor. The adjusted level of significance for the pairwise comparison in the 6-month mice study is 0.05 for both a common tumor and a rare tumor. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group. The tumor rates and the p-values of the tested tumor types are listed in Tables 6A, and 6B in the appendix for male and female mice, respectively.

The tumor incidence rates and the p-values of the pairwise comparisons between positive control group and vehicle control group are listed in Tables 7A and 7B in the appendix for male and female mice, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control group.

Tumor Types with Statistically Significant (at 0.05 significant level) Pairwise Comparisons of Positive Control Group and Vehicle Control Group in Mice

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle Control	75 mg Positive (PC) P - VC vs. PC
Male	Hematolymphoid System	M-Malignant Lymphoma	0/25 (23)	8/10 (10) 0.00001 **
	Skin/Subcutis	B-Adenoma, Sebaceous Cell	0/25 (23)	2/10 (5) 0.0265 **
		B-Papilloma, Squamous Cell	0/25 (23)	6/10 (7) 0.00001 **
	Spleen	M-Hemangiosarcoma	2/25 (23)	3/10 (5) 0.0269 **
	Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (23)	7/10 (8) 0.00001 **

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Sex	Organ name	Tumor name	0 mg/kg/day Vehicle Control	75 mg Positive (PC) P - VC vs. PC
Female	Harderian Gland	B-Adenoma	0/25 (25)	4/9 (6) 0.0005 **
	Hematolymphoid System	M-Malignant Lymphoma	0/25 (25)	10/10 (10) 0.00001 **
	Skin/Subcutis	B-Papilloma, Squamous Cell	0/25 (25)	2/10 (5) 0.0230 **
	Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (25)	4/10 (5) 0.0002 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both a common tumor and a rare tumor.

Based on the criteria of adjustment for multiple testing discussed above, there were no statistically significant positive dose response relationships among the NT-814 treated groups and vehicle control group for male and female mice when data of the positive control group were excluded. However, the incidence rates of tumor types listed in above table were statistically significantly higher for positive control group compared to vehicle control group.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Atiar Mohammad Rahman., Acting Team Leader, Biometrics-6
cc:
Dr. Prati Tamrakar
Dr. Andrea L. Benedict
Dr. Yi Tsong
Dr. Atiar Mohammad Rahman

File Name: NDA219469Carcin

Reference ID: 5223897

5 Appendix

Table 1A: Intercurrent Mortality Rate in Female Rats

	Vehicle Control		Low Dose		Mid-Low Dose		Mid-High Dose		High Dose	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 52	4	4.00	12	12.00	9	9.00	12	12.00	11	11.00
53 - 78	23	27.00	23	35.00	14	23.00	18	30.00	15	26.00
79 - 96	19	46.00	20	55.00	28	51.00	19	49.00	27	53.00
97 - 104	9	55.00	6	61.00	11	62.00	8	57.00	10	63.00
Accidental Death	1	1.00					1	1.00		
Terminal sacrifice	44	44.00	39	39.00	38	38.00	42	42.00	37	37.00
Total	100		100		100		100		100	

Table 2A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Low Dose		Mid Dose		High Dose		Positive C	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 13	1	4.00	.	.	.	.	.	.	3	30.00
14 - 26	2	12.00	2	8.00	1	4.00	2	8.00	6	90.00
Terminal sacrifice	22	88.00	23	92.00	24	96.00	23	92.00	1	10.00
Total	25	.	25	.	25	.	25	.	10	.

Table 2B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		Low Dose		Mid Dose		High Dose		Positive C	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 13	.	.	.	.	.	.	.	.	1	10.00
14 - 26	3	12.00	.	.	.	.	2	8.00	7	80.00
Terminal sacrifice	22	88.00	25	100.00	25	100.00	23	92.00	2	20.00
Total	25	.	25	.	25	.	25	.	10	.

Table 3A: Intercurrent Mortality Comparison in Female Rats

Test	**All Dose Groups**	**VC vs. Low**	**VC vs. Mid-Low**	**VC vs. Mid-High**	**VC vs. High**
Dose-Response (Likelihood Ratio)	0.7437	0.2813	0.4363	0.6546	0.3440
Homogeneity (Log-Rank)	0.8277	0.2767	0.4320	0.6522	0.3386

Reference ID: 5223897

Table 4A: Intercurrent Mortality Comparison in Male Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. PC
Dose-Response (Likelihood Ratio)	0.7246	0.6203	0.2826	0.6332	<.0001
Homogeneity (Log-Rank)	0.7662	0.6167	0.2898	0.6327	<.0001

Table 4B: Intercurrent Mortality Comparison in Female Mice

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. PC
Dose-Response (Likelihood Ratio)	0.7794	0.0384	0.0384	0.6737	<.0001
Homogeneity (Log-Rank)	0.1344	0.0770	0.0770	0.6736	<.0001

Table 5A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mg/kg/day Control P - Trend	7 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid-Low (ML) P - C vs. ML	60 mg/kg/day Mid-High (MH) P - C vs. MH	80 mg/kg/day High (H) P - C vs. H
Adipose, Other	B-Lipoma	0/100 (72)	0/100 (66)	1/100 (70)	0/100 (69)	0/100 (70)
		0.4006	NC	0.4930	NC	NC
Adrenal, Cortex	B-Adenoma	1/100 (72)	0/100 (66)	1/100 (71)	2/99 (68)	0/99 (69)
		0.4883	1.0000	0.7483	0.4784	1.0000
Adrenal, Medulla	B-Pheochromocytoma,	5/100 (73)	6/99 (65)	4/100 (70)	3/98 (67)	8/99 (69)
		0.2985	0.4190	0.7319	0.8329	0.2458
	M-Pheochromocytoma	0/100 (72)	2/99 (65)	1/100 (70)	0/98 (67)	0/99 (69)
		0.8393	0.2233	0.4930	NC	NC
	C-Pheochromocytoma	5/100 (73)	8/99 (65)	4/100 (70)	3/98 (67)	8/99 (69)
	/B+M	0.4222	0.2108	0.7319	0.8329	0.2458
Brain	B-Granular Cell	0/100 (72)	1/100 (66)	0/100 (70)	0/100 (69)	1/100 (70)
	Tumor	0.3184	0.4783	NC	NC	0.4930
	M-Glioma, Malignant,	0/100 (72)	2/100 (67)	0/100 (70)	1/100 (69)	1/100 (70)
	Mixed	0.3895	0.2305	NC	0.4894	0.4930
Cervix	B-Polyp, Endometrial	0/100 (72)	0/99 (66)	2/100 (71)	0/100 (69)	0/98 (69)
	Stromal	0.6379	NC	0.2448	NC	NC
	M-Schwannoma	0/100 (72)	0/99 (66)	1/100 (70)	0/100 (69)	0/98 (69)
		0.3988	NC	0.4930	NC	NC
Clitoral Gland	B-Basal Cell Tumor	0/99 (71)	0/95 (62)	0/95 (66)	1/98 (67)	0/99 (69)
		0.4060	NC	NC	0.4855	NC
	B-Papilloma,	0/99 (71)	1/95 (62)	0/95 (66)	0/98 (67)	0/99 (69)
	Squamous Cell	0.6030	0.4662	NC	NC	NC
	M-Carcinoma	0/99 (71)	0/95 (62)	0/95 (66)	1/98 (67)	0/99 (69)
	Squamous Cell	0.4060	NC	NC	0.4855	NC
	C-Squamous cell	0/99 (71)	1/95 (62)	0/95 (66)	1/98 (67)	0/99 (69)
	/B+M	0.4886	0.4662	NC	0.4855	NC
Femur	M-Osteosarcoma	1/100 (72)	0/100 (66)	0/100 (70)	0/100 (69)	0/100 (70)
		0.7925	1.0000	1.0000	1.0000	1.0000

Reference ID: 5223897

Organ name	Tumor name	0 mg/kg/day Control P - Trend	7 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid-Low (ML) P - C vs. ML	60 mg/kg/day Mid-High (MH) P - C vs. MH	80 mg/kg/day High (H) P - C vs. H
Heart	M-Schwannoma, Endocardial	0/100 (72) 0.6023	1/100 (66) 0.4783	0/100 (70) NC	0/100 (69) NC	0/100 (70) NC
Hematolymphoid System	M-Lymphoma	1/100 (72) 0.0020 *	3/100 (67) 0.2831	3/100 (71) 0.3046	6/100 (71) 0.0557	9/100 (72) 0.0087 **
Kidney	C-Amphophilic vacuolar/B+M	1/100 (72) 0.5111	1/100 (66) 0.7296	1/100 (70) 0.7447	1/99 (68) 0.7373	1/99 (69) 0.7410
	B-Adenoma	0/100 (72) 0.2382	0/100 (66) NC	1/100 (71) 0.4965	0/99 (68) NC	1/99 (69) 0.4894
	B-Amphophilic Vacuolar Adenoma	1/100 (72) 0.4427	1/100 (66) 0.7296	0/100 (70) 1.0000	1/99 (68) 0.7373	1/99 (69) 0.7410
	M-Amphophilic Vacuolar Carcinoma	0/100 (72) 0.3971	0/100 (66) NC	1/100 (70) 0.4930	0/99 (68) NC	0/99 (69) NC
Liver	B-Adenoma, Hepatocellular	0/100 (72) 0.1186	0/100 (66) NC	0/100 (70) NC	1/99 (68) 0.4857	1/99 (69) 0.4894
	C-Hepatocellular /B+M	0/100 (72) 0.0544	0/100 (66) NC	0/100 (70) NC	2/99 (68) 0.2341	1/99 (69) 0.4894
	M-Hepatocellular Carcinoma	0/100 (72) 0.3971	0/100 (66) NC	0/100 (70) NC	1/99 (68) 0.4857	0/99 (69) NC
Lymph Node, Mesenteric	B-Lymphangioma	0/100 (72) 0.4006	0/100 (66) NC	1/100 (70) 0.4930	0/100 (69) NC	0/100 (70) NC
Lymph Node, Other	M-Hemangiosarcoma	0/100 (72) 0.3994	0/100 (66) NC	1/100 (71) 0.4965	0/100 (69) NC	0/100 (70) NC
Mammary Gland	B-Adenoma	4/99 (71) 0.9978	1/100 (66) 0.9651	0/98 (69) 1.0000	0/98 (67) 1.0000	0/93 (64) 1.0000
	B-Fibroadenoma	45/99 (88) 1.0000	49/100 (86) 0.2675	43/98 (88) 0.6744	9/98 (69) 1.0000	15/93 (69) 1.0000
	B-Fibroma	0/99 (71) 0.5935	1/100 (66) 0.4818	0/98 (69) NC	0/98 (67) NC	0/93 (64) NC
	M-Adenocarcinoma	9/99 (74) 1.0000	9/100 (71) 0.5621	6/98 (71) 0.8428	0/98 (67) 1.0000	0/93 (64) 1.0000
	C-Adenoma /Adenocarcinoma	12/99 (74) 1.0000	10/100 (71) 0.7215	6/98 (71) 0.9538	0/98 (67) 1.0000	0/93 (64) 1.0000
	C-Fibroma /Fibroadenoma	45/99 (88) 1.0000	50/100 (87) 0.2454	43/98 (88) 0.6744	9/98 (69) 1.0000	15/93 (69) 1.0000
Ovary	B-Adenoma, Tubulo stromal	0/100 (72) 0.3977	0/100 (66) NC	1/100 (71) 0.4965	0/99 (68) NC	0/100 (70) NC
	B-Granulosa Cell	1/100 (72) 0.1847	0/100 (66) 1.0000	0/100 (70) 1.0000	0/99 (68) 1.0000	2/100 (70) 0.4894
	C-Granulosa Cell tumor/B+M	1/100 (72) 0.2458	0/100 (66) 1.0000	1/100 (70) 0.7447	0/99 (68) 1.0000	2/100 (70) 0.4894
	C-Granulosa cell tumor/B+M/Sex cord	2/100 (72) 0.5264	1/100 (66) 0.8608	1/100 (70) 0.8723	0/99 (68) 1.0000	2/100 (70) 0.6795
	M-Granulosa Cell	0/100 (72) 0.3988	0/100 (66) NC	1/100 (70) 0.4930	0/99 (68) NC	0/100 (70) NC
	M-Sex Cord Stromal	1/100 (72)	1/100 (66)	0/100 (70)	0/99 (68)	0/100 (70)

Reference ID: 5223897

Organ name	Tumor name	0 mg/kg/day Control P - Trend	7 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid-Low (ML) P - C vs. ML	60 mg/kg/day Mid-High (MH) P - C vs. MH	80 mg/kg/day High (H) P - C vs. H
		0.8776	0.7296	1.0000	1.0000	1.0000
Pancreas	B-Adenoma, Acinar	1/100 (72)	0/100 (66)	0/100 (70)	0/100 (69)	0/100 (70)
	Cell	0.7925	1.0000	1.0000	1.0000	1.0000
	B-Adenoma, Islet Cell	0/100 (72)	2/100 (66)	1/100 (70)	1/100 (69)	0/100 (70)
		0.7006	0.2269	0.4930	0.4894	NC
Parathyroid	B-Adenoma	0/97 (69)	0/93 (61)	0/93 (65)	1/91 (62)	0/94 (64)
		0.3925	NC	NC	0.4733	NC
Pituitary	B-Adenoma, Pars	26/99 (75)	18/100 (70)	29/100 (75)	10/100 (71)	6/100 (70)
	Distalis	1.0000	0.9122	0.3674	0.9991	1.0000
	M-Carcinoma, Pars	0/99 (71)	0/100 (66)	2/100 (71)	1/100 (69)	3/100 (71)
	Distalis	0.0453	NC	0.2482	0.4929	0.1223
	C-Pars Distalis /B+M	26/99 (75)	18/100 (70)	31/100 (76)	11/100 (71)	9/100 (71)
		1.0000	0.9122	0.2717	0.9981	0.9996
Skin/Subcutis	B-Fibroma	0/100 (72)	0/100 (66)	0/100 (70)	1/100 (69)	1/100 (70)
		0.1207	NC	NC	0.4894	0.4930
	B-Keratoacanthoma	0/100 (72)	0/100 (66)	1/100 (70)	1/100 (69)	0/100 (70)
		0.4828	NC	0.4930	0.4894	NC
	B-Schwannoma	0/100 (72)	1/100 (67)	0/100 (70)	0/100 (69)	0/100 (70)
		0.6006	0.4820	NC	NC	NC
	B-Tumor, Hair Follicle	1/100 (72)	0/100 (66)	0/100 (70)	0/100 (69)	1/100 (70)
		0.4828	1.0000	1.0000	1.0000	0.7447
	C-Fibroma	0/100 (72)	0/100 (66)	0/100 (70)	1/100 (69)	2/100 (71)
	/Fibroadenoma	0.0328	NC	NC	0.4894	0.2448
	C-Keratoacanthoma/	1/100 (72)	0/100 (66)	2/100 (70)	1/100 (69)	2/100 (71)
	Hair follicle /Carcinoma, basal cell	0.2355	1.0000	0.4894	0.7410	0.4947
	M-Carcinoma, Basal	0/100 (72)	0/100 (66)	1/100 (70)	0/100 (69)	1/100 (71)
	Cell	0.2435	NC	0.4930	NC	0.4965
	M-Fibrosarcoma	0/100 (72)	0/100 (66)	0/100 (70)	0/100 (69)	1/100 (70)
		0.2017	NC	NC	NC	0.4930
	M-Hibernoma	0/100 (72)	0/100 (66)	1/100 (71)	0/100 (69)	0/100 (70)
		0.3994	NC	0.4965	NC	NC
	M-Sarcoma-Nos	0/100 (72)	0/100 (66)	0/100 (70)	0/100 (69)	1/100 (70)
		0.2017	NC	NC	NC	0.4930
Thymus	B-Thymoma, Benign	0/92 (68)	1/94 (63)	1/97 (68)	0/93 (64)	0/95 (66)
		0.6771	0.4809	0.5000	NC	NC
	M-Thymoma	1/92 (69)	0/94 (63)	0/97 (68)	0/93 (64)	0/95 (66)
		0.7909	1.0000	1.0000	1.0000	1.0000
	Thymoma/B+M	1/92 (69)	1/94 (63)	1/97 (68)	0/93 (64)	0/95 (66)
		0.8602	0.7287	0.7482	1.0000	1.0000
Thyroid	B-Adenoma, C-Cell	15/100 (75)	16/100 (67)	7/99 (70)	3/99 (68)	0/98 (68)
		1.0000	0.3607	0.9731	0.9993	1.0000
	B-Adenoma, Follicular	1/100 (72)	0/100 (66)	1/99 (69)	0/99 (68)	1/98 (68)
	Cell	0.4915	1.0000	0.7410	1.0000	0.7373
	C-C-Cell/B+M	15/100 (75)	17/100 (68)	9/99 (71)	3/99 (68)	0/98 (68)
		1.0000	0.3028	0.9224	0.9993	1.0000
	M-Carcinoma, C-Cell	0/100 (72)	1/100 (66)	2/99 (70)	0/99 (68)	0/98 (68)
		0.7883	0.4783	0.2412	NC	NC
Uterus	B-Adenoma,	0/100 (72)	0/100 (66)	0/100 (70)	0/100 (69)	1/100 (70)

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Organ name	Tumor name	0 mg/kg/day Control P - Trend	7 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid-Low (ML) P - C vs. ML	60 mg/kg/day Mid-High (MH) P - C vs. MH	80 mg/kg/day High (H) P - C vs. H
	Endometrium	0.2017	NC	NC	NC	0.4930
	B-Keratoacanthoma	0/100 (72)	0/100 (66)	0/100 (70)	0/100 (69)	1/100 (70)
		0.2017	NC	NC	NC	0.4930
	B-Polyp, Endometrial	12/100 (76)	14/100 (69)	15/100 (73)	10/100 (70)	5/100 (71)
	Stromal	0.9820	0.3122	0.2943	0.6852	0.9740
	C-Endometrium/B+M	2/100 (72)	3/100 (67)	5/100 (71)	15/100 (71)	23/100 (75)
		0.00001 *	0.4658	0.2149	0.0006 **	0.00001 **
	C-Endometrium/B+M	2/100 (72)	3/100 (67)	6/100 (71)	16/100 (72)	25/100 (75)
	/Carcinoma, squamous cell	0.00001 *	0.4658	0.1330	0.0003 **	0.00001 **
	M-Adenocarcinoma,	2/100 (72)	3/100 (67)	5/100 (71)	15/100 (71)	22/100 (75)
	Endometrium	0.00001 *	0.4658	0.2149	0.0006 **	0.00001 **
	M-Carcinoma,	0/100 (72)	0/100 (66)	1/100 (71)	1/100 (69)	3/100 (70)
	Squamous Cell	0.0206 *	NC	0.4965	0.4894	0.1172
	M-Hemangiosarcoma	0/100 (72)	1/100 (66)	0/100 (70)	0/100 (69)	0/100 (70)
		0.6023	0.4783	NC	NC	NC
	M-Schwannoma	0/100 (72)	0/100 (66)	0/100 (70)	1/100 (69)	0/100 (70)
		0.4006	NC	NC	0.4894	NC
	M-Tumor, Mixed	0/100 (72)	0/100 (66)	0/100 (70)	1/100 (69)	0/100 (70)
	Muellerian,	0.4006	NC	NC	0.4894	NC
Vagina	B-Tumor, Granular	1/99 (71)	2/97 (65)	0/100 (70)	0/99 (68)	1/99 (69)
	Cell	0.7005	0.4667	1.0000	1.0000	0.7446

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6A: Tumor Rates and P-Values for Pairwise Comparisons in Male Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	10 mg/kg/day Low (L) P - C vs. L	30 mg/kg/day Mid (M) P - C vs. M	85 mg/kg/day High (H) P - C vs. H
Liver	B-Adenoma, Hepatocellular	0/25 (23)	0/25 (24)	1/25 (25)	0/25 (24)
		0.5104	NC	0.5208	NC
Lung	B-Adenoma, Bronchiolo-Alveolar	2/25 (24)	2/25 (24)	1/25 (25)	2/25 (24)
		0.4991	0.6957	0.8901	0.6957
Skin/Subcutis	M-Hemangiosarcoma	0/25 (23)	0/24 (23)	0/25 (25)	1/24 (23)
		0.2447	NC	NC	0.5000
Spleen	M-Hemangiosarcoma	2/25 (23)	1/25 (24)	0/25 (25)	0/25 (24)
		0.9876	0.8908	1.0000	1.0000
Testis	M-Hemangiosarcoma	0/25 (23)	0/25 (24)	1/25 (25)	0/25 (24)
		0.5104	NC	0.5208	NC
Whole Body	M-Hemangiosarcoma	2/25 (23)	1/25 (24)	1/25 (25)	1/25 (24)
		0.6937	0.8908	0.8976	0.8908

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. The p-values marked with an asterisk * indicate statistically significant dose responses at 0.05 and 0.05 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 and 0.05 for a common tumor and a rare tumor, respectively.

Reference ID: 5223897

Table 6B: Tumor Rates and P-Values for Pairwise Comparisons in Female Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (C) P - Trend	10 mg/kg/day Low (L) P - L vs. C	20 mg/kg/day Mid (M) P - M vs. C	70 mg/kg/day High (H) P - H vs. C
Harderian Gland	B-Adenoma	0/25 (25)	0/25 (25)	1/25 (25)	0/25 (24)
		0.4949	NC	0.5000	NC
Lung	B-Adenoma, Bronchiolo-Alveolar	1/25 (25)	1/25 (25)	1/25 (25)	0/25 (24)
		0.8419	0.7551	0.7551	1.0000
	M-Carcinoma, Bronchiolo-Alveolar	1/25 (25)	0/25 (25)	0/25 (25)	0/25 (24)
		1.0000	1.0000	1.0000	1.0000
	C-Bronchiolo-Alveolar/B+M	2/25 (25)	1/25 (25)	1/25 (25)	0/25 (24)
		0.9422	0.8827	0.8827	1.0000
Skin/Subcutis	B-Papilloma, Squamous Cell	0/25 (25)	0/25 (25)	0/25 (25)	1/25 (25)
		0.2500	NC	NC	0.5000
Spleen	M-Hemangiosarcoma	0/25 (25)	2/25 (25)	0/25 (25)	1/25 (24)
		0.4280	0.2449	NC	0.4898
Stomach, Nonglandular	M-Carcinoma, Squamous Cell	0/25 (25)	1/25 (25)	0/25 (25)	0/25 (24)
		0.7475	0.5000	NC	NC

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. The p-values marked with an asterisk * indicate statistically significant dose responses at 0.05 and 0.05 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 and 0.05 for a common tumor and a rare tumor, respectively.

Table 7A: Tumor Rates and P-Values Pairwise Comparisons of Vehicle Controls with Positive Control in Male Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (C)	75 mg/kg/day High (H) P - C vs. H
Hematolymphoid System	M-Malignant Lymphoma	0/25 (23)	8/10 (10)
			0.00001 **
Lung	B-Adenoma, Bronchiolo- Alveolar	2/25 (24)	0/10 (4)
			1.0000
	M-Carcinoma, Bronchiolo- Alveolar	0/25 (23)	1/10 (5)
			0.1786
Skin/Subcutis	B-Adenoma, Sebaceous Cell	0/25 (23)	2/10 (5)
			0.0265 **
	B-Papilloma, Squamous Cell	0/25 (23)	6/10 (7)
			0.00001 **
	M-Carcinoma, Squamous Cell	0/25 (23)	1/10 (4)
			0.1481
Spleen	M-Hemangiosarcoma	2/25 (23)	3/10 (5)
			0.0269 **
Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (23)	7/10 (8)
			0.00001 **
	M-Carcinoma, Squamous Cell	0/25 (23)	1/10 (5)
		0.0649	0.1786

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both a common tumor and a rare tumor.

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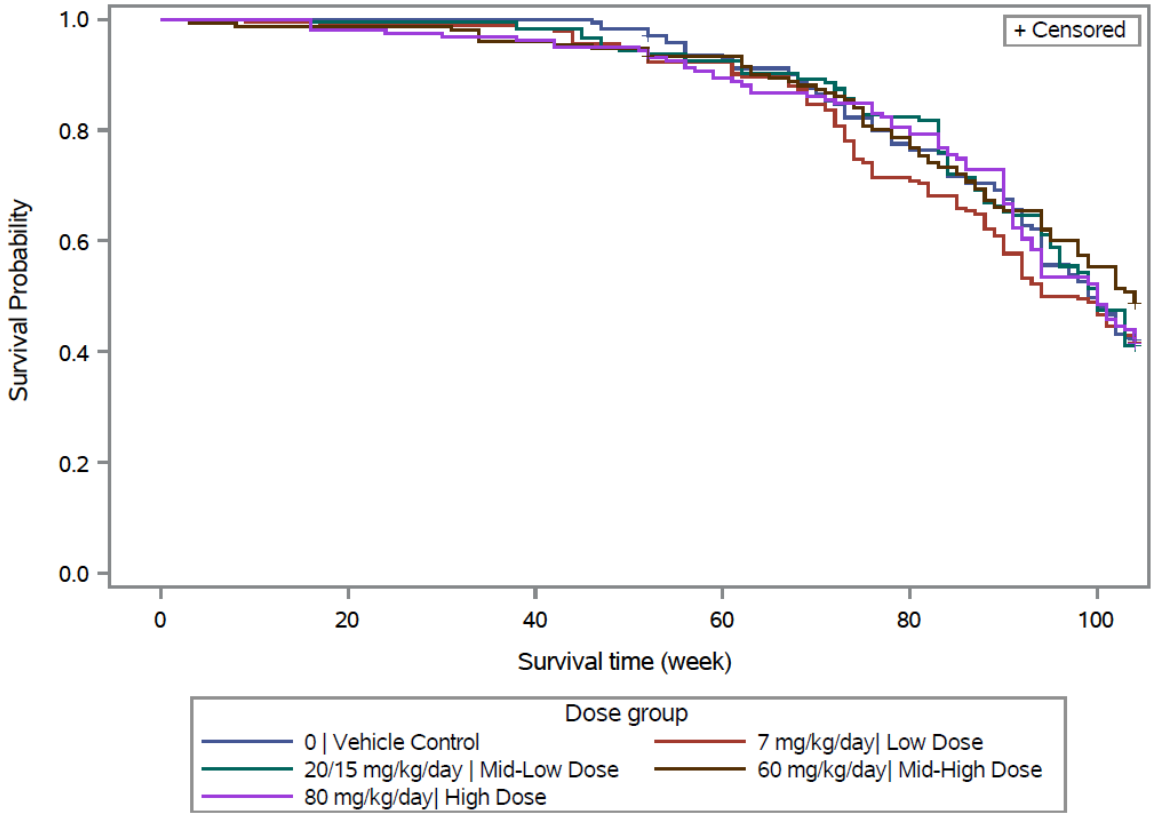
Table 7B: Tumor Rates and P-Values Pairwise Comparisons of Vehicle Controls with Positive Control in Female Mice

Organ name	Tumor name	0 mg/kg/day Vehicle (C)	75 mg/kg/day High (H) P - H vs. C
Footpad	B-Papilloma, Squamous Cell	0/25 (25)	1/10 (5)
			0.1667
Harderian Gland	B-Adenoma	0/25 (25)	4/9 (6)
			0.0005 **
Hematolymphoid System	M-Malignant Lymphoma	0/25 (25)	10/10 (10)
			0.00001 **
Lung	B-Adenoma, Bronchiolo- Alveolar	1/25 (25)	0/10 (5)
			1.0000
	M-Carcinoma, Bronchiolo- Alveolar	1/25 (25)	0/10 (5)
			1.0000
Skin/Subcutis	B-Papilloma, Squamous Cell	0/25 (25)	2/10 (5)
			0.0230 **
Spleen	M-Hemangiosarcoma	0/25 (25)	1/9 (5)
			0.1667
Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (25)	4/10 (5)
			0.0002 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both a common tumor and a rare tumor.

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Figure 1A: Kaplan-Meier Survival Functions for Female Rats



Reference ID: 5223897

Figure 2A: Kaplan-Meier Survival Functions for Male Mice

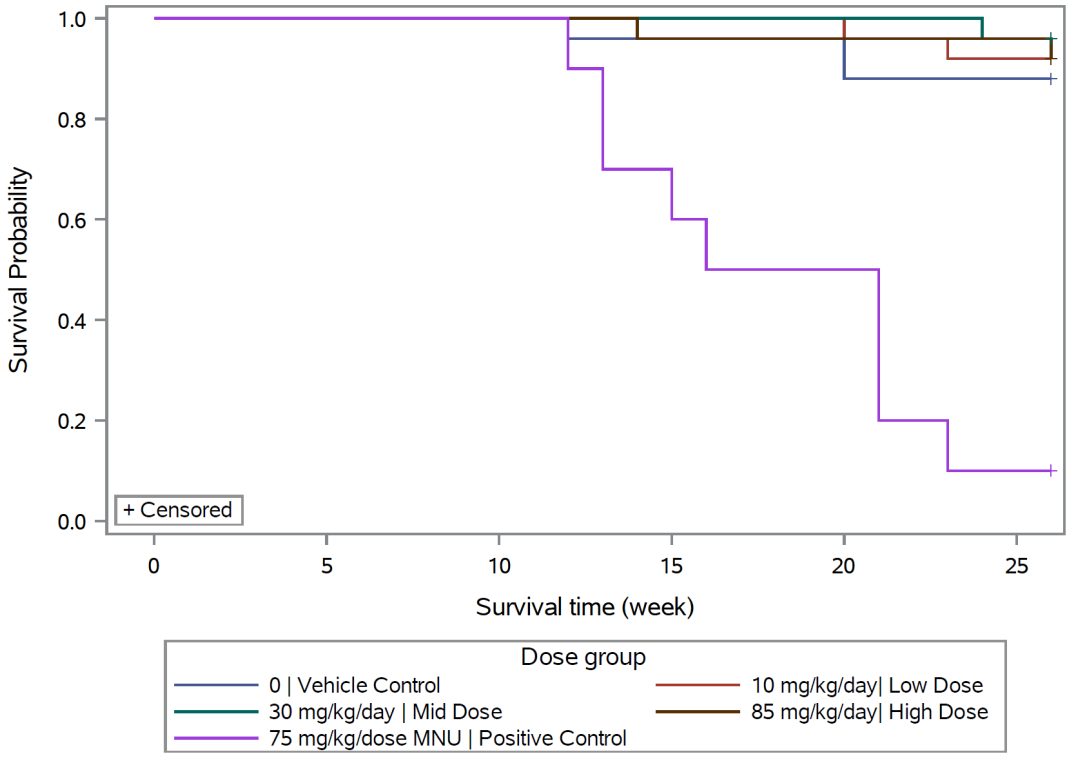
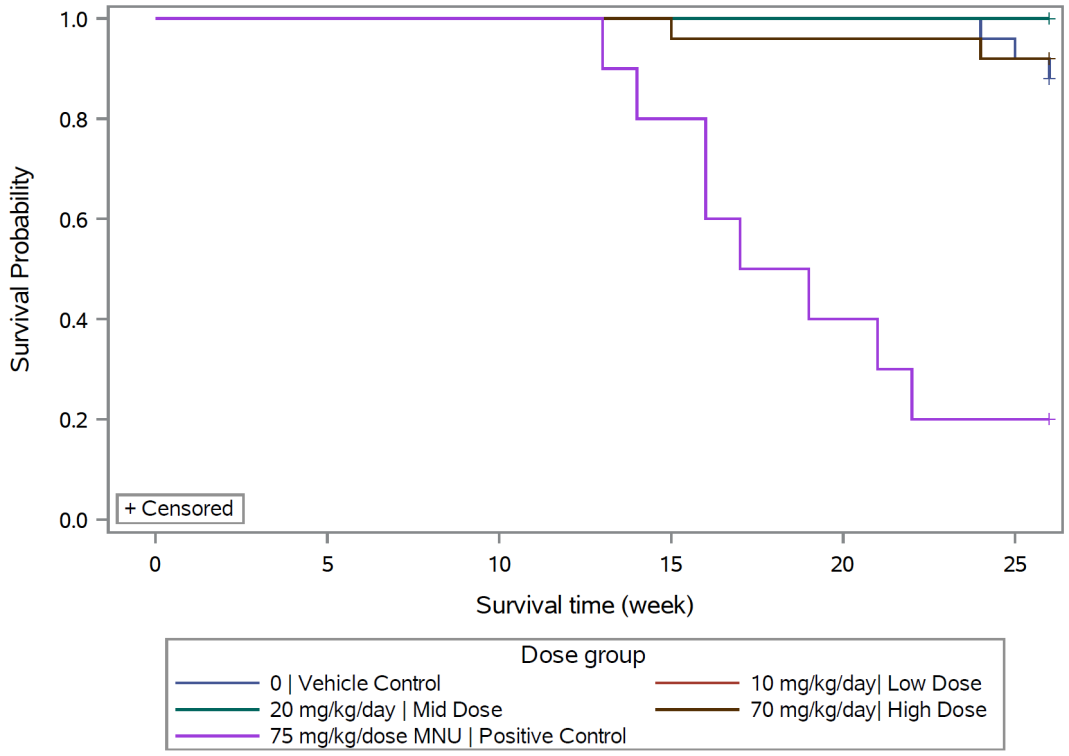


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



File Name: NDA219469Carcin

Reference ID: 5223897

References

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/s/

FENG ZHOU
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APPENDIX 2

Executive CAC Final Study Minutes
Date of Meeting: December 10, 2024

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Ron Wange, PhD, OND IO, Member
Chris Ellis, PhD, DPT-ID, Alternate Member
Kimberly Hatfield, PhD, DPT-RPURM, Pharm/Tox. Acting Division Director
Andrea Benedict, PhD, DPT-RPURM, Pharm/Tox. Team Leader
Edna Albuquerque, PhD, DPT-RPURM, Pharm/Tox. Reviewer
Pratistha Tamrakar, PhD, DPT-RPURM, Pharm/Tox. Reviewer
Sarah Lee, PhD, DPT-RPURM, Pharm/Tox. Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

Application Type and Number(s): NDA 219469
Drug Name: Elinzanetant
Applicant: Bayer HealthCare Pharmaceuticals Inc.

Background
Elinzanetant (BAY 3427080; NT-814; 7486; GSK 1144814A) is a Neurokinin (NK) 1 and NK3 receptor antagonist being proposed for the treatment of moderate to severe vasomotor symptoms associated with menopause. The Applicant submitted the final study reports for the 104-week rat carcinogenicity study and the 26-week transgenic rasH2 (Tg.rasH2) mouse study. The dose selections for both the rat and transgenic mouse studies were as per the Executive CAC recommendation (Refer to ExecCAC Meeting Minutes, Oct 19, 2020, for rat study and ExecCAC Meeting Minutes, Dec 06, 2022, for mouse study). The Applicant had previously submitted complete reports of a full battery of genotoxicity studies including an Ames test, an in-vitro mouse lymphoma L5178Y cell assay, and an in-vivo rat micronucleus assay, which did not reveal any evidence of a genotoxic potential of elinzanetant. The three principal elinzanetant metabolites M27, M30/34, and M18/21 also generated no genotoxicity signals in in-vitro and in-vivo assays.

Mouse Carcinogenicity Study
The Tg.rasH2 mouse carcinogenicity study was conducted in both male and female mice for the duration of 26 weeks. Elinzanetant was administered at doses 0 (vehicle: 1% aqueous methylcellulose), 10, 30, 85 mg/kg/day in males and 0, 10, 20, 70 mg/kg/day in females via oral gavage. The data was analyzed by the FDA statistical reviewer, Feng Zhou, MS, Division of Biometrics VI. There were no statistically significant relationships by trend or pair-wise analysis for the incidence of any tumor in male or female mice. Elinzanetant did not affect the overall survival rate, nor did it produce adverse clinical signs up to the high dose of 85 mg/kg/day in males and 70

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mg/kg/day in females. The positive control, a single dose of N-methyl-N-nitrosourea (MNU) at 75 mg/kg by IP injection on Day 1, resulted in the expected tumor response.

Rat Carcinogenicity Study

The rat carcinogenicity study was conducted in female Sprague-Dawley rats for the duration of 104 weeks. The Applicant conducted the study at the ExecCAC recommended doses: 0 (vehicle: 1% aqueous methylcellulose), 7, 20, and 60 mg/kg/day doses and added an additional 80 mg/kg/day group. Because elinzanetant is being developed for the clinical indication of moderate to severe vasomotor symptoms in postmenopausal women, the study was conducted only in female rats per the ExecCAC suggestion. The FDA statistical reviewer Feng Zhou, MS, Division of Biometrics VI, reviewed the tumor data. At ≥60 mg/kg/day, elinzanetant caused statistically significant increases, by both trend and pairwise analysis, in the incidence of: i) malignant lymphoma in the hematolymphoid system (80 mg/kg/day only); ii) malignant endometrial adenocarcinoma of the uterus; iii) combined malignant and benign endometrial tumors in the uterus; and iv) combined malignant and benign endometrial tumors and malignant squamous cell carcinoma in the uterus. The lowest dose of elinzanetant associated with significantly increased incidence of tumors was 60 mg/kg/day. Based on AUCs, the clinical exposure margins provided by this dose to the Maximum Recommended Human Dose (MRHD) of 120 mg/day is ~29.4x for elinzanetant and ~7.0x for M30/34 (the predominant metabolite in humans and animals). There was no statistically significant dose-response relationship for mortality, though a dose-dependent reduction of body weight gain was observed with elinzanetant treatment.

Table 1: Tumor Types with Statistically Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Controls in Female Rats

Organ name	Tumor name	0 mg/kg/day Control P - Trend	7 mg/kg/day Low (L) P - C vs. L	20 mg/kg/day Mid (M) P - C vs. M	60 mg/kg/day High (H) P - C vs. H	80 mg/kg/day Positive (PC) P - C vs. PC
Hematolymphoid System	M-Lymphoma	1/100 (72) 0.0020 *	3/100 (67) 0.2831	3/100 (71) 0.3046	6/100 (71) 0.0557	9/100 (72) 0.0087 **
Uterus	M-Adenocarcinoma, Endometrium	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	22/100 (75) 0.00001**
	M-Carcinoma, Squamous Cell	0/100 (72) 0.0206 *	0/100 (66) NC	1/100 (71) 0.4965	1/100 (69) 0.4894	3/100 (70) 0.1172
	C_Endometrium/B+M	2/100 (72) 0.00001 *	3/100 (67) 0.4658	5/100 (71) 0.2149	15/100 (71) 0.0006 **	23/100 (75) 0.00001 **
	C_Endometrium/B+M /Carcinoma,squamous cell	2/100 (72) 0.00001 *	3/100 (67) 0.4658	6/100 (71) 0.1330	16/100 (72) 0.0003 **	25/100 (75) 0.00001 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable. The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Executive CAC Conclusions

Mouse:

- The Committee concluded that the carcinogenicity study was adequate.

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- The Committee concluded that there was no evidence of drug-related neoplasms in male and female mice in the 6-month study.

Rat:

- The Committee concluded that the carcinogenicity study was adequate.
- The Committee concluded that the increased incidence of malignant lymphoma in the hematolymphoid system at 80 mg/kg/day was drug-related.
- The Committee concluded that the following findings in the uterus at ≥60 mg/kg/day were drug-related: increased incidence of malignant endometrial adenocarcinoma, combined malignant and benign endometrial tumors, and combined malignant and benign endometrial tumors and malignant squamous cell carcinoma.

Karen Davis Bruno, PhD
Chair, Executive CAC

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KAREN L DAVIS BRUNO
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APPENDIX 3

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs

FACSIMILE TRANSMITTAL SHEET

DATE: December 8, 2022

To: Harpreet Sandhu, PhD, MBA, Global Regulatory Affairs	**From:** Robeena M. Aziz, PhD, MPH, MS, CMA
Company: Bayer Healthcare and Pharmaceuticals	OND IO
Fax number: 862-404-3175	**Fax number**: 301-796-9858
Phone number: (b) (4)	**Phone number:** 240-402-1014
Subject: Response to Carcinogenicity Special Protocol Assessment Request – Final execCAC Report - IND 129492	
Total no. of pages including cover: 5	

Comments: Email to: Harpreet.sandhu@bayer.com

Document to be mailed: ☐ YES ☑ NO

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Executive CAC Protocol Minutes
Date of Meeting: December 6, 2022

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Ron Wange, PhD, OND IO, Member
Kimberly Hatfield, PhD, DPT-RPURM, Alternate Member and Pharm/Tox Supervisor
Leslie McKinney, PhD, DPT-RPURM, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the sponsor's proposed statistical evaluation for the carcinogenicity bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Standardized Study Data (December 2014) and the latest Study Data Technical Conformance Guide.

Application Type and Number(s): IND 129492
Drug Name: Elinzanetant (BAY 3427080, NT-814, GSK1144814A) capsule
Sponsor: Bayer Healthcare and Pharmaceuticals

Background

BAY 3247080 (elinzanetant, NT-814) is an antagonist of both the human neurokinin (NK)1 and NK3 receptors that is in development for the treatment of moderate to severe vasomotor symptoms in postmenopausal women. In nonclinical studies, the drug product is administered by oral gavage on a BID (twice daily) dosing schedule.

BAY 3427080 was negative for genetic toxicity in a full battery of in vitro (Ames and mouse lymphoma L5178Y TK+/- assay) and in vivo (rat bone marrow micronucleus assay) studies.

BAY 3427080 is cleared primarily by the liver. Analysis of patient plasma from phase 2 clinical studies identified three metabolites accounting for more than 10% of total drug AUC. These metabolites are M27, M18/21, and M30/34. They exhibit high affinity and activity at the human NK1 and NK3 receptors that is similar to the affinity and activity of elinzanetant in in vitro binding and cellular functional assays. The sponsor has conducted appropriate chronic repeat-dose toxicity studies with BAY 3427080 (parent) in rats and monkeys and with the M27 metabolite specifically in rats that provide adequate safety qualification for all of the disproportionate metabolites at a clinical maximum daily dose of 120 mg/day.

Reference ID: 5220939

In vitro genetic toxicology studies were also conducted for the disproportionate human metabolites. M27, M30/34, and M18/21 were negative for mutagenic effect in in vitro bacterial reverse mutation assays and in vitro micronucleus assays.

Mouse Carcinogenicity Study Dose Selection

Bayer proposed a 26-week study in the Tg-rasH2 mouse at doses of 10, 30, and 100 mg/kg to be administered BID yielding total daily doses of 20, 60, and 200 mg/kg/d. The control group will be dosed with the vehicle, 1% aqueous methylcellulose. A single 75 mg/kg intraperitoneal dose of N-methyl-N-nitrosourea will be administered to positive control groups.

Dose selection was based on maximum tolerated dose (MTD), determined in two 28-day GLP studies, the first conducted in wild type Tg-rasH2 mice (T1-5264-8) and the second in the transgenic strain (T105617-0 *unaudited draft*).

In the first study, doses of 10, 30, or 100 mg/kg/dose BID (i.e., 20, 60, and 200 mg/kg/d) were well-tolerated for the majority of animals. However, 3 out of 12 high-dose females were prematurely sacrificed due to poor condition and severe body weight losses of -16 to -21% on Days 8 to 15, indicating that 200 mg/kg/d exceeded the MTD in females. Two to three unscheduled sacrifices also occurred at each of the low and mid-doses and in the control group. The MTD for males was 200 mg/kg/d in this study. The sponsor's NOAEL for males and females was set at the low dose: 20 mg/kg/d. At the high dose of 200 mg/kg/d, on day 28, an exposure multiple of 10.8x (based on AUC_{0-24}) was achieved relative to the proposed clinical human dose of 120 mg/day.

In the second study in transgenic Tg-rasH2 mice, the sponsor explored doses around the MTDs observed in the wild-type Tg-rasH2 mice to better define an appropriate high-dose selection: 0, 150, 200, 250 mg/kg/d. The high dose of 250 mg/kg/d led to moribund condition and death in all males, which was attributed to BAY 3427080-related systemic atrophy of adipose tissue and skeletal muscle degeneration. Doses of up to 200 mg/kg/d in males and 250 mg/kg/d in females were otherwise generally well tolerated in the transgenic strain. Sponsor's NOAEL for males was set at 200 mg/kg/d, and for females, 250 mg/kg/d.

(b) (4)

Executive CAC Recommendations and Conclusions

- The Committee recommended doses of 0 (vehicle - 1% aqueous methylcellulose), 10, 30 and 85 mg/kg/day in male mice and 0 (vehicle - 1% aqueous methylcellulose), 10, 20 and 70 mg/kg/day in female mice with the high dose-based on the maximum tolerated dose (MTD) consisting of body weight loss (in females) and lethality (in males).
- The mid and low doses (for both male and female mice) were based on approximately one-third dose spacing.

Reference ID: 5020930

- The toxicokinetic groups in the transgenic mouse study are not needed by FDA.
- The Committee does not concur (b) (4)
- The Committee noted that the Sponsor submitted a draft report for the 4-week dose range finding study. The current recommendations provided by the Committee are contingent on the results of the final report not being notably different from those in the draft report, such that dose recommendations might have differed.
- If there are survival issues during the study, the Sponsor should contact the Review Division before any changes are made.

Karen Davis-Bruno, PhD
Chair, Executive CAC

Reference ID: 5[illegible]

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APPENDIX 4

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs

FACSIMILE TRANSMITTAL SHEET

DATE: October 21, 2020

To: Shefali Goyal, MSc, MS, US Head Executive Director, Regulatory Affairs	**From:** Robeena M. Aziz, PhD, MPH, MS, CMA
Company: Bayer HealthCare Pharmaceuticals, Inc.	OND IO
Fax number: (b) (4)	**Fax number**: 301-796-9858
Phone number: (b) (4)	**Phone number:** 240-402-1014

Subject: Response to Carcinogenicity Special Protocol Assessment Request – Final execCAC Report – IND 129492

Total no. of pages including cover: 4

Comments: Email to: shefali.goyal@bayer.com

Document to be mailed: ☐ YES ☑ NO

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Executive CAC Protocol Minutes
Date of Meeting: October 13, 2020

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Ron Wange, PhD, OND IO, Member
Newton, Woo, PhD, DPTN, Alternate Member
Mukesh Summan, PhD, DUOG, Pharm. Tox. Supervisor
Kimberly Hatfield, PhD, DUOG, Pharm. Tox. Team Leader
Frederic Moulin, DVM, PhD, ORPURM/DUOG, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

The Committee did not address the Sponsor's proposed statistical evaluation for the carcinogenicity bioassay, as this does not affect the Sponsor's ability to initiate the bioassay. The Sponsor may seek guidance on the statistical evaluation of bioassay results from Agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Standardized Study Data (December 2014) and the latest Study Data Technical Conformance Guide.

Application Type and Number(s): IND 129492
Drug Name: NT-814
Sponsor: Bayer HealthCare Pharmaceuticals, Inc

Background
NT-814 is an antagonist of both the human neurokinin (NK)1 and NK3 receptors developed by Bayer HealthCare Pharmaceuticals for the treatment of moderate to severe vasomotor symptoms in post-menopausal women. A submission to IND 129492 dated September 4, 2020, contained a draft protocol for a 104-week carcinogenicity study that the Sponsor proposes to conduct administering NT-814 twice daily by oral gavage in Sprague Dawley rats. NT-814 was neither genotoxic nor clastogenic in an adequate battery of in vitro and in vivo assays.

Rat Carcinogenicity Study Dose Selection
The data submitted to support dose selection for the carcinogenicity study comprise two oral chronic toxicity studies in Sprague Dawley rats of 13- and 26- weeks duration. The doses proposed by the Sponsor are different between sexes because the rate of NT-814 metabolism is greater in males than in females.

In males, the Sponsor proposed oral doses of (b) (4)

Reference ID: 4629837

[redacted] (b) (4).

In females, the Sponsor proposed oral doses of [redacted] (b) (4)
[redacted] (b) (4)
[redacted]

Executive CAC Recommendations and Conclusions

- The Committee recommended doses of 0 [aqueous solution of 1% methylcellulose (viscosity 400 cP)], 7, 20, and 60 mg/kg/twice daily (via oral gavage) for female rats only with the high dose based on achieving an AUC ratio greater than 25-fold of the clinical exposure. The mid- and low- doses were selected based on adequate spacing of AUC.
- The Committee noted that if the clinical dose changes such that the exposure ratio is no longer at least 25-fold at the high dose, then the study may not be acceptable.
- For male rats, the Committee could not concur on doses because an MTD was not established in the 26-week study or in the 13-week study, which had many discrepancies. The Sponsor would need to conduct and submit a new dose range finding study for ECAC concurrence on dose selection for male rats. Alternately, the Sponsor could increase the number of female rats proposed in the 2-year study and not include a male group because the indication is for moderate to severe vasomotor symptoms in postmenopausal females.
- The Committee noted that the Sponsor submitted a draft report for the 26-week toxicity study. The current recommendations provided by the Committee are contingent on the results of the final report not being notably different from those in the draft report, such that dose recommendations might have differed.
- If there are survival issues during the study, the Sponsor should contact the Review Division before any changes are made.

Karen Davis Bruno, PhD
Chair, Executive CAC

Reference ID: 4529837

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