CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	216578
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Submission Date	06/22/2022
Submission Type	Priority
Brand Name	(b) (4)®
Generic Name	Fezolinetant
Dosage Form and Strength	Film-coated tablet contains 45 mg fezolinetant
Dosage and Administration	One 45 mg tablet once daily with or without food
Proposed Indication	For the treatment (b) (4) of moderate and severe vasomotor symptoms (VMS) associated with menopause.
Applicant	Astellas Pharma Inc.
Associated IND	IND 130277
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1. EXECUTIVE SUMMARY

Fezolinetant is a nonhormonal selective NK3 receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center. The proposed indication is treatment of moderate or severe vasomotor symptoms associated with menopause. The recommended dose of fezolinetant for the general intended population is one 45 mg tablet once daily with or without food. Fezolinetant is considered as a new molecular entity (NME) in the US.

The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology, has reviewed the information contained in NDA 216578 and recommends approval of this NDA pending successful labeling negotiation. The key review issues with specific recommendations and/or comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	• Two pivotal Phase III studies (Study 2693-CL-0301 and 2693-CL-0302) demonstrated the safety and efficacy of fezolinetant for the proposed indication of treatment of moderate or severe vasomotor symptoms associated with menopause.
General dosing instructions	The recommended dosing regimen is one 45 mg tablet once daily with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dosage adjustment for fezolinetant is recommended for patients with mild or moderate renal impairment (eGFR 30 to < 90 ml/min/1.73 m^2). Avoid use in patients with severe renal impairment (eGFR 15 to <30 ml/min/1.73 m^2) or end-stage renal disease (eGFR < 15 mL/min/1.73 m^2) with or without hemodialysis. • Avoid use in patients with mild, moderate or severe hepatic impairment (Child-Pugh A, B or C). • Avoid use in patients with concomitant use of any CYP1A2 inhibitors.
Bridge between the to-be-marketed and clinical trial formulations	Two minor adjustments were conducted in the formulation development from the phase 3 to the to-be marketed tablet, quantitative adjustments for three ingredients in the (b) (4) tablet and modification of tablet color shade. The two formulations are bridged based on a bioequivalence (BE) study.
Labeling	Pending negotiation with the applicant. Our edits to the applicant's proposed labeling are consistent with guidance *"Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format"*

1.1 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Fezolinetant is a nonhormonal selective NK3 receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center.

In healthy women, fezolinetant C_{max} and AUC increased proportionally over a dosage range from 20 and 60 mg once daily (0.44 to 1.33 times the approved recommended dosage). Steady-state plasma concentrations of fezolinetant were reached after two once-daily doses, with minimal fezolinetant accumulation.

Absorption

The median (range) time to reach fezolinetant C_{max} is 1.5 (1 to 4) hours in healthy women.

Effect of Food

No clinically meaningful differences in fezolinetant pharmacokinetics were observed following administration with a high-calorie, high-fat meal.

Distribution

The mean apparent volume of distribution (V_z/F) of fezolinetant is 189 L. The plasma protein binding of fezolinetant is 51%. The blood-to-plasma ratio is 0.9.

Elimination

The apparent clearance at steady state of fezolinetant is 10.8 L/h. The mean terminal elimination half-life (t1/2) of fezolinetant is 13.1 hours in healthy women. The effective half-life for a typical subject (70 kg, white, non-smoking female) is 9.6 hours.

Metabolism

Fezolinetant is primarily metabolized by CYP1A2 in humans to oxidized major metabolite ES259564. ES259564 is approximately 20-fold less potent against human NK3 receptor. The metabolite-to-parent ratio ranges from 0.7 to 1.8.

Excretion

Following oral administration, fezolinetant is mainly eliminated in urine (76.9%) and to a lesser extent in feces (14.7%). In urine, a mean of 1.1% of the administered fezolinetant dose was excreted unchanged and 61.7% of the administered dose was excreted as ES259564. In feces, about 0.1% of the administered fezolinetant dose was excreted unchanged and 14.6% of the administered dose was excreted as ES259564.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen of 45 mg tablet once daily was selected based on two successful Phase 3 studies using this regimen. Exposure-response analyses for efficacy and safety provided supportive evidence for approving 45 mg once daily.

2.2.2 Therapeutic individualization

Renal Impairment:

In a dedicated renal impairment study (Study 0008), after a 30 mg oral dose of fezolinetant, subjects with mild, moderate, and severe renal impairment had mean fezolinetant exposures (AUClast) that were 29%, 31%, and 11% lower, respectively, compared to healthy, matched control subjects. The mean peak fezolinetant exposures (Cmax) in subjects with mild, moderate, and severe renal impairment were comparable to the healthy matched control subjects. Mean exposures of the major metabolite (ES259564) in subjects with mild, moderate, and severe renal impairment were 3%, 77% and 379% higher for AUClast, respectively, and 13%, 75% and 131% higher for Cmax as compared to healthy, matched control subjects.

In the population PK analysis, eGFR was not a significant covariate on the PK of fezolinetant. The mean (CV%) of population PK model predicted steady-state AUCs (ng.hr/mL) were 4159 (45.4%), 4097 (41.8%), and 4061 (36.6%) for subjects with normal, mildly impaired, and moderately impaired renal functions after 45 mg once daily dosing.

Despite lower exposure in patients with mild (19.2% decrease in AUClast) or moderate renal impairment (31.2% decrease in AUClast) in the dedicated renal impairment study, the population PK model-predicted exposure in patients with mild or moderate renal impairment had comparable exposure to patients with normal renal function; hence, no dose adjustment is recommended for mild or moderate renal impairment.

The use of fezolinetant is not recommended in patients with severe renal impairment because the exposure of the major metabolite (ES259564) in this subpopulation increased by ~4 fold compared to patients with normal renal function and the safety of the metabolite at this exposure level has not been assessed in any long-term clinical study.

There is no data to support the use of fezolinetant in patients with end-stage renal disease.

Hepatic Impairment:

In a dedicated hepatic impairment study (Study 0007), after a 30 mg oral dose of fezolinetant, patients with mild and moderate hepatic impairment had mean fezolinetant total exposures (AUCinf) 56% and 96% higher, respectively, than the healthy matched control subjects. The mean peak fezolinetant

exposures (Cmax) in mild and moderate hepatic impairment patients were 23% higher and 15% lower, respective, than the healthy matched control subjects.

The use of 45 mg once daily fezolinetant is not recommended because 1) there was a 56% increase in AUCinf in the mild hepatic impairment group which may not be fully explained by high PK variability; 2) no phase 3 data is available for patients with mild hepatic impairment; 3) patients with mild hepatic impairment may have increased risk for liver toxicity; and 4) no safety information for doses above 45 mg for chronic use is available.

We recommend avoiding use in patients with moderate hepatic impairment because 1) exposure in patients with moderate hepatic impairment increased by ~100% compared to healthy matched controls and we do not have a mitigation strategy (e.g., lowering the dose that would match 45 mg exposures); 2) no phase 3 data is available for patients with moderate hepatic impairment; and 3) patients with chronic liver impairment may have increased risk for transaminase increase (i.e., ALT/AST >3XULN) based on exposure-response analysis for safety

We recommend avoiding use in patients with severe hepatic impairment because there is no data available in this population.

Drug-Drug Interaction (DDI):

In a dedicated DDI study (Study 0006), concomitant administration of fluvoxamine (a strong CYP1A2 inhibitor) increased fezolinetant Cmax and AUC by ~100% and ~850%, respectively.

Using a physiological based pharmacokinetic (PBPK) modeling and simulation approach, concomitant use of a weak CYP1A2 inhibitor is predicted to increase fezolinetant AUC by 60 to 100% and concomitant use of a moderate CYP1A2 inhibitor is predicted to increase fezolinetant AUC by ~360%.

In the two pivotal phase 3 studies, a small number of patients (N = 42, n = 22 for 45 mg and n = 20 for 30 mg) had concomitant use of weak CYP1A2 inhibitors. TEAEs in these subjects were generally mild and resolved.

The concomitant use of 45 mg once daily fezolinetant with mild CYP1A2 inhibitors is not recommended for the following reasons,

1. PBPK modeling and simulation predicted 1.6- to 2-fold increase with concomitant use of weak CYP1A2 inhibitors.
2. Although TEAEs in subjects who received weak CYP1A2 inhibitors were generally mild and reversible, the number of subjects is relatively small.

We recommend avoiding concomitant use of moderate or strong CYP1A2 inhibitors because there was a substantial increase in exposure and no clinical data to support its use.

2.3 Outstanding Issues

None from a clinical pharmacology perspective.

2.4 Summary of Labeling Recommendations

Per guidance "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format", edits were made to Section 2.1 Recommended Dosage, Section 7 Drug Interactions sections, Section 8.6 Renal Impairment, Section 8.7 Hepatic Impairment, Section 12.2 Pharmacodynamics and Section 12.3 pharmacokinetics.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The Product

The applicant, Astellas Pharma Inc., submitted a New Drug Application (NDA) for (b) (4)™ (fezolinetant 45 mg tablet) for the treatment of moderate or severe vasomotor symptoms associated with menopause on June 2nd, 2022.

Fezolinetant is a nonhormonal, selective NK3 receptor antagonist. By antagonizing NKB/NK3-mediated signaling, fezolinetant modulates KNDy neurons' activity in the thermoregulatory center in the hypothalamus to treat moderate to severe VMS associated with menopause.

The proposed dose of (b) (4)™ is one 45 mg tablet once daily with or without food in the general population of individuals with moderate to severe VMS associated with menopause.

Regulatory History

IND 130277 was open for fezolinetant on March 28, 2016. Initially, the early clinical development program explored the potential for fezolinetant to treat other conditions (96 participants with polycystic ovary syndrome or uterine fibroids) but subsequently focused on VMS associated with menopause.

The Clinical Development Program

The fezolinetant clinical program is comprised of 18 completed studies: 11 phase 1 studies, 4 phase 2 studies and 3 phase 3 studies. The 18 completed studies have been conducted globally: North America, Europe, and Asia.

Primary evidence for the efficacy of fezolinetant in the treatment of moderate to severe VMS associated with menopause comes from the two pivotal phase 3 studies (studies 2693-CL-0301 and 2693-CL-0302).

Phase 2 studies ESN364_HF_204 (proof-of-concept) and ESN364_HF_205 (dose finding) provided supportive safety data for this application.

The fezolinetant clinical pharmacology program consisted of 11 Phase 1 studies. The pharmacokinetics of fezolinetant were evaluated in healthy male and female adult participants, postmenopausal participants with VMS and special populations (participants with mild to moderate hepatic impairment and participants with mild to severe renal impairment). The absorption, distribution, metabolism, and elimination, including, metabolite profiling, protein binding, inter-and intra-variabilities, and time dependency assessment of fezolinetant PK were characterized. Intrinsic factors including age, race, gender and body weight, and extrinsic factors including smoking, formulation and food intake were assessed in pooled population pharmacokinetic modeling analysis. Drug-drug interactions of fezolinetant were evaluated in a combination of in vitro and in vivo studies and further supported by PBPK modeling analyses. Food effect and relative bioavailability of different formulations (i.e., capsules for Phase 1 and 2, tablets for phase 3, and to-be-marketed tablets) were evaluated in phase 1 studies.

The pharmacokinetics of fezolinetant in special populations (renal and hepatic impairment) were assessed in dedicated studies.

Although both a 30 mg and 45 mg dose were evaluated in the pivotal phase 3 studies, the Applicant only intends to market a 45 mg tablet.

Characterization of the pharmacodynamics of fezolinetant includes exploratory assessments of sex hormones (Luteinizing hormone [LH], Follicle-stimulating hormone [FSH], estradiol [E2], estrone [E1], Sex hormone binding globulin [SHBG], dehydroepiandrosterone (DHT), androstenedione (A4) and testosterone [T]) and exposure-response analyses for fezolinetant efficacy, safety, and QT prolongations.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Fezolinetant is a nonhormonal selective NK3 receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory
Active Moieties	Fezolinetant is the active moiety; the major metabolite ES259564 is approximately 20-fold less potent against human NK3 receptor and considered non-pharmacologically active.
QT Prolongation	At a dose 20 times the maximum approved recommended dose, fezolinetant does not prolong the QT interval to any clinically relevant extent.
General Information	
Bioanalysis	LC-MS/MS methods were used to measure fezolinetant concentrations in plasma and urine.
Healthy vs. Patients	Fezolinetant pharmacokinetics were similar between healthy female subjects and patients with moderate to severe vasomotor symptoms associated with menopause.
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Multiple-dosing of 45 mg once daily was only tested in phase 3 studies. The population PK model-predicted steady-state concentration (mean±SD) is 183 (±92.5) ng/mL.
Range of Effective Dose or Exposure	Two dose levels, 30 mg and 45 mg once daily, were tested in pivotal Phase 3 studies and both treatments demonstrated statistically significance compared to placebo on four co-primary endpoints. The efficacy of 45 mg was more robust and clinical meaningful.
Maximally Tolerated Dose (MTD) or Exposure	The MTD of fezolinetant in female subjects was 900 mg.

Dose Proportionality	PK of fezolinetant is dose-proportional between 20 to 60 mg once daily.		
Accumulation	The recommended dose for approval 45 mg once daily was only tested as a single dose in food effect and Pivotal BE study. The model predicted median accumulation ratio (Rac) is 1.20.		
Variability	Intra-subject variability was estimated to be 9.3% and 10.7% (geometric %CV) based on AUCinf and AUClast in healthy female participants, respectively. Intra-subject variability for Cmax is 28.3% (Study 2693-CL-0010). Inter-subject variability was estimated to be 46% for apparent clearance (CL/F) and 15% for apparent volume of distribution (Vc/F) based on a population PK analysis in postmenopausal female participants with VMS (Report 2693-PK-0010).		
Absorption			
Bioavailability	Absolute bioavailability was not determined.		
Time to Maximum Concentration (Tmax)	After a single oral dose of 45 mg fezolinetant (To-be-marketed formulation) in healthy female subjects in a bioequivalence study (Study 0010), the median (min-max) of T_{max} was 1.5 hour (range: 0.5 - 4.0 hours).		
Food effect Geometric mean ratio [90% CI]	**AUC0-∞**	**Cmax**	**Tmax**
	[a]0.97 [0.86-1.08]	[a]0.77[0.62-0.95]	[a]Delayed by ~0.5 hours
	[a]Following a high-fat high calorie meal containing 800 - 1000 calorie (50% from fat)		
Distribution			
Volume of Distribution	The predicted apparent volume of distribution is 189 Liters.		
Plasma Protein Binding	Fezolinetant is approximately 50% bound to human plasma protein over a concentration range of 0.2 to 100 µg/mL. The average blood/plasma concentration ratio is 0.9.		
As Substrate of Transporters	Fezolinetant is not a substrate for P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP 1B1/OATP1B3). Renal transporters, i.e., organic cation transporter 2 (OCT2), organic anion transporter 1/3 (OAT1/OAT3), multidrug and toxin extrusion transporter (MATE)1, or MATE2-K, were not tested as < 1.1% fezolinetant dose was excreted unchanged from renal pathway. The metabolite, ES259564, is a substrate for P-gp, but not substrate for BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K.		
Elimination			

Terminal Elimination Half-Life	After a single oral dose of 45 mg fezolinetant (To-be-marketed formulation) in healthy female subjects in a bioequivalence study (Study 0010), the mean (±SD) terminal elimination half-life of fezolinetant is 13.1 (±4.6) hours.
Effective Elimination Half-Life	In VMS patients, the effective half-life of fezolinetant is predicted to be 9.6 hours for a typical subject (70 kg, white, non-smoking female).
Metabolism	
Fraction Metabolized (% dose)	90.4% of the drug is metabolized as a percent of the dose.
Primary Metabolic Pathway(s)	Fezolinetant is primarily metabolized by CYP1A2 in humans to oxidized major metabolite ES259564 and to a lesser extent by CYP2C9 and CYP2C19.
Excretion	
Primary Excretion Pathways **(% dose) ± SD**	- Urine: 76.9% (~1.1% unchanged fezolinetant) - Feces: 14.7% (~0.1% unchanged fezolinetant)
Interaction liability (Drug as perpetrator)	
Inhibition/Induction of Metabolism	Fezolinetant and ES259564 are not inhibitors of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A at concentrations up to 25 µM (approximately 36-fold of therapeutic concentration). Fezolinetant and ES259564 did not cause time dependent inhibition of these enzymes. Furthermore, fezolinetant and ES259564 do not cause significant induction of CYP1A2, CYP2B6 and CYP3A4 at concentrations up to 100 µM (approximately 140-fold of therapeutic concentration).
Inhibition/Induction of Transporter Systems	Fezolinetant and ES259564 are not inhibitors of P-gp, BCRP, OATP1B1, OAT1, OAT3, OATP1B3, OCT2, MATE1, and MATE2-K at clinically relevant concentrations.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The 45 mg and 30 mg once daily of fezolinetant were selected for pivotal Phase 3 studies (Studies 301 and 302) primarily based on safety and efficacy results obtained in the Phase 2 dose-finding study (Study 205).

In the 12-week placebo-controlled Phase 2 dose-finding study (Study 205), 15, 30, 60, and 90 mg twice daily (BID) and 30, 60, and 120 mg once daily (QD) were tested. The co-primary endpoints were mean

change in the frequency of moderate to severe VMS from baseline to Week 4 & Week 12 and mean change in the severity of moderate to severe VMS from baseline to Week 4 & Week 12.

All dose groups were significantly different from placebo with respect to mean change in the frequency of moderate to severe VMS at both weeks 4 and 12. The improvement in frequency of moderate to severe VMS relative to placebo at weeks 4 and 12 was greater than 2, indicative of a clinically relevant improvement, for all dose groups except 15 mg BID. In addition, all groups were significantly different from placebo with respect to mean change in the severity of moderate to severe VMS from baseline to week 4, but only 60 mg BID, 90 mg BID and 60 mg QD demonstrated significance with respect to mean change in severity at week 12.

Based on the phase 2 clinical efficacy and safety results and modeling and simulation analyses, the 30 mg QD dosing regimen was considered the lowest effective dose. In addition, a 45 mg QD dose, while not previously studied, was predicted to increase the probability of achieving efficacy endpoints while limiting the risk of potential exposure related transaminase elevations.

Clinical pharmacology information that supports the proposed dosing regimen of fezolinetant is presented below:

Exposure-response relationship for efficacy

Exposure-response analyses for efficacy were performed utilizing phase 3 data from Studies 2693-CL-0301 and 2693-CL-0302. Models were developed to characterize the relationship between fezolinetant exposure and both hot flash frequency and severity. The exposure-response analyses showed that fezolinetant exposure was predictive of both the frequency and severity of hot flashes. Although the relationship is shallow, increasing fezolinetant exposure is associated with better efficacy, i.e., 45 mg had slightly better efficacy than 30 mg. More details can be found in “ER (efficacy) Assessment Summary” of Appendix 4.5 Pharmacometrics Review.

Exposure-response (E-R) relationship for safety

In a pooled analysis including all pivotal phase 3 data and phase 2 data (from Studies ESN364_HF_204 and ESN364_HF_205) in subjects with VMS receiving total daily fezolinetant doses ranging from 30 mg to 180 mg, a statistically significant relationship between fezolinetant exposure (i.e., total daily dose or individual predicted steady-state Cavg) and ALT/AST elevation was identified. The hazard ratio (95% CI) for a liver transaminase elevation > 3 x ULN for the population mean fezolinetant concentration resulting from a 30 and 45 mg QD dose compared with placebo is 1.293 (1.157, 1.403) and 1.471 (1.245, 1.663), respectively. The hazard ratios (95% CI) for an ALT or AST elevation > 3 x ULN for baseline ALT values of 43 U/L (ULN) and 65 U/L (1.5 x ULN) relative to 18 U/L (the median observed value) were 2.604 (1.744, 3.530) and 6.044 (2.846, 10.710), respectively. Baseline ALT level was identified as a statistically significant and the single greatest predictor of postbaseline liver transaminase elevations in the pooled dataset and was included in the final model. More details can be found in “ER (safety) Assessment Summary” of Appendix 4.5 Pharmacometrics Review.

In general, the exposure-response analyses for efficacy showed improved reduction in VMS frequency and severity with increasing doses for fezolinetant compared to placebo. The exposure-response analyses for safety identified a potential association between fezolinetant exposure and the rate of ALT or AST > 3 x ULN when combining the data from the phase 2 and phase 3 studies. Overall, the exposure-response analyses support the current dose regimen of fezolinetant.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dose regimen of 45 mg once daily is supported by clinical efficacy, safety, PK, and PD data. The safety and efficacy of fezolinetant 45 mg QD for the treatment of moderate or severe VMS with menopause have been demonstrated in the pivotal Phase 3 studies, 2693-CL-0301 and 2693-CL-0302. Efficacy evaluations from the two studies consistently demonstrated the superiority of fezolinetant 45 mg QD over placebo across all four co-primary efficacy endpoints and clinically meaningful reduction in frequency of VMS from baseline. Note: Although both 30 and 45 mg once daily met all four co-primary endpoints in the phase 3 studies, the applicant is seeking approval for 45 mg once daily only. Fezolinetant 45 mg QD had a more meaningful and more consistent reduction in VMS than 30 mg QD. For details of the Phase 3 studies, please see the Medical Officer's review.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, we recommend avoiding use of fezolinetant for 1) patients with severe renal impairment or end-stage renal disease with or without dialysis and 2) patients with mild, moderate, or severe hepatic impairment.

Dedicated studies were conducted to evaluate impact of renal/hepatic impairment on the PK of fezolinetant. In addition, intrinsic covariates including creatinine clearance, body weight, age, race, and menopause status were evaluated in a population PK analysis (Report 2693-PK-0010).

<u>Renal Impairment</u>

- No dose adjustment for patients with mild or moderate renal impairment

In the renal impairment study 2693-CL-0008, female subjects with normal, mild, moderate, and severe renal impairment had comparable Cmax after a single oral administration of 30 mg fezolinetant. Subjects with mild or moderate renal impairment had 19.2% and 31.2% lower total exposure (AUClast), respectively, compared to healthy normal subjects.

A total of 201 subjects with normal renal function, 267 subjects with mild renal function, and 7 subjects with moderate renal impairment were enrolled into pivotal phase 3 studies (2693-CL-0301 and 2693-CL-0302). The steady-state AUCs of fezolinetant in participants with normal, mild, and moderate renal impairment from these two phase 3 studies were predicted based on a population PK analysis. The total exposure of fezolinetant in subjects with mild or moderate renal impairment was similar to the exposures in subjects with normal renal function. The mean (CV%) of population PK model-predicted steady-state AUCs (ng.hr/mL) were 4159 (45.4%), 4097 (41.8%), and 4061 (36.6%) for subjects with normal, mildly impaired, and moderately impaired renal functions after once daily dosing. In addition, creatine clearance was not identified as a statistically significant covariate for the clearance of fezolinetant. More details can be found in "Population PK Analysis" of Appendix 4.5 Pharmacometrics Review.

Despite lower exposure in patients with mild (19.2% decrease in AUClast) or moderate renal impairment (31.2% decrease in AUClast) in the dedicated renal impairment study, the population PK model-predicted exposure in patients with mild or moderate renal impairment had comparable exposure to patients with normal renal function; hence, no dose adjustment is recommended for mild or moderate renal impairment.

- Avoid use in patients with severe renal impairment or end-stage renal disease

In the renal impairment study in female participants, the total exposure based on AUClast was 9.6% lower than in healthy normal participants, but the exposure for the major metabolite, ES259564, was 4.8-fold higher. The clinical program has not assessed the safety of the metabolite at this exposure level in any long-term clinical study. Therefore, the use of fezolinetant is not recommended in patients with severe renal impairment. There is no data to support the use of fezolinetant in patients with end-stage renal disease.

Hepatic Impairment

- Patients with mild hepatic impairment

Based on the hepatic impairment study in female participants, mild hepatic impairment led to approximately 56% increase in fezolinetant AUC and 23% increase in Cmax. Based on the dedicated study, dosing patients with mild hepatic impairment 45 mg daily may lead to a ~50% higher exposure than what has been evaluated in phase 3 studies.

The exclusion criteria of all phase 3 studies (2693-CL-0301, 2693-CL-0302 and 2693-CL-0304) did not use Child-Pugh criteria for screening. In response to our Information Request, the applicant stated that "While not captured as Child-Pugh score, review of the components of the score does not support presence of chronic hepatic impairment as defined by Child-Pugh categories, and participants with chronic hepatic impairment were excluded from the study." Therefore, there are no clinical data to support a safe clinical use of fezolinetant in patients with mild hepatic impairment. In addition, based on the exposure-response analysis for liver toxicity, there is a potential association between exposure and

transaminase elevation (i.e., ALT/AST >3X ULN) with baseline ALT level being the most influential covariate in predicting transaminase elevation probability.

Based on overall assessment of benefit/risk, we recommend avoiding use of fezolinetant in patients with mild hepatic impairment.

- Patients with moderate or severe hepatic impairment

Moderate hepatic impairment led to 94 to 96% increase in fezolinetant AUC (Study 2693-CL-0007), and the PK of fezolinetant have not been evaluated in patients with severe hepatic impairment. As subjects with chronic moderate or severe hepatic impairment were excluded in the phase 3 studies, there are no clinical data to support a safe clinical use of fezolinetant in patients with moderate or severe hepatic impairment.

Based on an overall assessment of benefit/risk, we recommend avoiding use of fezolinetant in patients with moderate or severe hepatic impairment.

Body Weight

In a population PK analysis (Report 2693-PK-0010), body weight was identified as a predictive covariate on central volume of distribution, but not a statistically significant covariate of clearance. Participants weighing 100 kg were predicted to have a 17.2% lower fezolinetant Cmax than participants with a typical 75 kg weight. Participants weighing 55 kg were predicted to have a 25.6% higher fezolinetant Cmax than participants with a typical 75 kg weight. We recommend no dose adjustment based on body weight.

Age

Studies designed to assess the effect of age on fezolinetant PK have not been conducted to date. A population PK model including female participants ranging from 19 to 65 years of age showed no trends between age and PK parameters. No pediatric participants have been studied with fezolinetant. Therefore, we recommend no dose adjustment based on age.

Race

African American was identified as a predictive covariate on central volume of distribution, but not a statistically significant covariate of clearance. African American women were also predicted to have a small increase in central volume of distribution resulting in a small (6.6%) reduction in Cmax compared to non-African American women participants. We recommend no dose adjustment based on race.

Menopause status

Menopause status was not identified as a predictive covariate on central volume of distribution or clearance, indicating no significant PK difference between pre- and postmenopausal women.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes, we recommend avoiding use of fezolinetant for patients who are taking mild, moderate, or strong inhibitors of CYP1A2.

Dedicated studies were conducted to evaluate the impact of 1) concomitant use of a strong CYP1A2 inhibitor and 2) a standard high-fat high caloric meal on the PK of fezolinetant. In addition, extrinsic covariates including smoking (CYP1A2 inducer), food, and formulation were evaluated in a population PK analysis (Report 2693-PK-0010).

Concomitant use of CYP1A2 inhibitors

In a dedicated DDI study, concomitant use of fluvoxamine (a strong CYP1A2 inhibitor) resulted in a 9.4-fold increase in fezolinetant AUCinf and 1.8-fold increase in Cmax. The applicant did not conduct a dedicated DDI study to evaluate the impact of weak or moderate CYP1A2 inhibitors. Instead, they used a physiological-based pharmacokinetic (PBPK) approach to predict the magnitude of change in fezolinetant exposure with concomitant use of weak or moderate CYP1A2 inhibitors. The predicted results are shown in Table 1.

Table 1. PBPK Predicted Cmax and AUC Geometric Mean Ratios (GMR) for Fezolinetant in the Presence of CYP1A2 Inhibitors.

Co-administration treatment		PBPK predicted fezolinetant GMR	
		Cmax	AUCinf
Weak CYP1A2 inhibitor	Cimetidine 300 mg every 6 hours	1.3	2.0
	Cimetidine 400 mg BID	1.4	1.6
Moderate CYP1A2 inhibitor	Mexiletine 400 mg every 8 hours	1.4	4.6

Source: Table 3 in Appendix 4.4 PBPK review

- Concomitant use with weak CYP1A2 inhibitors

Using a PBPK approach, weak CYP1A2 inhibitors are predicted to increase fezolinetant exposure by 1.6- to 2-fold. In the phase 3 studies, 22 subjects received 45 mg fezolinetant had concomitant use of weak CYP1A2 inhibitors. Although treatment emergent adverse events (TEAEs) in these subjects were generally mild and resolved, the number of subjects with concomitant use of weak CYP1A2 inhibitors is relatively small.

Given the predicted 60% to 100% increase in exposure with concomitant use of weak CYP1A2 inhibitors and limited safety data from phase 3 studies, the concomitant use of 45 mg once daily fezolinetant with weak CYP1A2 inhibitors is not recommended.

- Avoid use in patients with concomitant use of moderate or strong CYP1A2 inhibitors

Moderate and strong CYP1A2 inhibitor were predicted to lead to 4.6- (based on PBPK model) and 9.4 -fold (based on a dedicated DDI study) increase in fezolinetant AUC. There are no clinical data to support such a high exposure in postmenopausal women. Therefore, the concomitant use of moderate and strong inhibitors of CYP1A2 should be avoided.

Smoking

In a dedicated study (Study 2693-CL-0006), smoking resulted in decreased fezolinetant exposure. When fezolinetant was administered alone, fezolinetant AUCinf decreased by about a half to a geometric least square (LS) mean ratio of 48.3% while Cmax decreased to a geometric LS mean ratio of 71.7%. Similarly, in population PK analysis, a 51% increase in clearance was predicted for smokers relative to non-smokers, resulting in a 33.9% reduction in steady-state AUC and an 8.6% reduction in steady-state Cmax.

Randomization of the two pivotal phase 3 studies were stratified by smoking status. In one study (Study 0301), 17 smokers and 129 nonsmokers received 45 mg QD fezolinetant. In the other study (Study 0302), 28 smokers and 117 nonsmokers received 45 mg QD fezolinetant. Based on a small sample size of smokers, the sub-group analysis by smoking status (no statistically testing specified in Statistic Analysis Plan [SAP]) from the phase 3 studies indicated that smoking has no impact on efficacy compared with nonsmokers despite the fact that smokers were expected to have reduced PK exposures.

Therefore, we recommend no dose adjustment for smokers.

Formulation

During development, a capsule formulation was used in phase 1 and 2 studies while a tablet formulation was used in phase 3 trials. The relative bioavailability of fezolinetant between the phase 3 tablet formulation and the capsule formulation was assessed at the highest strength of 120 mg in Study 2693-CL-0009. The results demonstrated that following a single dose administration, geometric LS means of AUCinf, AUClast, and Cmax of the tablet formulation were 8%, 9%, and 23% higher relative to the capsule formulation, respectively. While the 90% CI of Cmax (101-136%) exceeded the BE criteria of 80-125%, the 90% CI of AUCinf and AUClast were still contained in the criteria of 80-125%.

A BE study (Study 2693-CL-0010) was conducted to compare the pharmacokinetics of the to-be-marketed formulation to the formulation used in Phase 3 trials. The results showed that the test formulation (45 mg fezolinetant to-be-marketed tablet) was bioequivalent to the reference formulation (45 mg fezolinetant comprising one 30 mg and one 15 mg fezolinetant phase 3 tablet).

Food effect

In Study 0012, following a single 45 mg dose of fezolinetant (to-be-marketed formulation) to healthy female participants, a high-fat, high-calorie meal did not affect fezolinetant AUCinf and AUClast compared to under fasted conditions. The high-fat, high-calorie meal decreased Cmax by ~23% of fezolinetant and delayed the time to reach Cmax by ~ 30 minutes. The decrease in exposure is not considered clinically relevant. We recommend that fezolinetant can be administered with or without food.

4. APPENDICES

Fezolinetant is also referred to as ESN364 during clinical development.

4.1 Summary of Bioanalytical Method Validation and Performance

Concentrations of fezolinetant and its major metabolite, ES259564, in plasma and urine were determined by liquid chromatography - tandem spectrometry (LC-MS/MS) methods. A total of five LC-MS/MS methods for fezolinetant or fezolinetant and ES259564 with different concentration ranges, matrices (plasma or urine), sample processing (protein precipitation or solid phase extraction), analytical sites [(b) (4)], were developed and validated.[1]

Summary of key validation parameters of the LC-MS/MS method (2693-ME-0004) used to determine the plasma concentrations of fezolinetant and ES259564 in phase 3 studies (2693-CL-0301, 2693-CL-0302 and 2693-CL-0304), dose-ranging study (ESN364_HF_205) , the mass balance study (ESN364-CPK-103), in vivo DDI study (2693-CL-0006), hepatic impairment study (2693-CL-0007), renal impairment study (2693-CL-0008), relative bioavailability study (2693-CL-0009), BE study (2693-CL-0010) and food effect study (2693-CL-0012) is provided in Table 2 below.

Table 2 Summary of Key Validation Parameters for LC-MS/MS assays (2693-ME-0004)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a UHPLC-MS/MS method for the determination of ESN-364 and its metabolite ES259564 in lithium heparinized human plasma Report Number: Astellas Number = [2693-ME-0004] (b) (4) (b) (4) Amendment 1] Analytical Method Number: BA/18/680 – Versions 1 to 6
Method description	An LC-MS/MS method for the determination of fezolinetant and ES259564 (metabolite) concentrations in lithium heparinized human plasma. The plasma samples are purified using SPE and chromatographic separation is achieved on a phenylhexyl column with detection on a mass spectrometer.
Materials used for standard calibration curve and concentration	Fezolinetant (Batch N120137F) ES259564 (metabolite) (Batches B00278201/JKO_011-47, MD338J and MEL_025-63) Fezolinetant: 1.00, 5.00, 25.0, 50.0, 100, 250, 500 and 1000 ng/mL ES259564: 1.00, 5.00, 25.0, 50.0, 100, 250, 500 and 1000 ng/mL
Validated assay range	**1.00 to 1000 ng/mL**
Material used for QCs	Fezolinetant (Batch N120137F)

[1] Docubridge, NDA 216578, seq 0001, module 2.7.1, Summary of Biopharmaceutic Studies and associated analytical methods, Appendix Table 2.7.1.3, submitted on: 06/22/2022

and concentration	ES259564 (Batches B00278201/JKO_011-47, MD338J and MEL_025-63) Fezolinetant: 1.00, 3.00, 60.0, 810 ng/mL ES259564: 1.00, 3.00, 60.0, 810 ng/mL		
Regression model and weighting	Linear with a weighting factor of $1/X^2$		
Validation Parameters	**Method Validation Summary**		**Source Location**
Standard calibration curve performance during all runs	Number of standard calibrators from LLOQ to ULOQ	x 8	Table 3 and Table 4 of report 2693-ME-0004
	Cumulative accuracy (%bias) from LLOQ to ULOQ Fezolinetant ES259564	 -5.02 to 2.84 -6.69 to 2.95	Section 1.2 of report 2693-ME-0004 Amendment No.1
	Cumulative precision (%CV) from LLOQ to ULOQ Fezolinetant ES259564	 ≤ 4.04 ≤ 3.96	Section 1.2 of report 2693-ME-0004 Amendment No.1
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs** QCs for fezolinetant: LLOQ LQC MQC HQC DiQC (10-fold) QCs for ES259564: LLOQ LQC MQC HQC DiQC (10-fold)	 -15.92 to -8.28 -10.04 to -5.10 -9.09 to -2.14 -13.12 to -6.40 2.59 -5.15 to 3.18 -2.42 to 2.58 -4.34 to 3.88 -8.55 to -2.10 6.98	Tables 11, 13, 33 and 34 of report 2693-ME-0004
	Interbatch (%CV) QCs for fezolinetant: LLOQ LQC MQC HQC QCs for ES259564: LLOQ LQC MQC HQC	 6.76 4.49 5.03 4.42 7.14 5.42 5.05 4.44	Table 11 and Table 13 of report 2693-ME-0004
	TE		
Validation Parameters	**Method Validation Summary**		**Source Location**

Selectivity & matrix effect	**Selectivity:** The absence of interferences in blank samples was not required per the SOPs applicable at that time because the combination of sample extraction, chromatographic separation, and selective MS/MS (Triple quadrupole which follows a selective couple of mass: parent ion and selective daughter ion) ensures the absence of potential interfering impact. Additional selectivity was evaluated using 6 individual lots. No relevant interferences were observed (Study 2693-CL-0304). **Internal Standard (IS) normalized matrix factor:** Matrix effect was evaluated as part of the matrix factor test. Number of lots tested: 6 Concentration levels tested: LQC, MQC and HQC Fezolinetant Overall Precision (%CV): ≤ 4.83 ES259564 Overall Precision (%CV): ≤ 4.97 Matrix factor acceptance criteria were met.	Table 10 and Table 11 of report B1900365 Table 25 to Table 30 of report 2693-ME-0004
Interference & specificity	The specificity of the assay for fezolinetant was evaluated at the LLOQ (1.00 ng/mL) in the presence of ES259564 (metabolite) at 1000 ng/mL concentration. **Interference on fezolinetant from ES259564:** Number of replicates tested: 6 Range of observed bias: -15.98% to 2.47% Conclusion: **No interference was observed**. The specificity of the assay for ES259564 was evaluated at the LLOQ (1.00 ng/mL) in the presence of fezolinetant at 1000 ng/mL concentration. Interference on ES259564 from fezolinetant: Number of replicates tested: 6 Range of observed bias: -3.54% to 5.68% Conclusion: **No interference was observed.**	Table 15 and Table 16 of report 2693-ME-0004
Hemolysis effect	The hemolysis effect in human plasma was evaluated at 2 analyte concentration levels (low and high) and 2 levels of spiked hemolyzed human whole blood (1% and 2%). Fezolinetant: Number of sources tested: 2 Range of observed bias: 0.73% to 8.72% ES259564: Number of sources tested: 2 Range of observed bias: 1.05% to 10.13% The results showed no hemolysis effect in plasma spiked with 1% or 2% hemolyzed human whole blood.	Table 17 and Table 18 of report 2693-ME-0004

Validation Parameters	Method Validation Summary	Source Location
Lipemic effect	The lipemic effect in human plasma was evaluated at 2 analyte concentration levels (low and high) and 2 levels of hyperlipidemic human plasma (10 mg/mL and 20 mg/mL lipid concentrations). Fezolinetant: Number of sources tested: 2 Range of observed bias: -0.10% to 8.56% ES259564: Number of sources tested: 2 Range of observed bias: 0.96% to 9.45% The results showed no lipemic effect in hyperlipidemic human plasma with final lipid concentrations of 10 and 20 mg/mL	Table 19 and Table 20 of report 2693-ME-0004
Recovery	Concentration Level — Recovery (%) Fezolinetant: LQC — 94.25 MQC — 91.46 HQCH — 92.57 ES259564: LQC — 87.15 MQC — 87.64 HQC — 89.43 (b) (4) (IS) — 75.08 - 75.33	Table 21 and Table 23 of report 2693-ME-0004
Dilution factor	Fezolinetant: Highest concentration tested: 8100 ng/mL Number of dilution factors: 10 Range of observed bias (RE%): -1.64 to 7.48 ES259564: Highest concentration tested: 8100 ng/mL Number of dilution factors: 10 Range of observed bias (RE%): 3.65 to 10.48	Table 33 and Table 34 of report 2693-ME-0004
Bench-top/process stability	Fezolinetant: 24 hours at room temperature ES259564: 24 hours at room temperature	Table 46 and Table 48 of report 2693-ME-0004
Freeze-thaw stability	Fezolinetant: 5 cycles at -20°C and -65°C ES259564: 5 cycles at -20°C and -65°C	Table 41 through Table 44 of report 2693- ME-0004

Long-term storage	Fezolinetant: 382 days at -20°C and -65°C ES259564: 382 days at -20°C and -65°C	Table 63 through Table 66 of report 2693- ME-0004 Amendment 1
Parallelism	NA	NA
Carry-over	Each analytical run contained 2 calibration curves. A blank plasma sample (without IS) was injected immediately after each of 2 ULOQ samples. The average carry-over was lower than 20% for both analytes and lower than 5% for the IS indicating that carry-over had no impact on the results.	Table 7 and Table 8 of report 2693-ME-0004

CV: coefficient of variation; DiQC: dilution quality control; HQC: quality control at high concentration; IS: internal standard; LC-MS/MS: liquid chromatography with tandem mass spectrometry; LLOQ: lower limit of quantification; LQC: quality control at low concentration; MQC: quality control at medium concentration; MS/MS: tandem mass spectrometry; MRD: minimum required dilution; NA: not applicable; QC: quality control; RE: relative error of measurement; SPE: solid phase extraction; SOP: standard operating procedure; TE: total error; UHPLC-MS/MS: ultra-high performance liquid chromatography with tandem mass spectrometry; ULOQ: upper limit of quantification.

Reviewer comments:

This method is confirmed to show acceptable specificity, recovery, within-run and between-run accuracy and precision for the measurement of fezolinetant and ES259564. The freeze-thaw, processing, long-term stability covered sample storage and experiment periods. The incurred sample reanalysis passed acceptance criteria for key PK studies. This method is validated for the aforementioned clinical studies.

Method validation for other studies

LC-MS/MS methods used in other clinical studies (including urine samples) are validated and the summaries of method validation for each method are provided in the submission. [2] Upon detailed review, these bioanalytical methods are acceptable based on FDA Guidance for Industry on bioanalytical method validation. For the space reason, the method validations are not provided here.

4.2 Clinical vs. To-be-marketed Formulations

Three formulations were developed in the clinical development program of fezolinetant (Table 3).

Table 3 Summary of Fezolinetant formulations in clinical development

	Fezolinetant Drug Product Formulations

[2] Docubridge, NDA 216578, seq 0001, module 2.7.1, Summary of Biopharmaceutic Studies and associated analytical methods, Appendix table 2.7.1.8, 2.7.1.9, 2.7.1.14, 2.7.1.15, 2.7.1.16 and 2.7.1.17, submitted on: 06/22/2022

	Hard Gelatin Capsule	Phase 3 Tablet	To-be-marketed Tablet
Dosage Strengths	3 mg, 10 mg, 15 mg, 30 mg, 60 mg, 90 mg, 120 mg, and 180 mg	15 mg, 30 mg, and 120 mg	30 mg and 45 mg
	Clinical Study Number		
Phase 1 study	ESN364-CPK-101, ESN364-CPK-102, , 2693-CL-0006, 2693-CL-0009, 2693-CL-0020	2693-CL-0007, 2693-CL-0008, 2693-CL-0009, 2693-CL-0010, 2693-CL-0030	2693-CL-0010, 2693-CL-0012
Phase 2 study	ESN364_HF_204, ESN364_HF_205, ESN364-UF-02, ESN364-PCO-201		
Phase 3 study		2693-CL-0301, 2693-CL-0302, 2693-CL-0304	

Fezolinetant was initially developed as immediate-release, hard gelatin capsules for oral administration in 3, 10, 15, 30, 60, 90, 120 and 180 mg strengths. This formulation was used in phase 1 and phase 2 studies.

For the phase 3 program, including parallel phase 1 studies, an immediate-release tablet formulation (15, 30 and 120 mg dose strengths) was developed for oral administration. The composition of the phase 3 tablet is proportionally similar among the dose strengths, of which the 15 mg and 30 mg strength tablets were used in the phase 3 studies. The 120 mg strength tablet was only used in the relative bioavailability study 2693-CL-0009. The phase 3 tablet formulation was used in special population and drug-drug interaction studies to provide support for labeling claims.

The applicant conducted study 2693-CL-0009 with a single dose of 120 mg tablet and a single dose of 120 mg capsule to compare the relative bioavailability of the capsule formulation and the phase 3 tablet formulation. AUCinf and AUClast of a single oral dose of 120 mg tablet were slightly higher (by 8%) than those of a single dose of 120 mg capsule. BE criteria between capsule and tablet formulations were met with regard to fezolinetant AUCinf and AUClast. However, Cmax of capsule and tablet formulations failed to meet the BE criteria, where mean Cmax of capsule formulation increased approximately 22.5% with 90% CI of ratio at 110.43% to 135.92%. See **section 4.2.1** below for details.

The applicant also developed a to-be-marketed tablet formulation for commercial use. The to-be-marketed tablet formulation was developed at strengths of 30 mg and 45 mg, which are the doses studied in the phase 3 clinical studies.

Compared with phase 3 tablet formulation, the to-be-marketed tablets have changes in its (b) (4) tablet composition (b) (4) and tablet color shade. The applicant conducted a dedicated BE study (study 2693-CL-0010) to bridge the phase 3 tablet formulation and the to-be-marketed formulation. See **section 4.2.2** below for details.

4.2.1. Study 2693-CL-0009: Relative Bioavailability of Fezolinetant Between Tablet and Capsule Formulations

Title: A Phase 1 Crossover Study to Assess the Relative Bioavailability of fezolinetant Following a Single Dose of Tablet Formulation Compared to a Single Dose of Capsule Formulation in Healthy Postmenopausal Female Subjects

Primary Objective: This study assessed the relative bioavailability of a single dose of 120 mg fezolinetant tablet (test formulation) compared to a single dose of 120 mg fezolinetant capsule (reference formulation) under fasting conditions in healthy postmenopausal female participants.

Study design: This was a randomized, open-label, 2-period, 2-sequence, single dose crossover study in healthy postmenopausal female subjects. Each subject participated in 2 treatment periods separated by a washout of 4 days between study drug administrations in each period. Subjects were randomized to 1 of 2 sequences according to Table 4.

Table 4 Sequences and Study Treatment Assignments (2693-CL-0009)

Sequence	n	Period 1	Period 2
1	8	A	B
2	8	B	A

A: 120 mg tablet (new formulation); B: 120 mg capsule (reference formulation)

Pharmacokinetic samples were collected predose on day 1 of each period and at multiple time points postdose (i.e., 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours).

Subject Disposition: A total of 16 healthy postmenopausal female subjects were randomized, and 16 subjects completed the study. Data from all subjects were included in the analyses of safety and PK.

PK Results:

The dose of 120 mg fezolinetant was rapidly absorbed in both tablet (test formulation) and capsule (reference formulation). The median tmax is approximately 1.0 and 1.5-hour postdose for the tablet and capsule formulations, respectively **(**Table 5**)**.

Table 5 Study 2693-CL-0009: Plasma Pharmacokinetic Parameters of Fezolinetant by Formulation

Parameter Category/Statistics	Fezolinetant 120 mg	
	Tablet n = 16	Capsule n = 16
AUCinf (ng·h/mL)		
Mean (SD)	7600 (2010)	7070 (1950)
%CV	26.5	27.6
Median	7450	6660
Min - Max	4260 – 13,300	3790 – 12,100
AUClast (ng·h/mL)		

Mean (SD)	7530 (1910)	6950 (1830)
%CV	25.4	26.3
Median	7400	6580
Min - Max	4240 – 12,700	3750 – 11,500
Cmax (ng/mL)		
Mean (SD)	1190 (190)	983 (231)
%CV	16.0	23.5
Median	1200	929
Min - Max	843 - 1650	632 - 1390
tmax (h)		
Median	1.03	1.50
Min - Max	0.500 - 3.00	0.500 - 3.00
CL/F (L/h)		
Range	9.05 - 28.2	9.91 - 31.7
Vz/F (L)		
Range	119 - 502	151 - 605

CV: coefficient of variation; Max: maximum; Min: minimum; SD: standard deviation.
Source: Study 2693-CL-0009, End-of-Text Table 12.4.2

Statistical assessment of relative bioavailability of tablet formulation compared with capsule formulation are presented in Table 6 below.

Table 6 Study 2693-CL-0009: Statistical Assessment of Relative Bioavailability of Fezolinetant

Parameter	Fezolinetant 120 mg				Geometric LS Mean Ratio (%)†	90% CI of Ratio†
	Capsule		Tablet			
	n	Geometric LS Mean	n	Geometric LS Mean		
AUCinf (ng·h/mL)	16	6840	16	7370	107.80	(100.88, 115.21)
AUClast (ng·h/mL)	16	6730	16	7320	108.74	(101.86, 116.09)
Cmax (ng/mL)	16	957	16	1170	122.51	(110.43, 135.92)

All randomized participants who took at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter. Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with formulation and period as fixed effects and participant as a random effect.
CI: confidence interval; LS: least squares.
† Ratios and confidence limits were back-transformed to raw scale and values are expressed as percentages.
Source: Study 2693-CL-0009, End-of-Text Table 12.4.3

Conclusion: The results demonstrate that following a single dose administration, geometric LS means of AUCinf, AUClast and Cmax of tablet formulation increased approximately 8%, 9% and 23% respectively, relative to capsule formulation. To be noted, with 90% CI of Cmax (101-136%) exceeds the BE criteria of 80-125% criteria, the 90% CI of AUCinf and AUClast are still contained in the BE criteria of 80-125%.

4.2.2. Study 2693-CL-0010: Bioequivalence of the To-be-Marketed 45 mg Tablet Compared to One 30 mg and One 15 mg Phase 3 Tablet

Title:

A Phase 1 Crossover Study to Assess the Bioequivalence of Fezolinetant Following a Single Dose of Fezolinetant to-be-marketed Formulation (Test Formulation) Compared to a Single Dose of Fezolinetant Phase 3 Formulation (Reference Formulation) in Healthy Female Subjects

Primary Objective: This study assessed the bioequivalence of a single dose of one 45 mg fezolinetant to-be-marketed tablet (test formulation) compared to a single dose of one 30 mg and one 15 mg fezolinetant phase 3 tablets (reference formulation) under fasting conditions in healthy female participants.

Study design:
This was a randomized, open-label, 2-period, 2-sequence, single dose crossover study in healthy female subjects. Each subject participated in 2 treatment periods separated by a washout of at least 5 days between investigational product (IP) administrations in each period. Participants received a single oral dose of 45 mg fezolinetant to-be-marketed formulation (test formulation) or one 30 mg and one 15 mg fezolinetant phase 3 formulation (reference formulation) under fasting conditions on day 1 of each period. Subjects were randomized to 1 of 2 sequences according to Table 7.

Table 7 Sequences and Investigational Product Assignments (2693-CL-0010)

Sequence	n	Period 1	Period 2
1	11	A	B
2	11	B	A

A: one 45 mg fezolinetant to-be-marketed tablet (test formulation); B: 45 mg fezolinetant comprising one 30 mg and one 15 mg fezolinetant phase 3 tablet (reference formulation)

Pharmacokinetic samples were collected predose on day 1 of each period and at multiple time points postdose (i.e., 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours).

Subject Disposition: A total of 22 healthy female subjects were randomized, and 22 subjects completed the study. Data from all subjects were included in the analyses of safety and PK.

Pharmacokinetic Results

Table 8 Fezolinetant pharmacokinetic parameters of 45 mg to-be-marketed tablet (test formulation) and Phase 3 tablets [30 mg + 15 mg] (reference formulation)

Fezolinetant Parameter Category/Statistics	Fezolinetant 45 mg (to-be-marketed tablet)	Fezolinetant 45 mg (30 mg + 15 mg phase 3 tablets)
AUCinf (ng·h/mL)	n=14[§]	n=14[§]
Mean	3840	3960
%CV	25.0	24.4
Median	3430	4160
Min - Max	2670 – 5230	2080 – 5050
AUClast (ng·h/mL)	n=22	n=21
Mean	3220	3230
%CV	35.7	39.8
Median	2980	3140

Min - Max	1310– 5200	1220 – 5000
Cmax (ng/mL)	n=22	n=21
Mean	506	527
%CV	31.0	46.0
Median	488	438
Min - Max	222 - 900	246 - 1200
$t_{1/2}$ (h)	n=14[§]	n=14[§]
Mean	13.1	13.4
%CV	34.8	29.4
Median	12.2	12.4
Min - Max	6.92-24	7.88-22.4
tmax (h)	n=22	n=21
Median	1.50	1.50
Min - Max	0.483- 4.02	0.483- 4.02
CL/F (L/h)	n=14[§]	n=14[§]
Range	8.60- 16.8	8.91- 21.6
VZ/F (L)	n=14[§]	n=14[§]
Range	137 - 544	131 - 408

[§] *AUCinf, CL/F and t1/2 values from 7 participants were not reported and thus not included in the statistical assessment due to undefined elimination phase.*

Source: Derived from Study 2693-CL-0010, End-of-Text Table 9.4.2.1

Table 9 ES259564 pharmacokinetic parameters of 45 mg to-be-marketed tablet (test formulation) and Phase 3 tablets [30 mg + 15 mg] (reference formulation)

ES259564 Parameter Category/Statistics	Fezolinetant 45 mg (to-be-marketed tablet)	Fezolinetant 45 mg (30 mg + 15 mg phase 3 tablets)
AUCinf (ng·h/mL)	n=22	n=21
Mean	2570	2580
%CV	17.1	19.4
Median	2410	2450
Min - Max	1840 – 3320	1780 – 3620
AUClast (ng·h/mL)	n=22	n=21
Mean	2540	2550
%CV	17.2	19.5
Median	2400	2430
Min - Max	1830– 3270	1770-3570
Cmax (ng/mL)	n=22	n=21
Mean	259	259
%CV	30.3	27.3
Median	251	252
Min - Max	154 - 448	143 - 399
$t_{1/2}$ (h)	n=22	n=21
Mean	7.5	7.36
%CV	18	23.9
Median	7.24	7.42
Min - Max	4.83-10.7	4.76-11.7
tmax (h)	n=22	n=21
Median	2.02	1.98
Min - Max	0.983- 4.02	0.967- 4.02
MPR	n=22	n=21
Mean	0.856	0.893
Range	0.494- 1.7	0.429 - 1.66

MPR, metabolite-to-parent ratio

Source: Derived from Study 2693-CL-0010, End-of-Text Table 9.4.2.2

Results of statistical analyses are provided for both fezolinetant and ES259564 (Table 10 and Table 11). Bioequivalence criteria were met between the test and reference formulations as geometric LS mean ratio and 90% CI of ratios were contained within the bioequivalence limits of 80% to 125% for Cmax, AUClast and AUCinf for both fezolinetant and ES259564.

Table 10 Statistical Assessment of Bioequivalence for Fezolinetant

Parameter	Treatment B		Treatment A		Geometric LS Mean Ratio[†] (%)	90% CI of Ratio[†]	Geometric Intra-subject %CV
	n	Geometric LS Mean	n	Geometric LS Mean			
AUClast (h•ng/mL)	21[‡]	2950	22	3010	102.17	(96.53, 108.15)	10.7
AUCinf (h•ng/mL)	14[§]	3720	14[‡]	3680	99.00	(92.45, 106.01)	9.3
Cmax (ng/mL)	21[‡]	488	22	483	99.12	(85.54, 114.87)	28.3

A: one 45 mg fezolinetant to-be-marketed tablet (test formulation); B: 45 mg fezolinetant dose comprising one 30 mg and one 15 mg fezolinetant phase 3 tablets (reference formulation); CI: confidence interval; CV: coefficient of variation; IP: investigational product; LS: least squares.
Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with period and treatment as fixed effects and participants as a random effect.
The pharmacokinetic analysis set comprised all randomized participants who received at least 1 dose of IP for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
[†] Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
[‡] One participant (treatment sequence AB) who received treatment B had concentrations that were below the level of quantification on all sample timepoints pre- and postdose for both fezolinetant and ES259564. This participant was excluded from the summary and parameter calculations.
[§] AUCinf values from 7 participants were not reported and thus not included in the statistical assessment due to undefined elimination phase. AUClast including all evaluable participants, as well as AUCinf excluding these 7 participants, provided consistent bioequivalence results.
Source: Study 2693-CL-0010, End-of-Text Table 9.4.3.1

Table 11 Statistical Assessment of Bioequivalence for ES259564

Parameter	Treatment B		Treatment A		Geometric LS Mean Ratio[†] (%)	90% CI of Ratio[†]	Geometric Intra-subject %CV
	n	Geometric LS Mean	n	Geometric LS Mean			
AUClast (h•ng/mL)	21[‡]	2510	22	2510	100.08	(98.08, 102.12)	3.8
AUCinf (h•ng/mL)	21[‡]	2540	22	2530	99.89	(97.88, 101.95)	3.8
Cmax (ng/mL)	21[‡]	255	22	248	97.38	(90.86, 104.37)	13.0

A: one 45 mg fezolinetant to-be-marketed tablet (test formulation); B: 45 mg fezolinetant comprising one 30 mg and one 15 mg fezolinetant phase 3 tablets (reference formulation); CV: coefficient of variation; IP: investigational product; LS: least squares

Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with period and treatment as fixed effects and subjects as a random effect.
The pharmacokinetic analysis set comprised all randomized subjects who received at least one dose of IP for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
[†] Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
[‡] One subject (treatment sequence AB) who received treatment B, had concentrations that were below the level of quantification on all sample timepoints pre- and postdose for both fezolinetant and ES259564. This subject was excluded from the summary and parameter calculations.
Source: End-of-Text Table 9.4.3.2

Conclusions:
The test formulation (45 mg fezolinetant to-be-marketed tablet) is bioequivalent to the reference formulation (45 mg fezolinetant comprising one 30 mg and one 15 mg fezolinetant phase 3 tablets).

Reviewer comments:

A request of routine inspection for the clinical site of the BE study (PAREXEL Early Phase Clinical, Baltimore, MD) was sent to Office of Study Integrity and Surveillance (OSIS). OSIS declined to conduct an inspection for the site due to insufficient time for inspection to be completed for the given goal date. However, OSIS reported that the site was inspected in October 2018 under another NDA. After review of the inspection findings, OSIS concluded that data from the reviewed study were reliable.

In the current BE study (2693-CL-0010), no significant protocol deviations were identified. The risk of compromised data integrity is low.

4.3 Clinical PK and/or PD studies

4.3.1 **Healthy Subject PK and Initial Tolerability Study ESN364-CPK-101 (3 to 180 mg)**

Title: A Phase I, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of ESN364 to Evaluate Pharmacokinetics, Pharmacodynamics, Safety and Tolerability in Healthy Male and Healthy Female Volunteers of Childbearing Potential

Objectives:

The primary objectives of this study were to assess the safety and tolerability of ESN364 following single and multiple ascending oral dose administration in healthy males.

The secondary objectives were:

- Assess the PK of ESN364 following single ascending oral dose administration in healthy males, following multiple ascending oral dose administration in healthy males and females of childbearing potential.

- Assess the effect of food intake on the PK of ESN following oral administration in healthy males.
- Assess gender differences in PK of ESN364 following multiple ascending dose administration in healthy males and females of childbearing potential.
- To investigate the preliminary PD of ESN364 after single and multiple ascending oral dose administration in healthy males and females of childbearing potential.

Study Design:

This was a single center, randomized, double-blind, placebo-controlled, single, and multiple dose escalation study in 65 healthy male and female participants. An overview of the study design is presented in Table 12.

Table 12. Overview of Study ESN364-CPK-101

Region/ Country	Study No.	n	Population	Brief Study Description	Doses Evaluated	Study Description
Belgium	ESN364-CPK-101	Part 1: 17 Part 2: 24 Part 3: 24	Part 1: healthy male participants Part 2: healthy male participants Part 3: healthy female participants of childbearing potential	Single center, randomized, double-blind, placebo-controlled, single and MAD escalation in healthy male and female volunteers.	Part 1: Panel A: single dose of 3, 12, 46 and 180 mg Panel B: single dose of 6, 23, 90 and 23 mg Part 2: 20, 60 and 180 mg qd for 10 days Part 3: 20, 60 and 180 mg qd for 21 days	SAD and MAD Pharmacokinetics of Hard Gelatin Capsule; Phase 1

PK Assessment:

For Part 1, blood samples were taken predose (max 60 minutes before administration study drug), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours postdose. Urine was collected for the measurement of ESN634 predose (max 60 minutes before administration study drug) and at regular intervals: 0-4, 4-8, 8-12, and 12-24 hours postdose.

For Part 2, blood samples to be taken predose, and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours postdose on Day (D) 1 and D10. On D5, D7 and D9 trough plasma samples for ESN364 were collected before dosing. Urine was collected for the measurement of ESN634 predose and at regular intervals, i.e, 0-4, 4-8, 8-12, 12-24 and 24-48 hours after dosing on D1 and D10.

For Part 3, blood samples to be taken predose, and at, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours postdose on D1 and D21 and 72 hours postdose on D24. On D5, D7, D9, D11, D15, and D19 trough plasma samples for ESN364 were collected before dosing. Urine was collected for the measurement of ESN634 predose and at regular intervals, i.e, 0-4, 4-8, 8-12, 12-24, and 24-48 hours after dosing on D1 and D21.

PD Assessment (Only Part 3 is relevant as the study population was female subjects.):

For Part 3, the effect of ESN364 on testosterone (T), luteinizing hormone (LH), estradiol (E2), progesterone (P4), sex hormone binding globulin (SHBG), and follicle stimulating hormone (FSH) concentrations were measured in serum sampled before dosing on D5, D7, D9, D11, D13, D15, D17 and D19. On D1 and D21, pharmacodynamics were assessed at the same time points as the PK sampling for ESN364, i.e., predose, and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours postdose and 72 hours

postdose on D24. In addition, T, E2, P, FSH, SHBG, and LH were also assessed in the morning, on a weekly basis, on D28 and D35 and at the follow up visit on D42. In addition, T, LH, E2, P4, SHBG, and FSH levels were assessed three times on the day of admission (Day-1) on undefined time points but with at least two hours in between two samples.

Subject Disposition:

A total of 65 subjects were enrolled and treated. All but one subject completed the study. One subject (Subject (b) (6)) in Part 1, Panel B discontinued treatment after administration of 6 mg ESN364 due to an SAE (foot facture). This subject was replaced by a reserve subject (Subject (b) (6)).

Results:

Part 1- Single Ascending Dose in Healthy Male Participants – Panels A & B

This was an SAD escalation part, with fezolinetant doses of 3, 12, 46 and 180 mg (top dose) for panel A (8 healthy men per dose group), and 6, 23, 90 and 23 mg (fed) for panel B (9 healthy men per dose group).

PK profiles after oral administration of 3 to 180 mg were presented in Figure 3. PK parameters from Part 1 were listed in Table 13.

Figure 1. Mean ESN364 Plasma Concentration vs. Time Profiles (Part 1, Study ESN364-CPK-101)

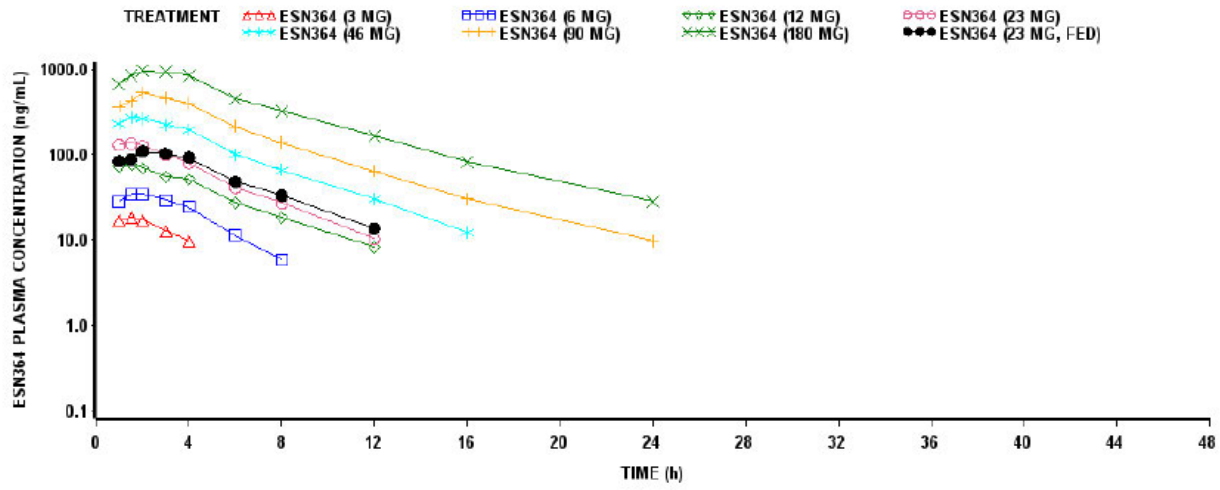


Table 13. Summary of ESN364 PK Parameters and Statistical Analysis on ESN364 PK Parameters

PK Parameter	Part 1: Single Ascending Dose									
	ESN364 3 mg N=6	ESN364 6 mg N=6	ESN364 12 mg N=6	ESN364 23 mg N=6	ESN364 46 mg N=6	ESN364 90 mg N=6	ESN364 180 mg N=6	ESN364 23 mg (fed) N=6	ANOVA (p-value)[a]	
									Dose	Food
C_{max} (ng/mL)	19.6 (18.3)	39.0 (24.8)	77.5 (12.2)	149 (18.2)	307 (15.1)	545 (16.6)	1110 (25.1)	131 (11.4)	0.9509	0.1875
AUC_{∞} (ng.h/mL)	NC[N=1]	193 (33.0)	461 (21.6)	719 (33.1)	1670 (30.7)	3360 (22.0)	7300 (37.1)	723 (32.5)	0.4034	0.9118
AUC_{last} (ng.h/mL)	73.5 (41.2)	167 (35.1)	418 (21.4)	681 (34.6)	1620 (31.0)	3280 (22.3)	7190 (37.7)	688 (31.4)	0.0020	0.8286
$t_{1/2}$ (h)	2.39 (26.3) N=4	2.71 (37.0)	3.69 (23.5)	3.00 (20.2)	3.35 (31.4)	4.13 (33.0)	4.19 (29.0)	2.89 (24.1)	NA	0.1986
t_{max} (h)	1.25 (1.00-1.50)	1.75 (1.00-3.00)	1.50 (1.00-1.50)	1.25 (1.00-2.00)	1.75 (1.00-3.00)	2.00 (1.00-4.00)	2.00 (1.00-3.00)	1.50 (1.00-3.00)	0.0554	0.3750

N = number of subjects, NA = not applicable, NC = not calculated
Values are arithmetic means (CV%) except median (min-max) for t_{max}
[a]For t_{max}: Kruskal-Wallis' test for dose effect and Wilcoxon Signed-Rank test. Source: Table 14.1.3.6, Table 14.1.3.9 and Table 14.1.3.10

Reviewer's comment:

- The pharmacokinetics of ESN364 were dose proportional in terms of Cmax and AUC_{∞} over the 3 to 180 mg dose range. The results of the pairwise comparison (Tukey's test) showed that the exposure measured by AUClast was non-dose proportional between the highest (180 mg) and the lowest (3 mg) dose groups which led to a significant analysis of variance (ANOVA) p-value for dose effect on AUC_{last}.
- ESN364 maximal mean concentrations were reached between 1.25 to 2 hours after dosing for the 3 to 180 mg doses.
- The elimination phase appeared parallel for all dose groups.
- The PK profile in the 23 mg dose group in fed conditions was different from the other dose group profiles with a longer absorption phase but the difference is not statistically significant (p = 0.3750).

Part 2- Multiple Ascending Dose in Healthy Male Participants – Panels (C, D, & E)

Part 2 consisted of 3 sequential groups of 8 healthy male participants with MAD escalation of 20, 60 and 180 mg. Participants received the study medication in a qd regimen after a light breakfast.

PK profiles after oral administration of 20, 60 and 180 mg are presented in Figure 1. Steady-state assessments for Part 2 are listed in Table 14.

Figure 2. Mean ESN364 Plasma Concentration vs. Time Profiles in Male Healthy Subjects (Part 2, Study ESN364-CPK-101)

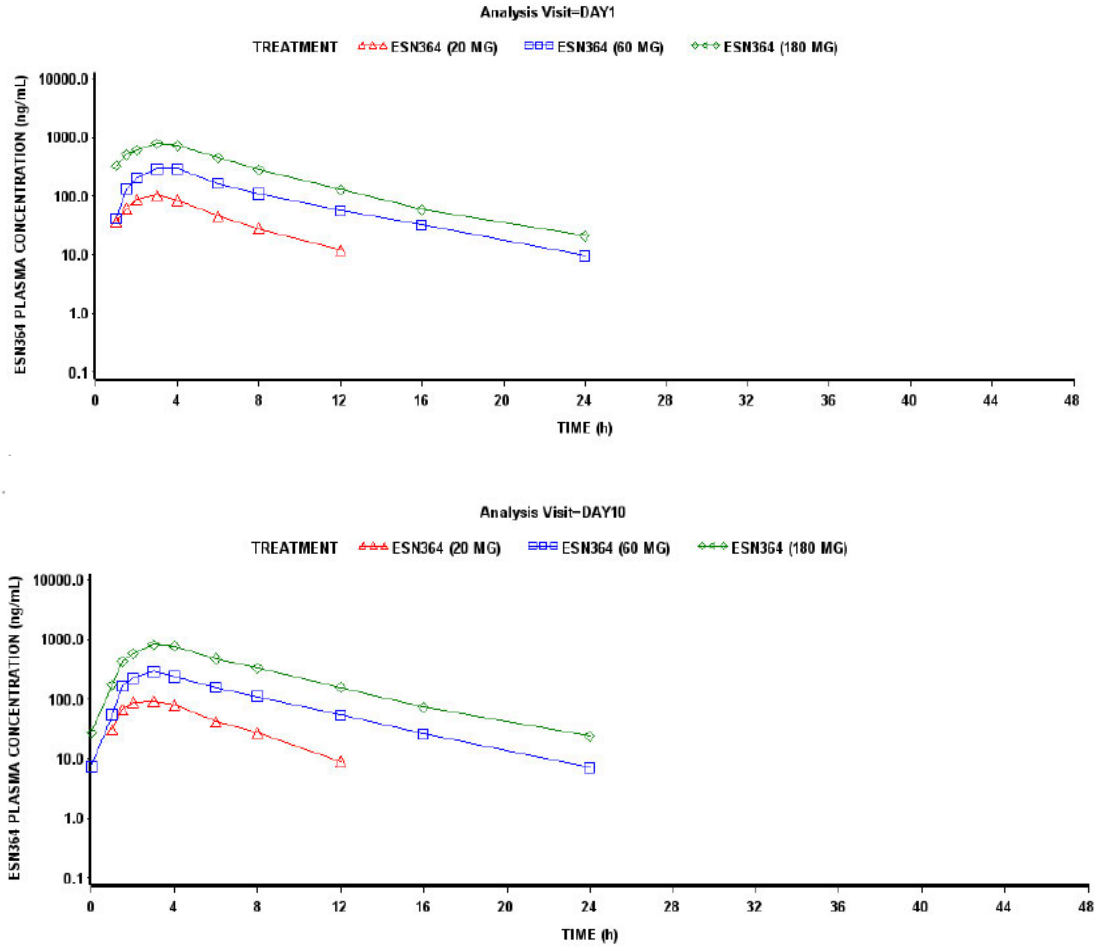


Table 14. Summary of Statistical Analysis for ESN364 Steady-State Assessment (Part 2, Study ESN364-CPK-101)

Dose Group ESN364	C_T (ng/mL) Mean (CV%) Day 2	Day 3	Day 5	Day 7	Day 9	Day 10	ANOVA (p-value)
60 mg q.d. (N=6)	9.69[a] (109)	8.12[a] (104)	7.44[a] (85.4)	7.38[a] (83.3)	6.06[a] (79.0)	7.40[a] (80.9)	0.7786
180 mg q.d. (N=6)	21.3 (81.3)	22.2 (72.7)	25.1 (61.3)	22.8 (68.6)	22.9 (59.1)	27.6 (80.1)	0.2783

[a]: BLQ values were replaced by LLOQ/2 for ANOVA; N = number of subjects; C_T (Ctau): Concentration at end of the dosing interval; Source: Table 9 of CSR for Study 101

Individual PK parameters and dose proportionality of ESN364 PK parameters assessed with inferential statistical analysis are presented in Table 15.

Table 15. Summary of ESN364 Individual PK Parameters and Statistical Analysis on ESN364 PK Parameters (Part 2, Study ESN364-CPK-101)

PK Parameter	Part 2: Multiple Ascending Dose								
	Day 1			Day 10			ANOVA (p-value)		
	ESN364 20 mg q.d. N=6	ESN364 60 mg q.d. N=6	ESN364 180 mg q.d. N=6	ESN364 20 mg q.d. N=6	ESN364 60 mg q.d. N=6	ESN364 180 mg q.d. N=6	Day	Dose	Dose*Day
C_{max} (ng/mL)	113 (17.6)	321 (32.9)	826 (21.8)	104 (12.8)	319 (23.3)	877 (15.6)	0.9640	0.5054	0.3439
t_{max} (h)	3.00 (1.50–4.00)	3.00 (2.00–4.02)	3.00 (1.00-3.00)	2.50 (1.50-4.00)	2.50 (1.50-3.00)	3.00 (2.00–4.00)	0.4072	Day 1 0.7738 Day 10 0.4028	
C_T[a] (ng/mL)	BLQ (NC)	9.69 (109)	21.3 (81.3) N=5	BLQ (NC)	7.20 (84.5)	24.0 (57.2)			
AUC_{last} (ng.h/mL)	582 (22.5)	2100 (46.9)	5530 (25.8)	539 (21.8)	2000 (28.9)	5940 (15.6)	0.8966	0.6189	0.4278
AUC_T[a](ng.h/mL)	NC N=0	2610 (28.7) N=4	5900 (28.6) N=4	NC N=0	2350 (7.27) N=4	5940 (15.6)			
C_{avg} (ng/mL)	NA	NA	NA	NC N=0	97.8 (7.27) N=4	247 (15.6)			
$t_{1/2,\lambda z}$ (h)	3.06 (30.5)	4.19 (22.0)	3.87 (29.7)	2.84 (32.5)	3.95 (15.0)	4.20 (19.0)			
Rac	NA	NA	NA	NC N=0	0.925 (25.2) N=4	1.11 (19.5) N=4			
CL_R (mL/min)	NA	9.60 (19.0) N=4	9.47 (28.7) N=4	NA	11.0 (24.4) N=4	9.93 (46.7)			

N = number of subjects, NA = not applicable, NC = not calculated
Values are arithmetic mean (CV%) except median (min-max) for t_{max} and geometric mean (geometric CV%) for R_{ac}
[a] T: dosing interval (24h)
[b] For t_{max}: Kruskal-Wallis' test for the dose effect; Wilcoxon rank-sum test for the day effect
Source: Table 14.1.3.7 and Table 14.1.3.9

Reviewer's comments:

Based on the 10-day PK data from multiple ascending dose oral administration of ESN364 in male healthy subjects in Part 2,

- The bioavailability of ESN364 increased proportionally with the dose from 20 to 180 mg q.d, as measured by C_{max} and AUC_{last}.
- Based on analyses of trough concentrations for the 60 and 180 mg qd dose groups, it could be concluded that steady state in fezolinetant plasma concentrations was quickly reached by day 2, i.e., after the first administration of study drug. No accumulation of ESN364 was observed after 10 days of 60 or 180 mg q.d. administration, with mean accumulation ratio (Rac) values of 0.925 and 1.11, respectively.

Part 3- Multiple Ascending Dose in Healthy Female Participants – Panels (F, G & H)

Part 3 consisted of 3 groups of 8 healthy women of childbearing potential administered ascending multiple doses of fezolinetant qd for 21 consecutive days. The suggested dose levels were: 23, 46 and 90 mg qd. Ascending multiple doses were adjusted to 20, 60 and 180 mg qd after a light breakfast based on the safety, tolerability, and PK data from part 1 (SAD).

After the first dose (Day 1), ESN364 maximal mean concentrations were reached at 3h after dosing with values of 142 ng/mL (20 mg q.d.), 322 ng/mL (60 mg q.d.), and 1490 ng/mL (180 mg q.d.). Similarly, after the 21st dose (Day 21), ESN364 maximal mean concentrations were reached at 3h after dosing with values of 175 ng/mL (20 mg q.d.), 418 ng/mL (60 mg q.d.), 4h after dosing with value of 1590 ng/mL (180 mg q.d.).

PK profiles after oral administration of 20, 60 and 180 mg in female healthy subjects were presented in Figure 3. Steady-state assessment for Part 3 were listed in Table 16.

Figure 3. Mean ESN364 Plasma Concentration vs. Time Profiles in Female Healthy Subjects (Part 3, Study ESN364-CPK-101)

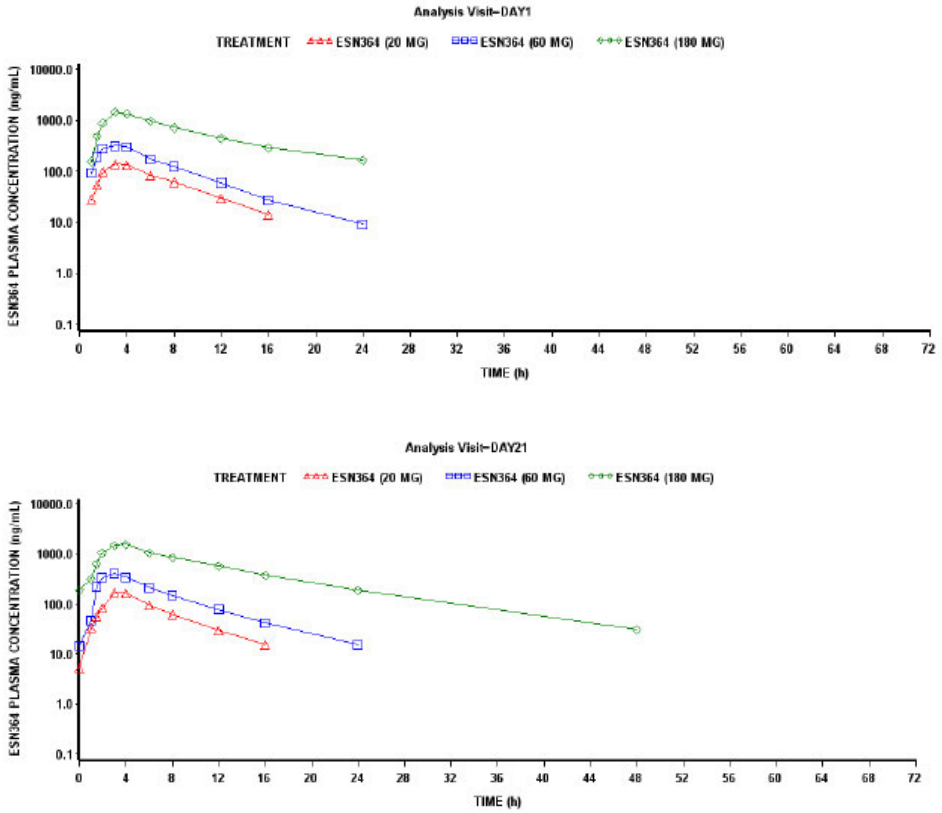


Table 16. Summary of Statistical Analysis for ESN364 Steady-State Assessment (Part 3, Female, Study ESN364-CPK-101)

Dose Group ESN364	Cτ (ng/mL) Mean (CV%) Day 2	Day 3	Day 5	Day 7	Day 9	Day 11	Day 15	Day 19	Day 21	ANOVA (p-value)
60 mg q.d. (N=6)	9.19[a] (72.9)	8.75[a] (89.6)	9.58[a] (86.0)	9.47[a] (80.1)	10.7[a] (63.4)	12.4[a] (84.3)	15.1[a] (64.1)	15.2[a] (76.6)	14.7[a] (61.8)	0.0169
180 mg q.d. (N=6)	166 (86.7)	167 (87.0)	171 (129)	180 (146)	167 (139)	167 (116)	167 (111)	186 (121)	193 (127)	0.4384

[a] BLQ values were replaced by LLOQ/2 for ANOVA; N = number of subjects; Cτ (Ctau): Concentration at end of the dosing interval; Source: Table 11 of CSR for Study 101

Individual PK parameters in female subjects and dose proportionality of ESN364 PK parameters assessed with inferential statistical analysis were presented in Table 17.

Table 17. Summary of ESN364 Individual PK Parameters and Statistical Analysis on ESN364 PK Parameters (Part 2, Female, Study ESN364-CPK-101)

PK Parameter	Part 3: Multiple Ascending Dose								
	Day 1			Day 21			ANOVA (p-value)		
	ESN364 20 mg q.d. N=6	ESN364 60 mg q.d. N=6	ESN364 180 mg q.d. N=6	ESN364 20 mg q.d. N=6	ESN364 60 mg q.d. N=6	ESN364 180 mg q.d. N=6	Day	Dose	Dose*Day
C_{max} (ng/mL)	153 (8.14)	336 (21.6)	1490 (28.9)	185 (20.8)	423 (20.5) N=5	1720 (38.7)	<.0001	0.0763	0.1991
t_{max} (h)	3.00 (2.00–4.00)	3.01 (2.00–4.00)	3.00 (2.07-3.00)	3.50 (2.00-4.00)	3.00 (3.00-4.00) N=5	4.00 (2.00–4.00)	0.1163	Day 1 0.4891 Day 21 0.6496	
C_T[a] (ng/mL)	BLQ (NC)	9.19 (72.9)	166 (86.7)	BLQ (NC)	15.6 (62.9)	190 (128)			
AUC_{last} (ng.h/mL)	1020 (24.4)	2330 (25.0)	12900 (46.9)	1130 (33.4)	2880 (20.4)	18400 (75.6)	0.0011	0.0462	0.2583
AUC_T[a](ng.h/mL)	NC N=2	2490 (19.6) N=5	12900 (46.9)	NC N=2	2920 (19.1) N=4	15600 (59.9)			
C_{avg} (ng/mL)	NA	NA	NA	NC N=2	122 (19.1) N=4	649 (59.9)			
$t_{1/2,\lambda z}$ (h)	4.32 (39.6)	4.22 (30.1)	7.06 (45.1)	4.27 (43.7)	4.84 (25.9)	6.34 (37.6)			
Rac	NA	NA	NA	NC N=2	1.23 (15.1) N=4	1.18 (24.7)			
CL_R (mL/min)	NA	8.84 (55.2) N=5	5.91 (35.1)	NA	6.83 (39.0) N=4	5.34 (41.6)			

N = number of subjects, NA = not applicable, NC = not calculated
Values are arithmetic mean (CV%) except median (min-max) for t_{max} and geometric means (CV%) for R_{ac}
[a]$_T$: dosing interval (24h)
[b]For t_{max}: Kruskal-Wallis' test for the dose effect; Wilcoxon rank-sum test for the day effect
Source: Table 14.1.3.8 and Table 14.1.3.9

Reviewer's comments:

Based on the 21-day PK data from multiple ascending dose oral administration of ESN364 in female healthy subjects in Part 3,

- Pharmacokinetics of ESN364 was not dose proportional in the range of 20 mg to 180 mg q.d. (p-value = 0.0763). However, the pairwise comparisons between the dose showed that the bioavailability of ESN364 increased dose proportionally between 20 and 60 mg q.d. but was above the dose proportionality for the highest 180 mg q.d.; Cmax and AUClast in 180 mg q.d. group were significantly above dose proportionality compared to 60 mg q.d., by estimated 34% and 78%, respectively.
- Mean Ctrough at Day 21 was slightly higher than Day 2 with large variability. Minimal accumulation of ESN364 was observed after 21 days of 60 or 180 mg q.d. administration, with mean Rac values of 1.23 and 1.18, respectively.

Gender Effect

When comparing ESN364 exposure after single dosing or at steady-state in Part 2 (healthy males) and Part 3 (healthy women), peak and plasma exposures were significantly lower in males (p-value <0.0001) (Table 18). Gender effect seems to not be completely similar in all dose groups (point estimates ranged between 42 to 84% for C_{max} and AUC_{last}). Time to peak exposure was similar for two genders. Half-life was shorter in males in the dose groups of 20 mg QD (point estimate = 70%) and 180 mg q.d. (point estimate = 64%).

Table 18. Statistical Analysis of Gender Effect on ESN634 PK parameters (MAD, Parts 2 and 3)

PK Parameter	ANOVA						
	Gender				Day	Dose	Gender*dose
	p-value	Comparison pair	PE	90%CI	p-value	p-value	p-value
C_{max} (ng/mL)	<0.0001	20 mg q.d. Male vs. Female	64.49	(55.29 – 75.22)	0.1077	0.0339	0.0076
		60 mg q.d. Male vs. Female	83.74	(71.54 – 98.02)			
		180 mg q.d. Male vs. Female	54.74	(46.92 – 63.85)			
AUC_{last} (ng.h/mL).	<0.0001	20 mg q.d. Male vs. Female	53.03	(42.17 – 66.68)	0.2209	0.0088	0.0125
		60 mg q.d. Male vs. Female	75.28	(59.87 – 94.66)			
		180 mg q.d. Male vs. Female	41.69	(33.15 – 52.42)			
$t_{1/2,\lambda z}$ (h)	0.0001	20 mg q.d. Male vs. Female	69.68	(56.25 – 86.31)	0.9624	0.0005	0.1204
		60 mg q.d. Male vs. Female	91.55	(73.91 – 113.40)			
		180 mg q.d. Male vs. Female	63.57	(51.32 – 78.75)			
t_{max} (h)	20 mg q.d. 0.2964 60 mg q.d. 0.1471 180 mg q.d. 0.3253						

p-value: ANOVA and Wilcoxon Rank-Sum test for tmax; Day 10 in the Part 2 and Day 21 in Part 3 was pooled (Day at stead-state) for the analysis; PE: point estimate; Source: Table 13 of CSR for Study 101.

PD results

Mean profiles of change from baseline (on Day 1 and Day 21) were presented in Figure 4, Figure 5, Figure 6, Figure 7, Figure 8, Figure 9, Figure 10, Figure 11.

Figure 4. Mean Change from Baseline in Testosterone (T) Concentration vs. Time Profiles (Day 1 and Day 21)

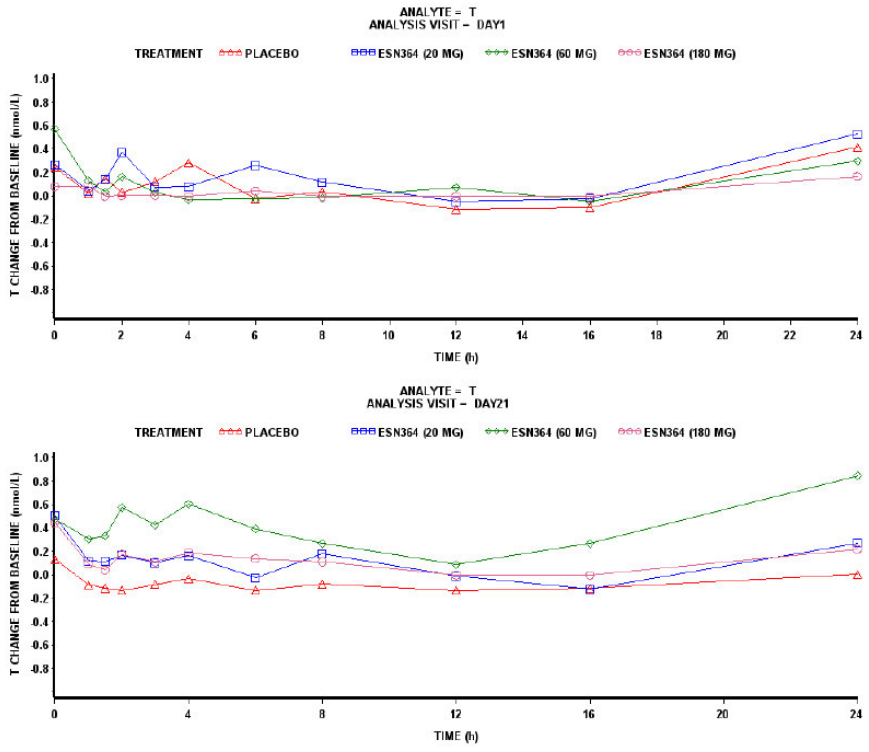


Figure 5. Mean Change from Baseline in Free Testosterone (FT) Concentration vs. Time Profiles (Day 1 and Day 21)

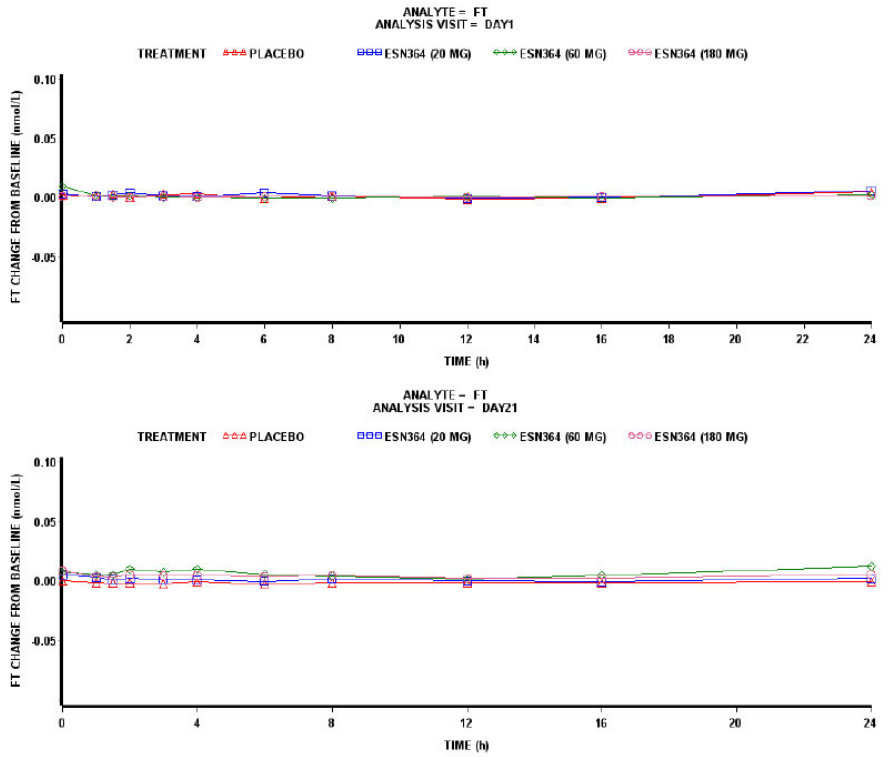


Figure 6. Mean Change from Baseline in Follicle Stimulating Hormone (FSH) Concentration vs. Time Profile (Day 1 and Day 21)

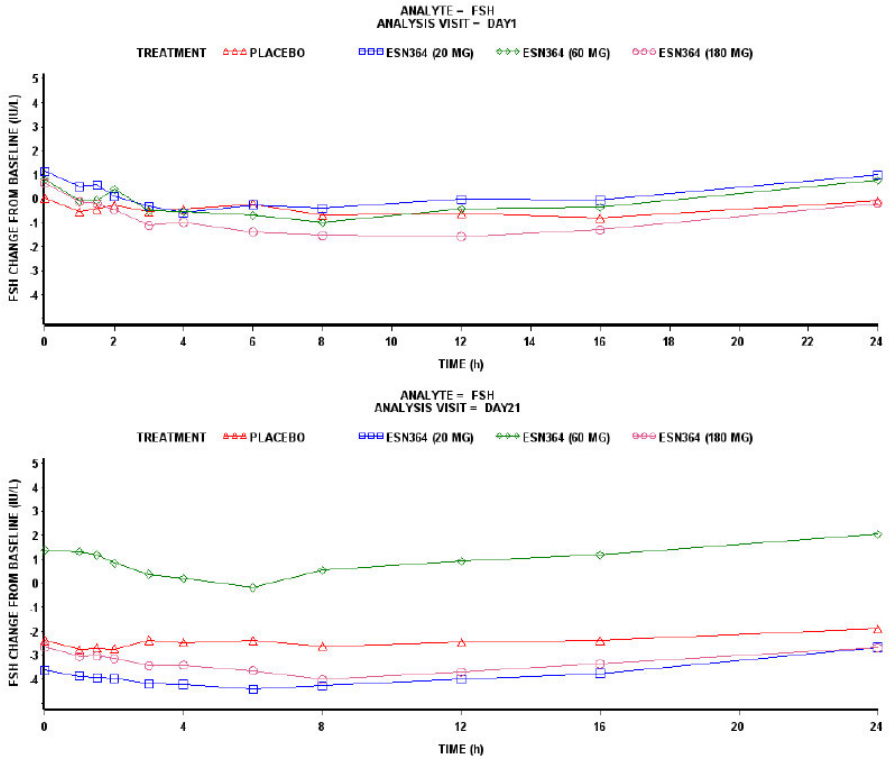


Figure 7. Mean Change from Baseline in Sex Hormone Binding Globulin (SHBG) Concentration vs. Time Profile (Day 1 and Day 21)

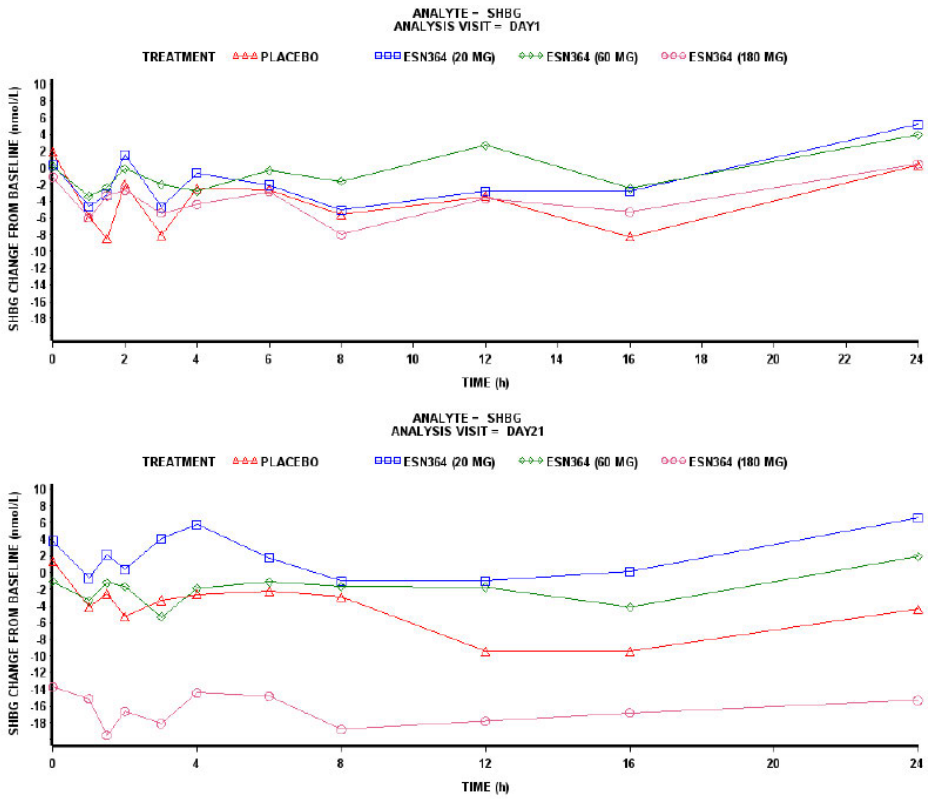


Figure 8. Mean Change From Baseline in Luteinizing Hormone (LH) Concentration *vs* Time Profiles (Day 1 and Day 21)

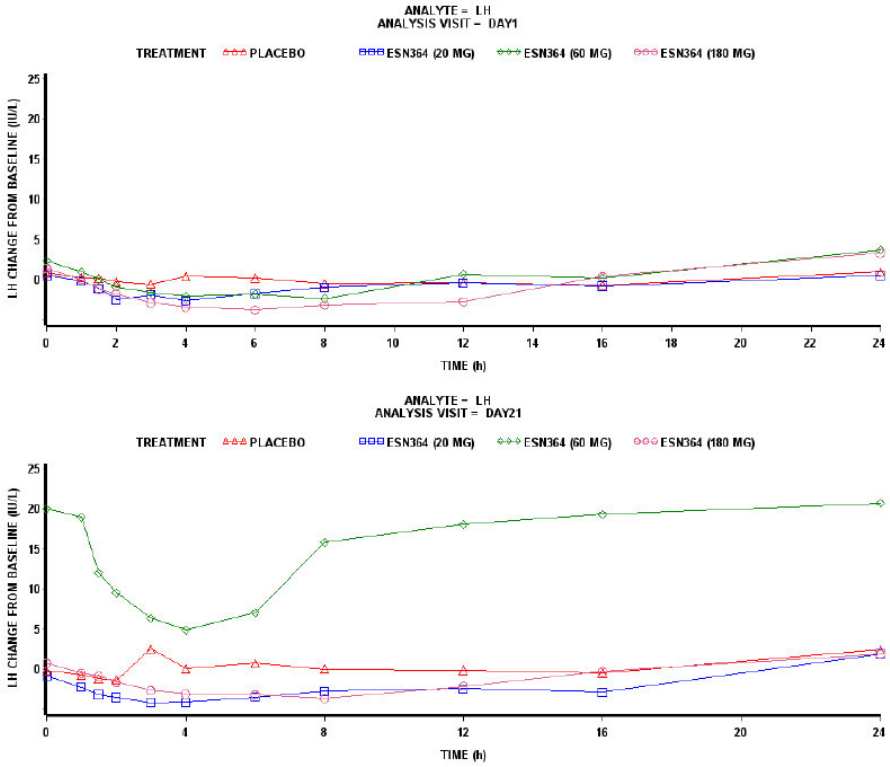


Figure 9. Mean Change From Baseline in Estradiol (E2) Concentration *vs* Time Profiles (Day 1 and Day 21)

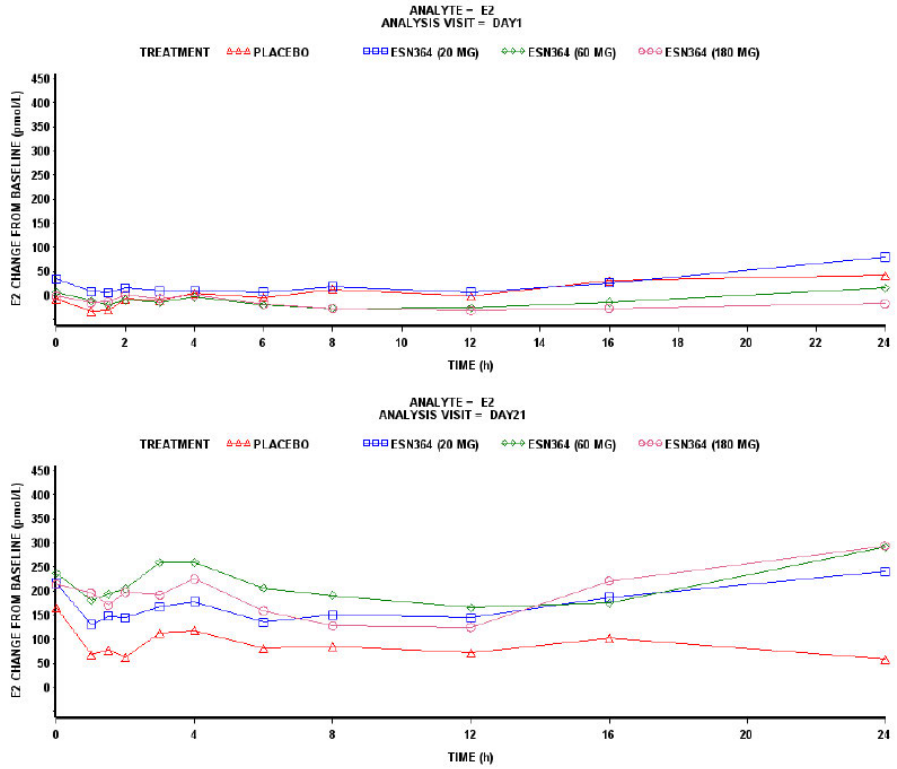


Figure 10. Mean Change From Baseline in Free Estradiol (FE2) Concentration *vs* Time Profiles (Day 1 and Day 21)

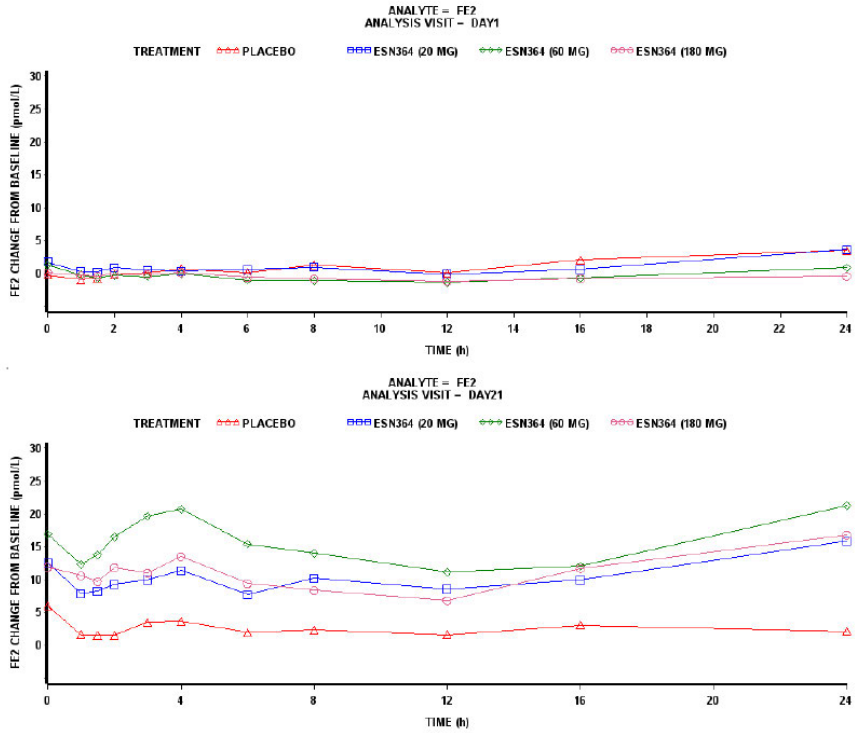
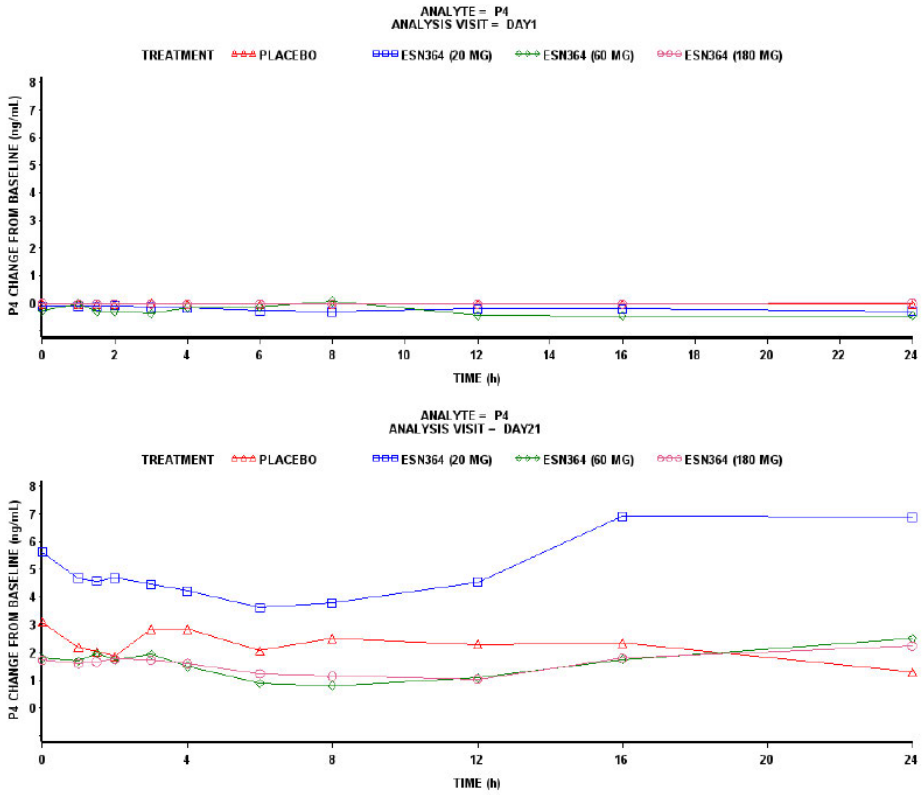


Figure 11. Mean Change From Baseline in Progesterone (P4) Concentration *vs* Time Profiles (Day 1 and Day 21)



Reviewer's comments:

- After a single administration of fezolinetant (20, 60 and 180 mg), T, FT, FSH, SHBG, LH, E2, FE2 and P4 plasma concentrations and profile shape were similar in active treatments (20, 60 and 80 mg q.d.) and placebo.
- After multiple administration of fezolinetant (Day 21),
    - higher plasma concentrations in T, E2 and FE2 were observed for the active treatments (20, 60 and 80 mg q.d.) compared to placebo.
    - a decrease in SHBG plasma concentrations was observed in the treatment 180 mg q.d. compared to placebo and the other active treatments.
    - compared to placebo, FSH and LH plasma concentrations were slightly decreased with the doses 20 and 180 mg q.d.; these concentrations seem increased with the dose 60 mg q.d. compared to placebo.
    - compared to placebo, P4 plasma concentrations were slightly decreased with the doses 60 and 180 mg q.d.; these concentrations seem increased with the dose 20 mg q.d. compared to placebo.

4.3.2 Healthy Subject PK and Initial Tolerability Study ESN364-CPK-102 (180 to 900 mg)

Title: A Phase I, Double Blind, Placebo Controlled, Single and Multiple Ascending Dose Study of ESN364 to Evaluate Pharmacokinetics, Safety, Tolerability and Maximum Tolerated Dose in Healthy Female and Healthy Male Volunteers

Objectives:

The primary objectives were:

- Assess the safety and tolerability of ESN364 following single and multiple ascending oral dose administration in healthy females.
- Assess the Maximum Tolerated Dose (MTD) of ESN364 following single ascending oral dose administration in healthy females.
- Assess the safety and tolerability of ESN364 following single oral dose administration in healthy males.

The secondary objectives were:

- Assess the pharmacokinetics (PK) of ESN364 following single ascending oral dose administration
- Assess the PK of ESN364 following multiple ascending oral dose administration in healthy females.
- Assess gender differences in PK of ESN364 following single ascending dose administration in healthy males and females (PK assessment in male subjects is not described in this review because the intended target population is females).
- To investigate the preliminary PD of ESN364 after single and multiple ascending oral dose administration in healthy males and females (PD assessment is not described in this review because the doses evaluated were 180 mg or higher which are not relevant to the dose that the applicant is seeking for approval).

Study Design:

This was a single center, Phase 1, double-blind, placebo-controlled, single, and multiple dose escalation study of ESN364 in healthy male and female volunteers consisting of 3 parts. An overview of the study was presented in Table 19.

Table 19. Overview of Study ESN364-CPK-102

Region/ Country	Study No.	n	Population	Brief Study Description	Doses Evaluated	Study Description
Belgium	ESN364-CPK-102	Part 1: 16 Part 2: 16 Part 3: 8	Part 1: healthy female participants Part 2: healthy female participants Part 3: healthy male participants	Single center, randomized, double-blind, placebo-controlled, single and MAD escalation in healthy male and female volunteers.	Part 1: Panel A: single dose of 180, 540 and 900 mg Panel B: single dose of 360, 720 and 900 mg Part 2: 540 and 720 mg qd for 7 days Part 3: Single dose of 720 and 900 mg	SAD and MAD Pharmacokinetics of Hard Gelatin Capsule; Phase 1

PK Assessment:

For Part 1, Blood samples for the measurement of ESN634 were to be taken predose (no more than 60 minutes before dosing), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours postdose. Urine was collected for the measurement of ESN634 predose (no more than 60 minutes before dosing) and at regular intervals: 0-4, 4-8, 8-12, and 12-24 hours postdose.

For Part 2, Blood samples for the measurement of ESN634 had to be taken predose (no more than 60 minutes before dosing), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours postdose on D1 and D7. On D5, a trough plasma sample for ESN364 was collected before dosing. Urine was collected for the measurement of ESN634 predose (no more than 60 minutes before dosing) and at regular intervals, i.e., 0-4, 4-8, 8-12 and 12-24 hours after dosing on D1 and D7.

For Part 3, Blood samples had to be taken predose (no more than 60 minutes before dosing), and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 48 hours postdose. Urine was collected for the measurement of ESN634 predose (no more than 60 minutes before dosing) and at regular intervals: 0-4, 4-8, 8-12, and 12-24 hours postdose.

Subject Disposition:

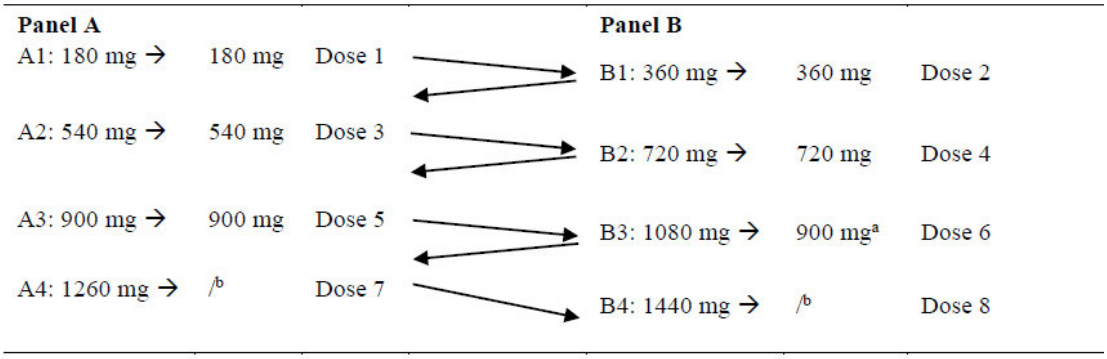
A total of 40 subjects were treated and completed the study.

Results:

Part 1- Single Ascending Dose in Healthy Female Volunteers

Two panels (A and B), each consisting of 8 healthy female participants received oral doses of fezolinetant for dose escalation to define the MTD for fezolinetant. It was planned that panel A would receive 180, 540, 900 and 1260 mg or placebo. Based on review by the investigator and sponsor's representative of the obtained safety data and available PK data in this part of the study, the 900 mg fezolinetant dose was eventually regarded as the MTD, and participants did not receive higher doses. Therefore, the participants in panel B received 360, 720 and 900 mg. The planned and actual dosing

scheme was as follows:



a. Based on review by the Investigator and Sponsor's representative of the obtained safety data and obtained PK data in this part of the study, the 900 mg ESN364 dose tested in Treatment Period A3 was eventually regarded as the MTD. Therefore, subjects in Treatment Period B3 also received 900 mg ESN364 instead of the planned 1080 mg ESN364.

b. After reaching an MTD of 900 mg ESN364 in Treatment Period A3, the planned Treatment Period 4 (A4-B4) was cancelled.

The individual PK parameters and dose proportionality assessment from Part 1 were provided in Table 20.

Table 20. Summary of ESN364 Pharmacokinetic Parameters and Dose Proportionality Assessment (Part 1, female, Study ESN364-CPK-102)

PK Parameter	180 mg ESN364 (Panel A) N=6	360 mg ESN364 (Panel B) N=6	540 mg ESN364 (Panel A) N=6	720 mg ESN364 (Panel B) N=6	900 mg ESN364 (Panel A) N=6	900 mg ESN364 (Panel B) N=6	ANOVA (p-value) Dose	ANOVA (p-value) Cohort
C_{max} (µg/mL)[a]	1.38 (33.9)	3.75 (28.3)	4.26 (33.7)	4.72 (25.5)	7.50 (39.5)	6.11 (21.8)	0.0235	0.9129
t_{max} (h)	3.00 (1.50-4.00)	2.51 (1.50-3.00)	3.00 (1.50-4.05)	4.00 (2.02-4.07)	4.05 (3.00-6.00)	3.50 (2.00-4.03)	0.1071	NA
t_{lag} (h)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	NA	NA
AUC_{last} (h.µg/mL)[a]	8.37 (34.3)	27.7 (48.3)	32.5 (62.8)	49.7 (39.4)	72.6 (65.8)	70.2 (37.2)	0.2516	0.3456
AUC_{∞} (h.µg/mL)[a]	8.50 (34.3)	28.2 (47.5)	32.8 (63.6)	50.4 (41.4)	73.2 (66.2)	71.0 (37.7)	0.2520	0.3416
$t_{1/2}$ (h)	4.28 (44.4)	5.32 (29.7)	5.54 (33.7)	6.40 (32.7)	6.25 (7.96)	6.35 (26.3)	NA	NA
CL/F (L/h)	24.4 (49.0)	15.0 (38.0)	22.1 (58.7)	15.7 (27.8)	16.2 (52.8)	14.5 (40.2)	NA	NA
V_z/F (L)	131 (19.5)	106 (22.2)	150 (25.1)	138 (28.5)	143 (50.2)	125 (27.1)	NA	NA
$Ae_{last\%}$ (%dose)	1.99 (41.2)	2.56 (52.7) n=4	1.99 (50.0)	1.86 (24.8)	2.07 (59.3)	1.93 (42.0)	NA	NA
$Ae_{\infty\%}$ (%dose)	2.04 (40.9)	2.77 (60.1) n=4	2.14 (56.3)	2.07 (31.2)	2.27 (61.7)	2.15 (42.4)	NA	NA
CL_R (L/h)	0.448 (31.1)	0.350 (12.2) n=4	0.383 (35.1)	0.304 (12.9)	0.303 (46.1)	0.297 (49.1)	NA	NA

N=number of subjects; n=number of subjects with data (1 subject had a quantifiable predose urine concentration and was excluded, another subject had a missing urine weight); NA: not applicable

a. Dose-normalized parameters were used in ANOVA.

Values are arithmetic means (CV%), except median (min-max) for t_{max} and t_{lag}.

Source: Table 14.2.2.7 and Table 14.2.2.10

Reviewer's comments:

- The pharmacokinetics of ESN364 were dose proportional in terms of AUC over the 180 mg to 900 mg dose range.
- A significant dose effect was observed on Cmax, with the dose normalized Cmax after 360 mg ESN364 treatment significantly higher than after 720 or 900 mg (Panel B) ESN364 treatment.
- The MTD in female subjects was 900 mg.

Part 2- Multiple Ascending Dose in Healthy Female Volunteers

Two sequential panels of 8 healthy female participants each were administered fezolinetant or placebo qd for 7 days to assess steady-state PK levels in the higher dose range. Based on the MTD of 900 mg fezolinetant achieved in part 1 of the study, the oral dose levels of fezolinetant for the MAD part 2 were 540 mg qd (MTD-2) and 720 mg qd (MTD-1) given for 7 consecutive days.

Steady-state analysis was shown in Table 21.

Table 21. Summary of ESN364 Steady-State Assessment (Part 2, Female, Study ESN364-CPK-102)

	CT (µg/mL)					
	Day 2	Day 3	Day 5	Day 7	Day 8	ANOVA (p-value)
540 mg ESN364 q.d. N=6	702 (93.4)	803 (101)	1313 (113)	1328 (112)	1308 (97.4)	0.0917
720 mg ESN364 q.d. N=6	942 (87.2)	1214 (87.5)	2164 (83.8)	2265 (94.3)	1865 (79.0)	<0.0001

N=number of subjects with data
Values are arithmetic means (CV%).
Source: Table 14.2.2.2 and Table 14.2.2.12

The individual PK parameters and dose proportionality assessment from Part 2 were provided in Table 22.

Table 22. Summary of ESN364 Pharmacokinetic Parameters and Statistical Analysis (Part 2, Female, Study ESN364-CPK-102)

PK parameter	540 mg ESN364 q.d. N=6		720 mg ESN364 q.d. N=6		ANOVA (p-value)		
	Day 1	Day 7	Day 1	Day 7	Dose	Day	Dose*Day
C_{max} (µg/mL)[a]	5.40 (34.0)	7.11 (44.7)	4.67 (34.2)	7.66 (18.9)	0.1445	0.0012	0.1594
t_{max} (h)	4.00 (1.52-4.02)	3.49 (3.00-4.02)	3.00 (2.00-12.00)	3.49 (1.97-4.02)	Day 1: 0.6702 Day 7: 0.6324	0.9844	NA
Cτ (ng/mL)	0.702 (93.4)	1.31 (97.4)	0.942 (87.2)	1.86 (79.0)	NA	NA	NA
AUCτ (h.µg/mL)[a]	48.7 (53.6)	78.4 (70.5)	48.4 (51.4) n=5	92.0 (50.0)	0.7089	0.0007	0.3492
$t_{1/2}$ (h)	7.26 (36.6)	8.92 (31.4)	6.40 (37.7) n=5	10.0 (34.4)	NA	NA	NA
CL_{ss}/F (L/h)	NA	10.6 (71.7)	NA	10.5 (68.3)	NA	NA	NA
V_{ss}/F (L)	NA	118 (52.8)	NA	136 (57.3)	NA	NA	NA
$C_{min,ss}$ (µg/mL)	NA	1.17 (111)	NA	1.82 (80.2)	NA	NA	NA
C_{avg} (µg/mL)	NA	3.26 (70.5)	NA	3.83 (50.0)	NA	NA	NA
Rac	NA	1.47 (34.3)	NA	1.74 (29.1) n=5	NA	NA	NA
PTR (%)	NA	217 (48.5)	NA	173 (70.1)	NA	NA	NA
CL_R (L/h)	0.308 (17.3)	0.341 (32.4)	0.369 (23.0) n=4	0.452 (32.8)	NA	NA	NA
Aeτ% (%dose)	2.76 (53.7)	4.74 (61.9)	2.75 (63.7) n=5	6.24 (67.7)	NA	NA	NA

[a]: Dose-normalized parameters were used in ANOVA; N=number of subjects; n=number of subjects with data (for 1 subject, half-life and related parameters could not be estimated, another subject had a missing urine sample); NA: not applicable; PTR: Peak-to-trough ratio; Rac: Drug accumulation ratio.

Source: Table 9 of CSR for Study 102

Reviewer's comments:

- Steady state was achieved by day 5 for both 540 mg and 720 mg daily dosing.
- The PK were dose proportional in terms of AUC and Cmax over the 540 to 720 mg dose range. A significant day effect was observed, consistent with the accumulation ratio of 1.5 to 1.7.
- The t1/2, CL/F and Vz/F were comparable after the 2 administrations.

4.3.3 Mass Balance Study ES364-CPK-103

Title: A Phase 1, Open-label Study to Investigate the Absorption, Metabolism and Excretion of 14C-ESN-364 in Healthy Menopausal Female Volunteers

Primary Objectives:

- To evaluate the pharmacokinetics (PK) of ESN-364 and total radioactivity, in particular, absorption, rates and routes of excretion and extent of metabolism of ESN-364, following administration of a single dose of 14C-labeled ESN-364.
- To determine the mass balance of total radioactivity.

Study Design:

A total of 6 healthy menopausal female subjects (40-75 years, 50-100 kg, and 18-30 kg/m^2, all inclusive) were planned to be enrolled. The subjects received a single oral dose with 180 mg ESN-364 (fezolinetant) containing 270 µg of 14C-ESN-364 (1.68 Megabecquerel [MBq] [45 µCi]) under fasted conditions. Screening was done from Day -21 until Day -1. Eligible subjects were admitted to the clinical research center on Day -1. Subjects were to remain in the clinical research center until Day 8 on the condition that:

1. There were no medical reasons for a longer stay, AND
2. Sufficient recovery of administered radioactivity in excreta was achieved (90% or more of the administered dose), OR
3. The total excretion (urine + feces) per 24 hours was less than 1% of the administered dose during 2 consecutive 24-hour intervals. The cumulative amount excreted up to the last collection interval in the in-house period (i.e., $AE_{0\text{-}168h}$ up to maximally $AE_{0\text{-}240h}$) was calculated by the sum of the amounts excreted up to this collection interval.

If these conditions had not been met by Day 8, subjects were to remain in the clinical research center until condition 2 or 3 had been met, but with a maximum prolongation of 3 days (up to and including Day 11). If after the 3-day prolongation, condition 2 or 3 had still not been met, subjects were to be requested to continue collecting all their urine and/or feces at home for another 2 days (Day 12 and Day 13) until condition 2 or 3 had been met. If after these additional 2 days, condition 2 or 3 still had not been met, condition 2 could be disregarded and condition 3 had to be met by collecting 24-hour intervals for urine and feces once a week for up to 2 weeks (on Days 20 and 27, respectively). After this time if condition 3 still had not been met no further samples were to be collected and the subject would be discharged from the study. In case of remaining total radioactivity after the planned collection

period, the amounts excreted in the intervals after the planned collection period were to be estimated by interpolation (if needed). For this interpolation, the excretion rate between the previous interval and the next interval was to be determined and used for calculation of the amounts excreted in that interval.

Subject Disposition:

Six subjects were initially approved, but 1 subject was not dosed due to high blood pressure on Day 1. Therefore, 5 subjects were included in the study and dosed. All 5 subjects completed the study as per protocol.

Results:

Following single oral administration of 180 mg ^{14}C-ESN-364 containing 1.68 MBq, geometric mean Cmax in plasma was 1528 ng/mL for ESN-364 and 1425 ng/mL for ES259564, respectively. The geometric mean AUC0-last value was 5449 ng h/mL for ESN-364 and 9749 ng · h/mL for ES259564. The geometric mean AUC0-inf was 5463 ng · h/mL for ESN-364 and 9778 ng · h/mL for ES259564. Tmax was 0.52 hours for ESN-364 and 1.50 hours for ES259564. The geometric mean t1/2 was 5.26 hours for ESN-364 and 6.59 hours for ES259564 (Table 23).

Following single oral administration of 180 mg 14C-ESN-364 containing 1.68 MBq, geometric mean Cmax for total radioactivity was 3396 ng eq/mL in plasma and 3144 ng eq/mL in whole blood. The geometric mean AUC0-last was 18116 ng eq h/mL for plasma and 15533 ng eq h/mL for whole blood. Geometric mean AUC0-inf was 18711 ng eq h/mL for radioactivity in plasma and 16774 ng eq h/mL for radioactivity in whole blood. Tmax was 0.52 hours for total radioactivity in both plasma and whole blood. The geometric mean t1/2 was 4.72 and 4.47 hours for total radioactivity in plasma and whole blood, respectively (Table 23).

Table 23. Summary Statistics of Pharmacokinetic Parameters for ESN-364, ES259564, Total Radioactivity in Plasma, and Total Radioactivity in Blood

Analyte	C_{max} (ng[eq]/mL)[a]	T_{max} (h)[b]	$AUC_{0\text{-last}}$ (ng[eq].h/mL)[a]	$AUC_{0\text{-inf}}$ (ng[eq].h/mL)[a]	Half-life (h)[a]
ESN-364 in plasma	1528 (1286 - 1831)	0.52 (0.50 - 1.00)	5449 (4049 - 7978)	5463 (4075 - 7987)	5.26 (3.76 - 6.02)
ES259564 in plasma	1425 (1166 - 1777)	1.50 (0.52 - 1.53)	9749 (8341 - 10727)	9778 (8355 - 10770)	6.59 (5.02 - 12.2)
Total radioactivity in plasma	3396 (2858 - 3997)	0.52 (0.50 - 1.00)	18116 (14805 - 22182)	18711 (15547 - 22881)	4.72 (3.90 - 5.08)
Total radioactivity in whole blood	3144 (2552 - 3632)	0.52 (0.50 - 1.00)	15533 (13186 - 19214)	16774 (13812 - 20453)	4.47 (3.77 - 5.59)

PK = pharmacokinetic

a: Geometric mean and range b: Median and range

Source: Table S1 of Study ESN364-CPK-103 CSR

All urine and feces were collected daily up to 144 hours (Day 7) postdose. Based on quick counts, the recovery criteria regarding collection of radioactivity were already met by all 5 subjects on Day 7. Therefore, no urine and feces were collected from 144 hours postdose onwards. All subjects were discharged on Day 8, after the last scheduled assessments were performed.

Overall, the arithmetic mean total recovery ($fe_{total\ 0\text{-}inf}$) of ^{14}C-radioactivity in urine and feces was 90.9% of the administered dose of radioactivity. Individual total recovery of ^{14}C-radioactivity ranged between 87.2% and 95.0%.

The major route of excretion of ^{14}C-radioactivity was via urine (arithmetic mean=76.9%). The remainder of ^{14}C-radioactivity was excreted in feces (arithmetic mean=14.7%). Individual recovery ranged between subjects from 68.8% to 82.3% in urine and from 10.4% to 18.5% in feces.

Table 24. Summary of the Cumulative Recovery of ^{14}C-Radioactivity in Urine, Feces and Total

Statistic	$fe_{urine,0\text{-}inf}$ (%) (N=5)	$fe_{feces,0\text{-}inf}$ (%)[a] (N=4)	$fe_{total\ 0\text{-}inf}$ (%) (N=5)
Arithmetic mean	76.9	14.7	90.9
SD	6.2	3.4	3.3
Minimum	68.8	10.4	87.2
Maximum	82.3	18.5	95.0

N = number of subjects; SD = standard deviation
[a] Terminal elimination phase could not be determined reliably for one subject (Subject (b) (6)). For this subject $fe_{feces,0\text{-}last}$ was used in the calculation of $fe_{total,0\text{-}inf}$.
Source: Table 15.2.17

Following single oral administration of 180 mg ^{14}C-labeled ESN-364, very minor amounts of unchanged ESN-364 were found in urine and feces. By 24 hours postdose, an arithmetic mean of 1.1% and 0.1% of the administered ESN-364 dose was excreted unchanged in urine and feces, respectively. No relevant additional excretion of ESN-364 was observed after this time point. (Note: data from feces samples can be found in study report for Study 2693-ME-0006, Table 12).

An arithmetic mean of 61.7% ($fe_{urine,0\text{-}inf}$) of the administered ESN-364 dose was excreted in urine as metabolite ES259564. Most of the ES259564 metabolite was already excreted by 24 hours postdose (55.9% of the administered ESN-364 dose).

The geometric mean renal clearance (CLR) was 0.333 L/h for unchanged ESN-364 and 11.3 L/h for metabolite ES259564.

Reviewer's comment:

Following single oral administration of 180 mg ^{14}C-ESN-364 containing 1.68 MBq to 5 healthy post-menopausal female subjects,

- Recovery of radioactivity was acceptable. A mean recovery of 90.9 % ^{14}C-radioactivity was observed. Individual total recovery of ^{14}C-radioactivity ranged between 87.2% and 95.0%. The radioactivity was mainly eliminated in urine (76.9%) and to a lesser extent in feces (14.7%).
- In urine, a mean of 1.1% of the administered ESN 364 dose was excreted unchanged and 61.7% of the administered ESN 364 dose was excreted as metabolite ES259564. This suggests that ESN-

364 is extensively metabolized and that metabolite ES259564 is mainly renally excreted. These data also suggest the presence of other metabolites of ESN 364.

- In feces, a mean of 0.1% of the administered ESN 364 dose was excreted unchanged.
- Overall, exposure to ES259564 was similar for Cmax but approximately 2-fold higher for AUCs compared to parent. T1/2 was similar.
- The exposure values (Cmax and AUC) of ESN-364 and ES259564 compared to exposure values of total radioactivity suggest that other metabolites may exist in the systemic circulation.
- The arithmetic mean ^{14}C-blood/plasma ratios were 0.9 between 0.5 and 16 hours postdose, indicating almost equal distribution of ^{14}C-radioactivity over plasma and red blood cells without any relevant accumulation of ^{14}C-radioactivity in red blood cells.
- Mean exposure (AUC0-inf) ratio for the metabolite relative to parent (ES259564/ESN-364 ratio) was 1.84 (ranging from 1.35 to 2.46) and the mean exposure ratio for parent relative to total radioactivity (ESN-364/total radioactivity ratio) was 0.30 (ranging from 0.23 to 0.35), indicating that the exposure to the main metabolite ES259564 was higher than to ESN-364.

4.3.4 Regional Pharmacokinetic Study 2693-CL-0020 (Japanese Male and Female)

Title: Placebo-controlled, Single and Multiple Oral Dose Study in Healthy Japanese Male and Healthy Japanese Pre- and Postmenopausal Female Subjects

Primary Objectives: To evaluate the safety and tolerability of single oral dose of fezolinetant in nonelderly healthy Japanese male participants. To evaluate the safety and tolerability of single and multiple oral doses of fezolinetant in healthy Japanese male and healthy Japanese pre- and postmenopausal female participants.

Study Design:

The study consisted of 2 parts: part 1 was conducted in 16 healthy Japanese male participants (single dose of 15 mg or 60 mg fezolinetant or placebo), and part 2 was conducted in 28 healthy Japanese men, and pre- or postmenopausal women (180 mg fezolinetant or placebo for 10 days).

For part 1, fezolinetant or placebo was administered in a parallel manner as a single oral dose under fasting conditions in two cohorts. In each cohort, 8 healthy Japanese male subjects were assigned to receive fezolinetant or placebo at a ratio of 3:1.

- Cohort 1-1: 8 healthy Japanese males received a single dose of fezolinetant 15 mg or placebo
- Cohort 1-2: 8 healthy Japanese males received a single dose of fezolinetant 60 mg or placebo

For Part 2, single and multiple doses of fezolinetant or placebo are administered in 3 cohorts of subjects.

- Cohort 2-1: 12 healthy Japanese male subjects received single and multiple doses of fezolinetant 180 mg or placebo once daily for 10 days.
- Cohort 2-2a: 8 healthy Japanese premenopausal female subjects received single and multiple doses of fezolinetant 180 mg or placebo once daily for 10 days.

- Cohort 2-2b: 8 healthy Japanese postmenopausal female subjects received single and multiple doses of fezolinetant 180 mg or placebo once daily for 10 days.

In each cohort, subjects were assigned to receive fezolinetant or placebo at a ratio of 3:1 and on Day 1 of single dose phase, the subjects received a single administration of the assigned dose under fasting conditions. After 2 days of washout period, the subjects received oral administration of the same dose once a day for 10 days. Cohort 2-2a and Cohort 2-2b were conducted in a parallel manner. From Day 1 to Day 9 of the multiple dose phase, the subjects received the dose after breakfast, while on Day 10, the subjects received the dose after fasting for at least 10 hours.

Subject Disposition: For Part 1, a total of 16 healthy male subjects were randomized, and 16 subjects completed the study. Data from all subjects were included in the analyses of safety, PK and PD.

For Part 2, a total of 28 healthy male and female subjects were randomized, and 26 subjects completed the study. Data from all subjects were included in the analyses of safety, PK and PD. 2 subjects who received fezolinetant 180 mg discontinued the study due to TEAE during multiple dose phase. All randomized subjects were included in the analyses of safety, PK and PD.

PK results: The pharmacokinetic profile of fezolinetant was investigated following single and multiple dosing in this study in healthy Japanese male and premenopausal female and postmenopausal female subjects (Table 25 and Table 26).

Table 25 Summary of Pharmacokinetic Parameters of fezolinetant (Part 1)

Parameter Statistic	fezolinetant 15 mg (N = 6)	fezolinetant 60 mg (N = 6)
AUC_{24} (h·ng/mL)		
Mean (SD)	526 (185)	3110 (1060)
%CV	35.1	34.2
Median	450	2990
Min - Max	407 - 894	1610 - 4660
AUC_{inf} (h·ng/mL)		
Mean (SD)	535 (201)	3140 (1090)
%CV	37.6	34.8
Median	449	3020
Min - Max	410 - 936	1620 - 4770
AUC_{inf} (%extrap)		
Mean (SD)	1.85 (1.36)	0.974 (0.649)
%CV	73.8	66.6
Median	1.39	0.739
Min - Max	0.723 - 4.47	0.406 - 2.24
AUC_{last} (h·ng/mL)		
Mean (SD)	523 (187)	3110 (1060)
%CV	35.7	34.2
Median	445	2990
Min - Max	402 - 894	1610 - 2940
CL/F (L/h)		
Mean (SD)	30.4 (7.63)	21.5 (8.64)
%CV	25.1	40.3
Median	33.4	20.0
Min - Max	16.0 - 36.6	12.6 - 37.1
C_{max} (ng/mL)		

Mean (SD)	135 (19.6)	679 (168)
%CV	14.5	24.7
Median	140	679
Min - Max	111 - 155	484 - 884
$t_{1/2}$ (h)		
Mean (SD)	3.29 (1.51)	3.81 (0.505)
%CV	46.0	13.2
Median	2.55	3.67
Min - Max	2.08 - 5.68	3.39 - 4.81
t_{lag} (h)		
Median	0	0
Min - Max	0	0
t_{max} (h)		
Median	1.00	1.50
Min - Max	1.00 - 1.50	1.00 - 3.00
V_Z/F (L)		
Mean (SD)	131 (30.6)	115 (36.8)
%CV	23.3	32.1
Median	123	106
Min - Max	102 - 189	80.8 - 182

%CV, coefficient of variation; Max, maximum; Min, minimum; PKAS, pharmacokinetics analysis set
Source: Study 2693-CL-0020, Table A12.4.3.1

In Part 1, following single dosing of fezolinetant 15 and 60 mg, median tmax of fezolinetant and ES259564 were 1.00 hour to 1.50 hours. Mean t1/2 of fezolinetant and ES259564 were 3.29 to 3.81 hours and 4.58 to 5.04 hours. CL/F and Vz/F ranged from 16.0 to 36.6 L/h and 102 to 189 L in 15 mg group and 12.6 to 37.1 L/h and 80.8 to 182 L in 60 mg group. The ranges of CL/F and Vz/F overlapped in both treatment groups.

Table 26 2693-CL-0020: Summary of Pharmacokinetic Parameters of Fezolinetant (Single and Multiple Doses, Part 2)

Parameter Statistic	Single Dose (Day 1)			Multiple Dose (Day 10)		
	Fezolinetant 180 mg/ Male n = 9	Fezolinetant 180 mg/ Premenopausal Female n = 6	Fezolinetant 180 mg/ Postmenopausal Female n = 6	Fezolinetant 180 mg/ Male n = 8	Fezolinetant 180 mg/ Premenopausal Female n = 6	Fezolinetant 180 mg/ Postmenopausal Female n = 5
AUC24h (h·ng/mL)						
Mean (SD)	8560 (3240)	11200 (3930)	15900 (5800)	NC	NC	NC
%CV	37.8	35.1	36.5	NC	NC	NC
AUCtau (h·ng/mL)						
Mean (SD)	NC	NC	NC	12300 (3050)	16200 (5690)	27200 (9290)
%CV	NC	NC	NC	24.8	35.0	34.2
AUCinf (h·ng/mL)						
Mean (SD)	8780 (3400)	11600 (4190)	17600 (7430)	NC	NC	NC
%CV	38.7	36.2	42.1	NC	NC	NC
AUClast (h·ng/mL)						
Mean (SD)	8750 (3400)	11500 (4200)	17400 (7180)	NC	NC	NC
%CV	38.9	36.4	41.3	NC	NC	NC
CL/F (L/h)						
Mean (SD)	23.9 (9.87)	17.6 (7.28)	11.9 (4.88)	15.6 (4.53)	12.4 (4.71)	7.31 (2.56)
%CV	41.3	41.4	41.1	29.1	38.1	35.1
Cmax (ng/mL)						
Mean (SD)	1790 (485)	1970 (610)	2320 (541)	2170 (436)	2370 (699)	3490 (710)
%CV	27.1	30.9	23.3	20.1	29.5	20.4
t1/2 (h)						
Mean (SD)	4.93 (1.31)	4.83 (0.799)	7.24 (1.71)	6.66 (1.13)	6.27 (0.626)	8.98 (2.39)
%CV	26.6	16.5	23.7	16.9	10.0	26.6
tmax (h)						
Median	1.50	1.50	2.00	1.25	1.75	1.50
Min - Max	1.00 - 3.00	1.00 - 4.00	1.00 - 3.00	1.00 - 3.00	1.50 - 3.00	1.00 - 1.50
VZ/F (L)						
Median	162 (75.3)	117 (31.4)	114 (23.6)	153 (63.3)	110 (35.8)	88.2 (12.4)
Min - Max	46.4	26.8	20.6	41.4	32.7	14.1
PTR						
Median	NC	NC	NC	46.6 (57.8)	32.5 (39.7)	16.4 (16.0)
Min - Max	NC	NC	NC	123.9	122.1	97.6
Rac (AUC)						
Median	NC	NC	NC	1.47 (0.318)	1.46 (0.150)	1.57 (0.151)
Min - Max	NC	NC	NC	21.7	10.3	9.6

The PK analysis set was the set of participants among the safety population who had had at least 1 time point of sample taken for drug concentration assessment.
Participants in part 2 were healthy Japanese male and pre- or postmenopausal female participants who received single and multiple doses of fezolinetant.
CV: coefficient of variation; Max: maximum; Min: minimum; n: number of participants; NC: not calculated; PTR: peak to trough ratio.
Source: Study 2693-CL-0020, Tables B12.4.3.1.1 and B12.4.3.1.2

In Part 2, following single and multiple dosing of fezolinetant 180 mg, median tmax of fezolinetant and ES259564 were 1.25 to 2.00 hours and 2.00 to 3.00 hours. The t1/2 was longer in postmenopausal female subjects compared to male and premenopausal female subjects. In postmenopausal female subjects, a higher Cmax and AUC were observed compared to male and premenopausal female subjects.

A slight accumulation of fezolinetant and ES259564 was observed after 10 days of fezolinetant 180 mg administration, with mean Rac (AUC) ranged 1.46 to 1.57 and 1.14 to 1.22, respectively. Single dosing data indicated a dose proportional increase in AUCinf, AUClast and Cmax over the dose range of 15 to 180 mg fezolinetant. With once daily multiple dosing, steady state reached on the day 3 of dosing in all treatment groups.

PD results:

In Part 1, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG) and total and free testosterone were measured as PD parameters. (Table 27**)**

Table 27 Change from Baseline of Pharmacodynamic Parameters (Part 1)

Parameter **Statistic**	**Placebo** **(N = 4)**	**fezolinetant 15 mg** **(N = 6)**	**fezolinetant 60 mg** **(N = 6)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
LH			
AUC_{12} (h·mIU/mL)	-4.86 (12.6)	-12.1 (16.9)	-21.4 (11.9)
AUC_{24} (h·mIU/mL)	-10.7 (28.1)	-12.7 (28.2)	-23.2 (35.5)
AUC_{48} (h·mIU/mL)	-40.3 (61.9)	-15.5 (38.7)	1.92 (74.7)
C_{min} (mIU/mL)	-2.47 (1.44)	-2.06 (1.16)	-2.30 (0.794)
t_{min} (h) †	7.50 (1.50 - 24.0)	4.00 (3.00 - 6.00)	7.00 (4.00 - 12.0)
FSH			
AUC_{12} (h·mIU/mL)	-2.83 (2.38)	-3.59 (5.27)	-4.61 (2.88)
AUC_{24} (h·mIU/mL)	-5.00 (3.17)	-4.24 (10.1)	-9.20 (7.46)
AUC_{48} (h·mIU/mL)	-6.07 (3.54)	-0.419 (16.7)	-7.07 (13.7)
C_{min} (mIU/mL)	-0.513 (0.188)	-0.483 (0.427)	-0.629 (0.330)
t_{min} (h) †	6.00 (3.00 - 12.0)	6.00 (6.00 - 12.0)	12.0 (6.00 - 16.0)
SHBG			
AUC_{12} (h·nmol/L)	27.6 (131)	65.8 (106)	96.6 (113)
AUC_{24} (h·nmol/L)	60.6 (338)	120 (216)	310 (187)
AUC_{48} (h·nmol/L)	216 (685)	337 (460)	815 (363)
C_{min} (nmol/L)	-4.91 (5.96)	1.84 (8.14)	0.932 (8.89)
t_{min} (h) †	16.0 (0 - 16.0)	5.00 (1.50 - 16.0)	9.00 (3.00 - 16.0)
total testosterone			
AUC_{12} (h·ng/mL)	1.86 (2.23)	-12.5 (9.40)	-23.7 (10.6)
AUC_{24} (h·ng/mL)	6.41 (8.59)	-5.55 (15.7)	-30.7 (21.1)
AUC_{48} (h·ng/mL)	23.6 (18.8)	20.0 (23.5)	-14.9 (33.0)
C_{min} (ng/mL)	-0.433 (0.142)	-2.55 (0.858)	-3.71 (1.09)
t_{min} (h) †	12.0 (8.00 - 12.0)	6.00 (6.00 - 8.00)	12.0 (6.00 - 12.0)

free testosterone			
AUC_{12} (h·pg/mL)	13.5 (26.9)	-29.5 (33.4)	-55.0 (29.8)
AUC_{24} (h·pg/mL)	16.0 (71.9)	-23.7 (57.0)	-79.7 (47.2)
AUC_{48} (h·pg/mL)	63.5 (150)	51.9 (93.9)	-49.9 (60.5)
C_{min} (pg/mL)	-3.16 (2.47)	-7.38 (2.11)	-9.11 (3.19)
t_{min} (h) †	12.0 (8.00 - 16.0)	6.00 (6.00 - 12.0)	12.0 (8.00 - 12.0)

†, Median (minimum - maximum)

Source: Tables A12.5.8.1, A12.5.9.1, A12.5.10.1, A12.5.11.1 and A12.5.12.1

In Part 1, mean LH, FSH, total and free testosterone serum concentrations decreased after a single dosing of fezolinetant compared to placebo and greater in 60 mg group than 15 mg group. Maximum decrease was observed between 6 to 12 hours postdose. Thereafter, all of these concentrations returned to baseline by 24 hours postdose. There was no notable change of mean SHBG serum concentration after a single dosing of fezolinetant.

In Part 2, LH, FSH, SHBG, total and free testosterone, estradiol and progesterone were measured as PD parameters (Table 28 and Table 29).

Table 28 Change from Baseline of Pharmacodynamic Parameters in Part 2 on Day 1

Parameter Statistic	Single Dose (Day 1)					
	Male		Premenopausal Female		Postmenopausal Female	
	Placebo (N = 3)	fezolinetant 180 mg (N = 9)	Placebo (N = 2)	fezolinetant 180 mg (N = 6)	Placebo (N = 2)	fezolinetant 180 mg (N = 6)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
LH						
AUC_{12} (h·mIU/mL)	3.54 (4.85)	-21.6 (9.29)	-3.97 (NA)	-21.0 (14.9)	2.31 (NA)	-138 (38.3)
AUC_{24} (h·mIU/mL)	9.21 (6.38)	-37.9 (21.6)	-4.08 (NA)	-20.3 (28.0)	-9.66 (NA)	-194 (85.7)
AUC_{48} (h·mIU/mL)	11.6 (20.5)	-36.0 (35.7)	-16.8 (NA)	-3.55 (45.3)	-8.92 (NA)	-196 (79.8)
C_{min} (mIU/mL)	-0.849 (0.510)	-2.26 (0.675)	-1.17 (NA)	-2.62 (1.39)	-4.41 (NA)	-16.2 (4.75)
t_{min} (h) †	8.00 (4.00 - 24.0)	12.0 (6.00 - 24.0)	27.0 (6.00 - 48.0)	7.00 (4.00 - 16.0)	12.8 (1.50 - 24.0)	10.0 (6.00 - 16.0)
FSH						
AUC_{12} (h·mIU/mL)	-0.869 (2.09)	-8.76 (5.07)	-6.63 (NA)	-18.7 (17.4)	7.46 (NA)	-111 (35.2)
AUC_{24} (h·mIU/mL)	-0.676 (5.49)	-19.4 (9.84)	-13.4 (NA)	-32.6 (33.3)	-10.6 (NA)	-215 (85.6)
AUC_{48} (h·mIU/mL)	5.63 (14.7)	-21.7 (16.7)	-31.9 (NA)	-44.4 (60.5)	15.4 (NA)	-206 (209)
C_{min} (mIU/mL)	-0.239 (0.180)	-1.13 (0.510)	-0.950 (NA)	-2.41 (2.02)	-6.21 (NA)	-16.0 (3.68)
t_{min} (h) †	12.0 (8.00 - 16.0)	12.0 (6.00 - 24.0)	24.8 (1.50 - 48.0)	8.00 (6.00 - 16.0)	32.0 (16.0 - 48.0)	10.0 (6.00 - 16.0)
SHBG						
AUC_{12} (h·nmol/L)	-42.2 (104)	-9.60 (40.7)	11.8 (NA)	17.5 (136)	156 (NA)	75.4 (112)
AUC_{24} (h·nmol/L)	-74.7 (239)	-10.6 (82.4)	-50.5 (NA)	48.4 (365)	275 (NA)	162 (242)
AUC_{48} (h·nmol/L)	-49.6 (477)	81.2 (131)	-107 (NA)	234 (663)	581 (NA)	388 (588)
C_{min} (nmol/L)	-7.77 (5.43)	-6.54 (2.71)	-12.1 (NA)	-10.4 (16.0)	-2.97 (NA)	-9.44 (13.7)
t_{min} (h) †	16.0 (12.0 - 16.0)	12.0 (0 - 16.0)	8.50 (1.00 - 16.0)	6.00 (4.00 - 16.0)	8.50 (1.00 - 16.0)	10.0 (6.00 - 48.0)
Total testosterone						
AUC_{12} (h·ng/mL)	7.22 (10.6)	-25.4 (9.93)	-0.169 (NA)	-0.256 (0.308)	-0.0513 (NA)	-0.258 (0.320) ‡
AUC_{24} (h·ng/mL)	20.7 (17.9)	-49.5 (17.4)	-0.449 (NA)	-0.673 (0.658)	-0.411 (NA)	-0.910 (0.406) ‡
AUC_{48} (h·ng/mL)	59.8 (29.9)	-52.7 (38.8)	0.351 (NA)	-0.186 (0.929)	-0.191 (NA)	-1.43 (0.806) ‡
C_{min} (ng/mL)	-0.303 (1.00)	-3.59 (0.782)	-0.0717 (NA)	-0.0739 (0.0425)	-0.0533 (NA)	-0.0667 (0.0113) ‡
t_{min} (h) †	8.00 (8.00 - 12.0)	12.0 (8.00 - 24.0)	14.0 (12.0 - 16.0)	12.0 (6.00 - 16.0)	10.0 (8.00 - 12.0)	12.0 (1.00 - 16.0) ‡

Parameter Statistic	Single Dose (Day 1)					
	Male		Premenopausal Female		Postmenopausal Female	
	Placebo (N = 3)	fezolinetant 180 mg (N = 9)	Placebo (N = 2)	fezolinetant 180 mg (N = 6)	Placebo (N = 2)	fezolinetant 180 mg (N = 6)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Free testosterone						
AUC_{12} (h·pg/mL)	12.9 (30.3)	-53.9 (19.2)	-0.463 (NA)	0.300 (1.83)	0.438 (NA)	-0.583 (1.32)
AUC_{24} (h·pg/mL)	39.3 (47.3)	-109 (41.3)	-1.76 (NA)	-0.867 (3.02)	-2.56 (NA)	-3.55 (2.49)
AUC_{48} (h·pg/mL)	138 (95.3)	-105 (88.2)	1.84 (NA)	2.20 (5.21)	-3.96 (NA)	-6.42 (5.33)
C_{min} (pg/mL)	-1.66 (2.71)	-8.15 (1.33)	-0.400 (NA)	-0.272 (0.122)	-0.433 (NA)	-0.361 (0.124)
t_{min} (h) †	8.00 (8.00 - 12.0)	12.0 (6.00 - 16.0)	8.50 (1.00 - 16.0)	16.0 (6.00 - 16.0)	16.0 (16.0 - 16.0)	12.0 (12.0 - 16.0)
Estradiol						
AUC_{12} (h·pg/mL)	NC	NC	68.4 (NA)	-34.0 (179) ‡	NA (NA)§	83.6 (NA) ¶
AUC_{24} (h·pg/mL)	NC	NC	242 (NA)	96.3 (669) ‡	NA (NA)§	260 (NA) ¶
AUC_{48} (h·pg/mL)	NC	NC	859 (NA)	834 (1670) ‡	NA (NA)§	676 (NA) ¶
C_{min} (pg/mL)	NC	NC	-0.600 (NA)	-25.0 (19.8) ‡	NA (NA)§	-1.13 (NA) ¶
t_{min} (h) †	NC	NC	7.00 (6.00 - 8.00)	8.00 (6.00 - 16.0) ‡	NA §	12.0 ¶
Progesterone						
AUC_{12} (h·ng/mL)	NC	NC	-0.449 (NA)	-1.56 (2.34) ††	-0.103 (NA) ¶	-4.13 (NA) ‡‡
AUC_{24} (h·ng/mL)	NC	NC	-0.849 (NA)	-3.89 (5.11) ††	-0.263 (NA) ¶	-8.85 (NA) ‡‡
AUC_{48} (h·ng/mL)	NC	NC	-0.989 (NA)	-8.09 (11.3) ††	-0.583 (NA) ¶	-18.2 (NA) ‡‡
C_{min} (ng/mL)	NC	NC	-0.0583 (NA)	-0.243 (0.278) ††	-0.0133 (NA) ¶	-0.395 (NA) ‡‡
t_{min} (h) †	NC	NC	1.25 (1.00 - 1.50)	16.0 (1.00 - 48.0) ††	2.00 ¶	10.0 (4.00 - 16.0) ‡‡

†, Median (minimum - maximum); ‡, n = 5; §, n = 0; ¶, n = 1; ††, n = 4; ‡‡, n = 2

Source: Tables B12.5.8.1.1, B12.5.9.1.1, B12.5.10.1.1, B12.5.11.1.1, B12.5.12.1.1, B12.5.13.1.1 and B12.5.14.1.1

Table 29 Change from Baseline of Pharmacodynamic Parameters in Part 2 on Day 10

Parameter Statistic	Multiple Dose (Day 10)					
	Male		Premenopausal Female		Postmenopausal Female	
	Placebo (N = 3)	fezolinetant 180 mg (N = 8)	Placebo (N = 2)	fezolinetant 180 mg (N = 6)	Placebo (N = 2)	fezolinetant 180 mg (N = 5)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
LH						
AUC_{tau} (h·mIU/mL)	3.02 (13.7)	-13.3 (18.2)	-6.07 (NA)	4.65 (41.7)	50.4 (NA)	-230 (111)
C_{min} (mIU/mL)	-0.986 (0.679)	-1.95 (0.606)	-1.28 (NA)	-1.96 (1.15)	-3.24 (NA)	-15.8 (4.02)
t_{min} (h) †	48.0 (8.00 - 48.0)	8.00 (4.00 - 12.0)	20.0 (16.0 - 24.0)	5.00 (3.00 - 6.00)	2.00 (1.00 - 3.00)	12.0 (6.00 - 12.00)
FSH						
AUC_{tau} (h·mIU/mL)	-8.64 (10.0)	-12.9 (12.0)	-73.4 (NA)	-67.4 (154)	140 (NA)	-253 (190)
C_{min} (mIU/mL)	-0.582 (0.584)	-0.994 (0.602)	-3.42 (NA)	-3.64 (6.18)	-1.67 (NA)	-16.6 (8.42)
t_{min} (h) †	12.0 (8.00 - 48.0)	12.0 (8.00 - 16.0)	16.0 (16.0 - 16.0)	6.00 (6.00 - 48.0)	9.50 (3.00 - 16.0)	12.0 (6.00 - 16.0)
SHBG						
AUC_{tau} (h·nmol/L)	-349 (186)	46.6 (169)	-370 (NA)	-199 (685)	101 (NA)	179 (961)
C_{min} (nmol/L)	-17.2 (8.19)	-2.73 (4.77)	-18.5 (NA)	-30.6 (33.2)	-25.0 (NA)	-21.2 (55.0)
t_{min} (h) †	1.50 (1.00 - 12.0)	5.00 (1.00 - 16.0)	7.50 (3.00 - 12.0)	5.00 (0 - 16.0)	4.00 (0 - 8.00)	8.00 (0 - 48.0)
Total testosterone						
AUC_{tau} (h·ng/mL)	-4.67 (43.3)	-47.2 (24.5)	1.24 (NA)	-0.428 (1.22)	0.0538 (NA)	-0.392 (0.434) ‡
C_{min} (ng/mL)	-1.14 (2.00)	-3.59 (0.962)	-0.0167 (NA)	-0.0689 (0.0586)	-0.0533 (NA)	-0.0683 (0.00430) ‡
t_{min} (h) †	8.00 (8.00 - 12.0)	10.0 (6.00 - 12.0)	12.0 (12.0 - 12.0)	12.00 (6.00 - 16.0)	9.00 (6.00 - 12.0)	14.0 (6.00 - 16.0) ‡
Free testosterone						
AUC_{tau} (h·pg/mL)	52.8 (53.2)	-101 (52.3)	-2.03 (NA)	-2.06 (2.32)	-7.28 (NA)	-4.27 (1.26)
C_{min} (pg/mL)	-1.86 (2.43)	-8.10 (1.65)	-0.350 (NA)	-0.356 (0.100)	-0.533 (NA)	-0.367 (0.111)
t_{min} (h) †	8.00 (6.00 - 12.0)	12.0 (6.00 - 12.0)	16.0 (16.0 - 16.0)	12.0 (1.50 - 16.0)	9.00 (6.00 - 12.0)	12.0 (0 - 16.0)
Estradiol						
AUC_{tau} (h·pg/mL)	NC	NC	1880 (NA)	-570 (1970) §	NA (NA) ¶	-729 (NA)††
C_{min} (pg/mL)	NC	NC	58.4 (NA)	-41.7 (78.2) §	NA (NA) ¶	-31.4 (NA)††
t_{min} (h) †	NC	NC	10.0 (8.00 - 12.0)	12.0 (1.50 - 12.0) §	NA ¶	0††
Progesterone						
AUC_{tau} (h·ng/mL)	NC	NC	174 (NA)	29.6 (72.3) ‡	-0.320 (NA) ††	-0.498 (NA) ††
C_{min} (ng/mL)	NC	NC	5.24 (NA)	0.643 (1.90) ‡	-0.0133 (NA) ††	-0.0233 (NA) ††
t_{min} (h) †	NC	NC	4.00 (0 - 8.00)	3.50 (0 - 12.0) ‡	0 ††	0 ††

†, Median (minimum - maximum); ‡, n = 4; §, n = 5; ¶, n = 0; ††, n = 1

Source: Tables B12.5.8.1.2, B12.5.9.1.2, B12.5.10.1.2, B12.5.11.1.2, B12.5.12.1.2, B12.5.13.1.2 and B12.5.14.1.2

In part 2, mean LH, FSH, total and free testosterone serum concentrations decreased after single and multiple dosing of fezolinetant. Maximum decrease was observed between 6 to 12 hours postdose. Thereafter, these concentrations returned to baseline by 48 hours postdose. There were no remarkable changes of SHBG serum concentration in fezolinetant dose groups compared to placebo groups.

The individual estradiol and progesterone serum concentrations showed high variability and were quantifiable in a limited number of subjects.

Pharmacodynamic parameters of LH, FSH, total testosterone and free testosterone were observed to have a similar tendency in terms of AUC and Cmin after single and multiple dosing.

For LH and FSH, a decrease was observed in males, premenopausal females and postmenopausal females. For total and free testosterone, a decrease was observed in males.

In all pharmacodynamic parameters, no tendencies were observed in Cpredose from Day 1 to Day 10.

Conclusion:

- AUC and Cmax of fezolinetant and ES259564 were similar between healthy Japanese male and premenopausal female and slightly higher in postmenopausal female.
- Visual inspection of the single dosing data indicated a dose proportional increase in AUCinf, AUClast and Cmax over the dose range of 15 to 180 mg fezolinetant when it was assessed in healthy Japanese male.
- With once daily multiple dosing of 180 mg fezolinetant, fezolinetant and ES259564 concentrations reached steady state by day 3 of dosing.
- Slight accumulation of fezolinetant and ES259564 were observed after multiple dosing of fezolinetant.
- The treatment of fezolinetant had an impact of decrease on LH and FSH serum concentrations in male, premenopausal female, and postmenopausal female. In male, the treatment of fezolinetant had an impact of decrease on total and free testosterone serum concentrations.
- The pharmacodynamic parameters of LH, FSH, total testosterone and free testosterone decreased with increased dose of fezolinetant within the dose range of 15 to 180 mg in males.
- The pharmacodynamic parameters of LH and FSH decreased in both pre- and postmenopausal female after administration of fezolinetant.
- Single and multiple oral doses of fezolinetant in healthy Japanese male and female (pre- and postmenopausal) subjects were safe and well tolerated.

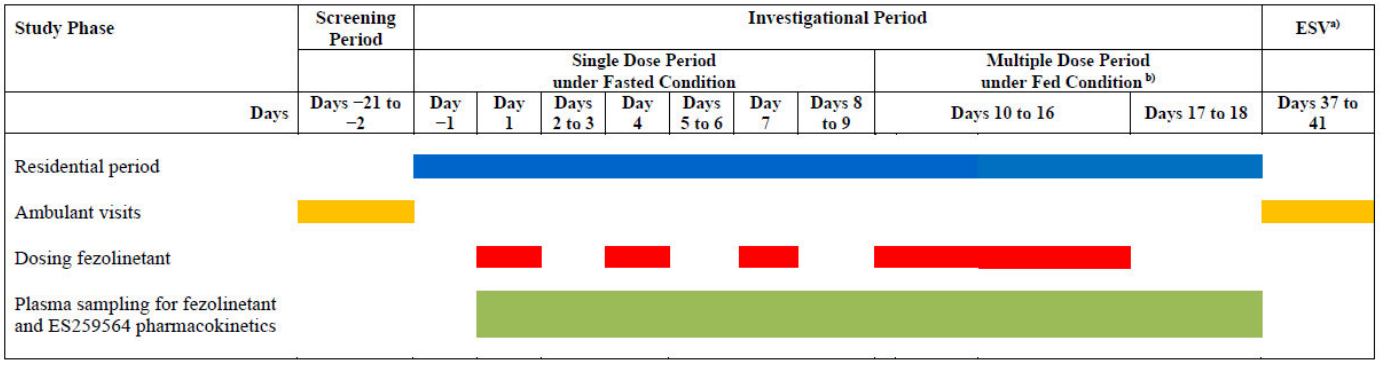
4.3.5 Regional Pharmacokinetic Study 2693-CL-0030 (CHINESE FEMALE)

Title: An Open-Label, Single and Multiple Dose Study to Evaluate the Pharmacokinetics and Safety of Fezolinetant in Healthy Chinese Female Subjects

Primary Objective: This study was designed to evaluate the pharmacokinetic(s) (PK) and safety of fezolinetant after single-dose and multiple-dose administration in healthy Chinese female subjects.

Study Design: This is an open-label study incorporating a single-dose and multiple-dose period to evaluate the pharmacokinetics and safety of fezolinetant (**Figure 12**).

Figure 12 Study design scheme of 2693-CL-0030



ESV: end-of-study visit
a). ESV took place 19 to 23 days after the last pharmacokinetic sample was collected (or at early discontinuation from the study).
b). Dose administration on days 1, 4, 7 and 16 was in the morning after an approximate 10-hour fast and approximately 4 hours before the next meal. Dose administration on days 10 through 15 was after breakfast. Each dose administration was with 150-mL of water.

Participants received single doses of 15 mg fezolinetant on day 1, 30 mg on day 4, and 60 mg on day 7. Repeated doses of 30 mg fezolinetant were given daily from day 10 to day 16. Blood samples were collected pre-dose on days 10, 11, 12, 13, 14, and 15 and at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hours post-dose on day 1, 4, 7, and 16.

Subject Disposition: A total of 16 healthy postmenopausal female subjects were randomized, and 16 subjects completed the study. Data from all subjects were included in the analyses of safety and PK.

PK results:

PK parameters of fezolinetant are summarized for single ascending dose and multiple doses in Chinese female subjects (Table 30**)**

Table 30 Pharmacokinetic Parameters of Fezolinetant (Single and Multiple Dose)

	Single Dose			Multiple Dose
Parameter Statistics	**Fezolinetant Day 1 15 mg n = 16**	**Fezolinetant Day 4 30 mg n = 16**	**Fezolinetant Day 7 60 mg n = 16**	**Fezolinetant Day 16 30 mg qd n = 16**
Cmax (ng/mL)				
Mean (SD)	221 (87.9)	439 (92.9)	834 (268)	481 (104)
%CV	39.7	21.1	32.1	21.7
tmax (h)				
Min, Max	0.500, 4.00	0.500, 3.00	1.00, 4.00	0.500, 4.00

Median	1.50	1.50	1.75	1.25
tlag (h)				
Min, Max	0, 0	0, 0	0, 0	0, 0
Median	0	0	0	0
AUC24h (h*ng/mL)				
Mean (SD)	1240 (362)	2330 (659)	4520 (1240)	NC
%CV	29.3	28.3	27.4	NC
AUCtau (h*ng/mL)				
Mean (SD)	NC	NC	NC	2690 (839)
%CV	NC	NC	NC	31.2
AUCinf (h*ng/mL)				
Mean (SD)	1330 (441)	2530 (794)	4930 (1470)	NC
%CV	33.2	31.3	29.8	NC
AUCinf (%extrap)				
Mean (SD)	2.01 (1.24)	1.14 (0.413)	1.15 (0.353)	NC
%CV	61.5	36.1	30.8	NC
AUClast (h*ng/mL)				
Mean (SD)	1300 (432)	2500 (776)	4870 (1440)	NC
%CV	33.2	31.0	29.6	NC
t1/2 (h)				
Mean (SD)	6.12 (1.72)	7.69 (0.71)	7.44 (0.707)	9.74 (1.320)
%CV	28.0	9.2	9.5	13.6
CL/F (L/h)				
Mean (SD)	12.6 (4.84)	12.9 (3.95)	13.2 (3.82)	12.2 (3.89)
%CV	38.3	30.6	28.9	31.8
Vz/F (L)				
Mean (SD)	104 (27.1)	142 (40.8)	139 (32.5)	171 (56.3)
%CV	26.0	28.8	23.4	32.9
PTR				
Mean (SD)	NC	NC	NC	29.9 (14.6)
%CV	NC	NC	NC	48.9
Rac (AUC)				
Mean (SD)	NC	NC	NC	1.15 (0.132)
%CV	NC	NC	NC	11.4
Rac (Cmax)				
Mean (SD)	NC	NC	NC	1.12 (0.224)
%CV	NC	NC	NC	20.1

All registered participants who received at least 1 dose of the study drug and have had at least 1 time point of sample taken for study drug concentration assessments (pharmacokinetic analysis set).
CV: coefficient of variation; Max: maximum; Min: minimum; n: number of participants; NC: not calculated; PTR: peak to trough ratio.
Source: Study 2693-CL-0030, Tables 6 and 7

Fezolinetant exhibited rapid absorption with median tmax 1.50 to 1.75 hours after single dose administration of fezolinetant tablets in the fasted state, then the plasma levels declined with mean t1/2 of 6.12 to 7.69 hours at dose levels of 15, 30, and 60 mg.

There was an observed dose proportional increase in Cmax, AUCinf, and AUClast for fezolinetant across the 15, 30, and 60 mg doses studied. The drug exposure parameters had a low to moderate variability (21.1% to 39.7%) at the dose levels tested.

Following multiple administration of 30 mg fezolinetant qd for 7 days (day 10 to day 16), median tmax was 1.25 hours and the steady state was achieved on the second day after starting multiple dose administration (day 11). Fezolinetant had minimal accumulation after 7 days of qd dosing of 30 mg with accumulation ratios (Rac [AUC] and Rac [Cmax]) of 1.15 and 1.12, respectively.

Metabolite ES259564 following single dose of fezolinetant had a median tmax of 1.50 to 2.00 hours and the plasma levels declined with mean t1/2 ranging from 5.72 to 6.31 hours across the doses tested.

Metabolite ES259564 showed a dose proportional increase in Cmax, AUCinf and AUClast following single dose administration of 15, 30 and 60 mg fezolinetant. After multiple administration of 30 mg fezolinetant qd for 7 days (from day 10 to day 16), there was a marginal accumulation (Rac [AUC] and Rac [Cmax] were both 1.17) of the metabolite.

Metabolite ES259564 systemic exposure was less than (not exceeding 70%) the parent AUC. The metabolite to parent ratio (MPR) ranged from 0.652 to 0.696 following single and multiple dose administration of fezolinetant.

Conclusion:

- Fezolinetant exhibited rapid absorption and formation of the ES259564 metabolite in healthy female Chinese subjects. A median tmax of 1.50 to 1.75 hours was exhibited after single-dose administration of fezolinetant tablets in the fasted state and a median steady state tmax of 1.25 hours after multiple-dose administration.
- Plasma levels of fezolinetant declined with a mean t1/2 of 6.12 to 7.69 hours at dose levels of 15, 30 and 60 mg and the steady state was achieved on the second day of the multiple-dose period (Day 11) after multiple administration of 30 mg fezolinetant.
- There was a dose-proportional increase in Cmax, AUCinf, and AUClast for fezolinetant and its metabolite, ES259564, across the 15, 30, and 60 mg doses. Fezolinetant and its metabolite showed minimal accumulation after 30 mg multiple-dose administration once daily for 7 days and the metabolite ES259564 systemic exposure was less than the parent AUC (not exceeding 70%).
- Oral administration of fezolinetant was safe and well-tolerated after single-dose (15 to 60 mg) and 7-day multiple-dose (30 mg once daily) administration in healthy Chinese female subjects. No new safety findings were identified during the study.

4.3.6. Dedicated Hepatic Impairment Study 2693-CL-0007

Title: A Phase 1 Study to Investigate the Effect of Mild and Moderate Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of Fezolinetant Compared to Subjects with Normal Hepatic Function

Study Objectives:

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetics of a single oral dose of fezolinetant and ES259564 (fezolinetant metabolite) in female participants with mild and moderate hepatic impairment compared to healthy female participants with normal hepatic function	• Fezolinetant plasma: ○ AUC_{inf}, AUC_{last}, C_{max}, CL/F and V_z/F • ES259564 (fezolinetant metabolite) plasma: ○ AUC_{inf}, AUC_{last} and C_{max}
Secondary	
• To evaluate the safety and tolerability of a single oral dose of fezolinetant in female participants with mild and moderate hepatic impairment and healthy female participants with normal hepatic function	• Nature, frequency and severity of AEs • Clinical laboratory tests (hematology, biochemistry and urinalysis) • Vital signs (blood pressure and pulse) • Routine 12-lead ECG

Objectives	Endpoints
Exploratory	
• To evaluate the pharmacokinetics of a single oral dose of fezolinetant and ES259564 (fezolinetant metabolite) in female participants with mild and moderate hepatic impairment compared to healthy female participants with normal hepatic function	• Fezolinetant plasma: ○ AUC_{inf}(%extrap), t_{lag}, t_{max} and $t_{½}$ • Fezolinetant urine: ○ Ae_{inf}, Ae_{last}, Ae_{last}%, Ae_{inf}% and CL_R • ES259564 (fezolinetant metabolite) plasma: ○ AUC_{inf}(%extrap), t_{lag}, t_{max}, $t_{½}$ and MPR • ES259564 (fezolinetant metabolite) urine: ○ Ae_{inf}, Ae_{last} and CL_R

AE: adverse event; ECG: electrocardiogram: MPR: metabolite-to-parent ratio

Study Design:

This was an open-label, single oral dose study in female participants comprising 3 groups (groups 1.1 to 1.3) based on hepatic function. The study was conducted at 4 study sites in the US. Eligible participants were admitted to the clinical unit on day -1 and were residential for a single period of 6 days/5 nights. On day 1, participants received a single oral dose of 30 mg fezolinetant under fasting conditions followed by a 96-hour in-house blood and urine sampling period. Participants were to remain semirecumbent for 4 hours postdose. Standard safety and tolerability assessments were conducted.

Inclusion/Exclusion Criteria:

Female participants between 18 to 75 years of age, inclusive, were enrolled in this study. Each participant had either normal hepatic function, or mild (Child-Pugh classification Class A, score 5 or 6) or moderate (Child-Pugh classification Class B, score 7 to 9) hepatic impairment. Healthy participants with normal hepatic function were matched (1:1) to the participants with mild and/or moderate hepatic impairment by age (± 10 years), BMI (± 20%), race and sex.

PK Assessment:

- Blood samples for fezolinetant pharmacokinetics and ES259564 (fezolinetant metabolite) concentrations were collected predose on day 1 and at the following postdose time points on day 1: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hour(s).
- Urine samples for fezolinetant pharmacokinetics and ES259564 (fezolinetant metabolite) concentrations were collected predose on day 1 and at the following postdose intervals on day 1: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 72 and 72 to 96 hours.

Subject Disposition:

A total of 26 participants (8 participants with mild hepatic impairment, 8 participants with moderate hepatic impairment and 10 participants with normal hepatic function) were enrolled and completed the treatment, the investigational period, and the follow-up as per the protocol.

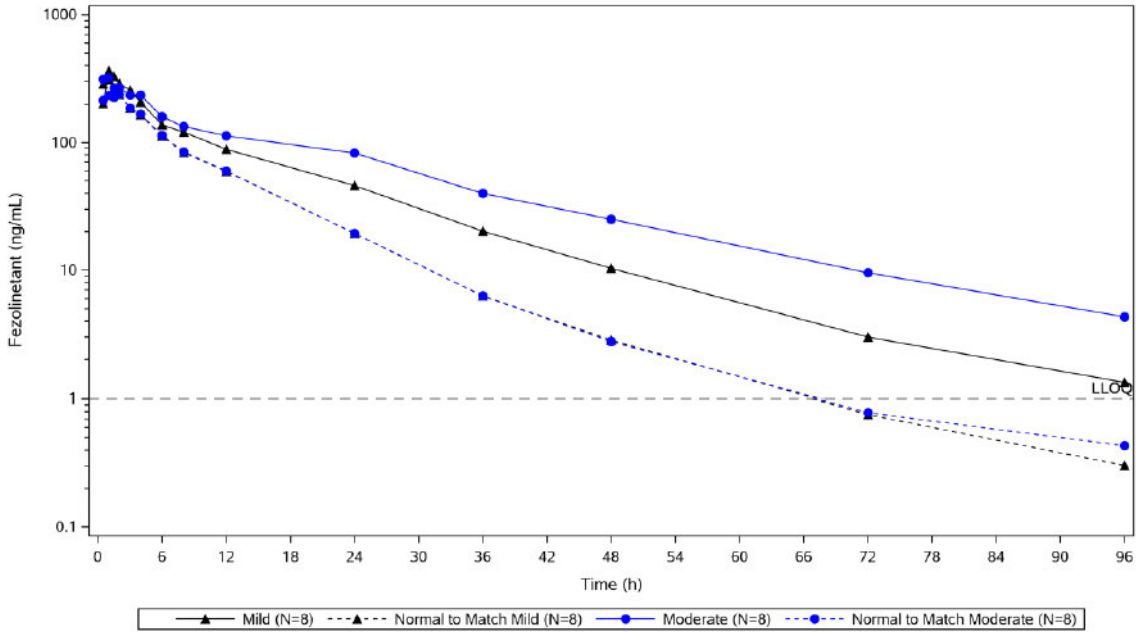
One participant in the normal hepatic function group (who was matched to both a participant with mild hepatic impairment and a participant with moderate hepatic impairment) completed the study, was excluded from the pharmacokinetic analysis due to excluded concomitant medication use and was replaced by a new participant in the normal hepatic function group.

Results:

Plasma PK of ESN364

Mean plasma concentration-time profiles of fezolinetant by hepatic function group are presented in Figure 4. A summary of the PK parameters of fezolinetant by hepatic function group were presented in Table 31. Results of the statistical assessment of the effect of hepatic impairment on the PK of fezolinetant were provided in Table 32. These analyses used PK analysis set, which included all enrolled participants who received at least 1 dose of investigational product for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter. Note: Normal participants may have been enrolled to match more than 1 impaired participant in different impairment groups; these participants were not re-treated.

Figure 13. Mean (SD) Plasma Concentration-time Profiles of Fezolinetant by Hepatic Function Group



Source: Figure 3 of Study 2693-CL-0007

Table 31. Plasma Pharmacokinetic Parameters of Fezolinetant by Hepatic Function Group

Parameter Category/Statistics	Hepatic Function Group			
	Mild	Normal to Match Mild	Moderate	Normal to Match Moderate
AUC_{inf} (h•ng/mL)				
n	8	8	8	8
Mean (SD)	3570 (1140)	2300 (793)	4810 (2080)	2340 (797)
%CV	31.9	34.4	43.3	34.1
Median	3740	2230	4390	2370
Min, Max	1870, 4960	1260, 3360	2110, 7290	1260, 3360
AUC_{last} (h•ng/mL)				
n	8	8	8	8
Mean (SD)	3530 (1130)	2280 (785)	4680 (1980)	2320 (789)
%CV	31.9	34.4	42.3	34.1
Median	3710	2210	4340	2350
Min, Max	1840, 4900	1250, 3330	2040, 7010	1250, 3330
C_{max} (ng/mL)				
n	8	8	8	8
Mean (SD)	408 (121)	358 (65.7)	323 (55.8)	384 (81.7)
%CV	29.5	18.3	17.3	21.3
Median	413	356	309	401
Min, Max	276, 623	272, 435	270, 436	272, 515
CL/F (L/h)				
n	8	8	8	8
Mean (SD)	9.48 (3.97)	14.7 (5.73)	7.56 (3.70)	14.5 (5.81)
%CV	41.9	39.0	48.9	40.1
Median	8.02	13.5	6.94	12.7
Min, Max	6.05, 16.0	8.94, 23.8	4.12, 14.2	8.94, 23.8
V_z/F (L)				
n	8	8	8	8
Mean (SD)	158 (31.5)	211 (70.0)	226 (188)	231 (84.6)
%CV	19.9	33.1	83.0	36.6
Median	154	216	147	243
Min, Max	113, 204	104, 299	103, 651	104, 351
$t_{\frac{1}{2}}$ (h)				
n	8	8	8	8
Mean (SD)	12.7 (3.84)	10.8 (5.01)	19.3 (6.13)	12.2 (6.06)
%CV	30.1	46.2	31.8	49.8
Median	14.3	9.31	17.6	9.90
Min, Max	6.77, 17.6	6.82, 21.5	13.5, 31.7	6.82, 21.5

Source: Table 11 of Study 2693-CL-0007

Table 32. Statistical Assessment of the Effect of Hepatic Impairment on the Plasma Pharmacokinetics of Fezolinetant

Parameter	Comparison (Test/Reference)	Reference		Test		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
		n	Geometric LS Mean	n	Geometric LS Mean		
AUC_{inf} (h•ng/mL)	Mild/Normal to Match Mild	8	2170	8	3380	155.89	(108.04, 224.92)
	Moderate/Normal to Match Moderate	8	1960	8	3850	196.11	(131.64, 292.15)
AUC_{last} (h•ng/mL)	Mild/Normal to Match Mild	8	2150	8	3350	155.82	(108.01, 224.80)
	Moderate/Normal to Match Moderate	8	1940	8	3750	193.63	(130.53, 287.23)
C_{max} (ng/mL)	Mild/Normal to Match Mild	8	336	8	413	122.72	(100.40, 149.99)
	Moderate/Normal to Match Moderate	8	429	8	366	85.14	(73.94, 98.05)

† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.

Source: Table 12 of Study 2693-CL-0007

Reviewer's comments:

- After a single oral dose of 30 mg fezolinetant, compared to respective normal hepatic function groups,
    - mild hepatic impairment group had 56% increase in AUCs and 23% increase in Cmax of fezolinetant.
    - moderate hepatic impairment group had ~95% increase in AUCs and 15% decrease in Cmax of fezolinetant.

Plasma PK of ES259564 (the major metabolite)

Results of the statistical assessment of the effect of renal impairment on the PK of ES259564 were provided in Table 33.

Table 33. Statistical Assessment of the Effect of Hepatic Impairment on the Plasma Pharmacokinetics of ES259564

Parameter	Comparison (Test/Reference)	Reference		Test		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
		n	Geometric LS Mean	n	Geometric LS Mean		
AUC_{inf} (h•ng/mL)	Mild/Normal to Match Mild	8	1660	8	1900	114.31	(96.00, 136.11)
	Moderate/Normal to Match Moderate	8	1690	8	1910	113.28	(96.02, 133.63)
AUC_{last} (h•ng/mL)	Mild/Normal to Match Mild	8	1640	8	1860	113.53	(95.20, 135.40)
	Moderate/Normal to Match Moderate	8	1660	8	1870	112.45	(94.99, 133.13)
C_{max} (ng/mL)	Mild/Normal to Match Mild	8	154	8	121	79.03	(62.55, 99.86)
	Moderate/Normal to Match Moderate	8	159	8	84.5	53.02	(36.33, 77.37)

Source: Table 12 of Study 2693-CL-0007

Reviewer's comments:

- After a single oral dose of 30 mg fezolinetant, compared to respective normal hepatic function groups,
    - mild hepatic impairment group had 14% increase in AUCs and 21% decrease in Cmax of ES259564.
    - moderate hepatic impairment group had 13% increase in AUCs and 47% decrease in Cmax of ES259564.

4.3.7. Dedicated Renal Impairment Study 2693-CL-0008

Title: A Phase 1 Open-label Study to Investigate the Effect of Renal Impairment on the Pharmacokinetics, Safety and Tolerability of Fezolinetant Compared to Subjects with Normal Renal Function

Study Objectives:

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetics of a single oral dose of fezolinetant and ES259564 (fezolinetant metabolite) in female participants with varying levels of renal impairment (mild, moderate and severe) compared to healthy female participants with normal renal function	• Fezolinetant plasma: ○ AUC_{inf}, AUC_{last}, C_{max} and CL/F • ES259564 (fezolinetant metabolite) plasma: ○ AUC_{inf}, AUC_{last} and C_{max}
Secondary	
• To evaluate the safety and tolerability of a single oral dose of fezolinetant in female participants with varying levels of renal impairment (mild, moderate and severe) and healthy female participants with normal renal function	• Nature, frequency and severity of AEs • Clinical laboratory tests (hematology, biochemistry and urinalysis) • Vital signs (blood pressure and pulse) • Routine 12-lead ECG
Exploratory	
• To evaluate the pharmacokinetics of a single dose of fezolinetant and ES259564 (fezolinetant metabolite) in female participants with varying levels of renal impairment (mild, moderate and severe) compared to healthy female participants with normal renal function	• Fezolinetant plasma: ○ AUC_{inf}(%extrap), t_{lag}, t_{max}, $t_{½}$ and V_z/F • Fezolinetant urine: ○ Ae_{inf}, Ae_{last}, Ae_{last}%, Ae_{inf}% and CL_R • ES259564 (fezolinetant metabolite) plasma: ○ AUC_{inf}(%extrap), t_{lag}, t_{max} and $t_{½}$ • ES259564 (fezolinetant metabolite) urine: ○ Ae_{inf}, Ae_{last} and CL_R

AE: adverse event; ECG: electrocardiogram

Study Design:

This was an open-label, single oral dose study comprising 4 groups of participants based on renal function. Eligible participants with mild, moderate and severe renal impairment and healthy participants with normal renal function were admitted to the clinical unit on day -1 and were residential for a single period of 6 days/5 nights. On day 1, participants received a single oral dose of 30 mg fezolinetant under fasting conditions followed by a 96-hour in-house blood and urine sampling period. Participants were to remain awake, seated or semirecumbent, and avoided lying on either the left or right side for at least 4 hours postdose. Standard safety and tolerability assessments were conducted.

Inclusion/Exclusion Criteria:

Female participants between 18 to 75 years of age, inclusive, were enrolled in this study.

Participants were enrolled into 1 of 4 groups based on renal function. Renal function was measured by eGFR using the MDRD formula:

- Participants with mild (eGFR 60 to < 90 mL/min per 1.73 m^2) renal impairment
- Participants with moderate (eGFR 30 to < 60 mL/min per 1.73 m^2) renal impairment
- Participants with severe (eGFR < 30 mL/min per 1.73 m2) renal impairment and not on hemodialysis. At least 50% of participants should have had an eGFR of ≤ 20 mL/min per 1.73 m^2
- Healthy participants with normal (eGFR ≥ 90 mL/min per 1.73 m^2) renal function

Healthy participants with normal renal function were enrolled following the enrollment of mild and/or moderate and/or severe impairment participants and were demographically matched (1:1) by age (± 10 years), BMI (± 20%) and race to the enrolled impairment participant(s).

PK Assessment:

Blood samples for fezolinetant and ES259564 (fezolinetant metabolite) concentrations were collected predose on day 1 and at the following postdose time points on day 1: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 60, 72 and 96 hours.

Urine samples for fezolinetant and ES259564 (fezolinetant metabolite) concentrations were collected predose on day 1 and at the following postdose intervals on day 1: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72 and 72 to 96 hours.

Subject Disposition:

A total of 27 participants (6 participants with mild renal impairment, 6 participants with moderate renal impairment, 5 participants with severe renal impairment and 10 participants with normal renal function) were enrolled, assigned to, and received a single oral dose of 30 mg fezolinetant under fasted conditions in an open-label manner on day 1 and completed the treatment and the follow-up periods as per the protocol.

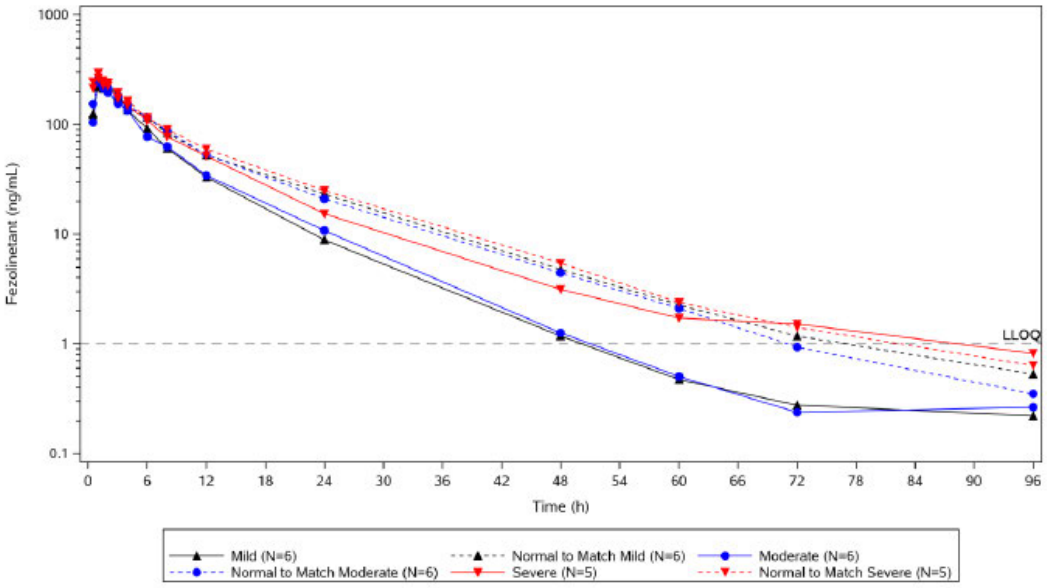
One participant with normal renal function withdrew on day 3 during the investigational period (Subject (b) (6), withdrawal by subject but agreeable to complete the end of study visit [ESV]; this participant completed ESV and was included in the safety analysis but was excluded from the pharmacokinetic analysis due to withdrawal from the study during the investigational period. The participant was replaced by a new participant with normal renal function.

Results:

Plasma PK of ESN364

Mean plasma concentration-time profiles of fezolinetant by renal function group were presented in Figure 4. A summary of the PK parameters of fezolinetant by renal function group were presented in Table 34. Results of the statistical assessment of the effect of renal impairment on the PK of fezolinetant were provided in Table 35. These analyses used PK analysis set, which included all enrolled participants who received at least 1 dose of investigational product for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter. Note: Normal participants may have been enrolled to match more than 1 impaired participant in different impairment groups; these participants were not re-treated.

Figure 14. Mean (SD) Plasma Concenttration-time Profiles of Fezolinetant by Renal Function Group



Source: Figure 3 of Study 2693-CL-0008

Table 34. Plasma PK Parameters of Fezolinentant by Renal Function Group

Parameter Category/Statistics	Renal Function Group					
	Mild	Normal to Match Mild	Moderate	Normal to Match Moderate	Severe	Normal to Match Severe
AUC_{inf} (h•ng/mL)						
n	5	6	5	6	3	5
Mean (SD)	1430 (525)	2220 (1350)	1300 (306)	2200 (1210)	2400 (823)	2470 (1190)
%CV	36.7	61.1	23.6	54.9	34.3	48.1
Median	1330	2260	1260	2070	2210	1900
Min, Max	875, 2300	684, 4420	1000, 1620	918, 4420	1680, 3300	1420, 4420
AUC_{last} (h•ng/mL)						
n	6	6	6	6	5	5
Mean (SD)	1600 (659)	2190 (1340)	1540 (721)	2170 (1200)	2110 (716)	2440 (1180)
%CV	41.3	61.3	46.7	55.3	33.8	48.5
Median	1330	2250	1390	2050	2040	1880
Min, Max	858, 2540	669, 4380	976, 2900	902, 4380	1410, 3270	1370, 4380
C_{max} (ng/mL)						
n	6	6	6	6	5	5
Mean (SD)	272 (71.5)	270 (51.7)	267 (90.0)	260 (44.0)	308 (68.1)	286 (39.7)
%CV	26.3	19.2	33.7	16.9	22.1	13.9
Median	282	259	231	259	322	271
Min, Max	152, 360	199, 332	192, 406	199, 332	199, 380	238, 328
CL/F (L/h)						
n	5	6	5	6	3	5
Mean (SD)	23.1 (7.56)	20.1 (14.7)	24.2 (5.68)	17.2 (8.91)	13.5 (4.37)	14.1 (5.47)
%CV	32.7	73.0	23.5	51.9	32.4	38.7
Median	22.6	13.3	23.8	14.6	13.5	15.8
Min, Max	13.1, 34.3	6.79, 43.9	18.5, 30.0	6.79, 32.7	9.10, 17.8	6.79, 21.2
t_{max} (h)						
n	6	6	6	6	5	5
Median	1.25	1.25	1.25	1.00	1.00	1.00
Min, Max	0.500, 2.00	1.00, 2.00	0.500, 1.52	1.00, 2.00	0.500, 2.00	1.00, 2.00
$t_{\frac{1}{2}}$ (h)						
n	5	6	5	6	3	5
Mean (SD)	6.74 (2.10)	11.6 (9.41)	7.04 (1.47)	8.15 (3.26)	13.7 (1.84)	12.8 (9.81)
%CV	31.1	81.5	20.9	40.0	13.4	76.7
Median	7.63	8.57	7.58	8.18	12.7	7.94
Min, Max	4.23, 8.78	4.30, 29.4	5.44, 8.70	4.62, 13.8	12.6, 15.8	5.35, 29.4

Source: Table 11 of Study 2693-CL-0008

Table 35. Statistical Assessment of the Effect of Renal Impairment on Plasma Pharmacokinetics of Fezolinetant

Parameter	Comparison (Test/Reference)	Reference		Test		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
		n	Geometric LS Mean	n	Geometric LS Mean		
AUC_{inf} (h•ng/mL)	Mild/Normal to Match Mild	6	1980	5	1240	62.74	(34.48, 114.15)
	Moderate/Normal to Match Moderate	6	2240	5	1080	48.02	(31.95, 72.18)
	Severe/Normal to Match Severe	5	2150	3	2540	117.93	(60.13, 231.28)
AUC_{last} (h•ng/mL)	Mild/Normal to Match Mild	6	1830	6	1480	80.76	(43.05, 151.51)
	Moderate/Normal to Match Moderate	6	2000	6	1380	68.84	(40.12, 118.11)
	Severe/Normal to Match Severe	5	2240	5	2030	90.44	(55.14, 148.35)
C_{max} (ng/mL)	Mild/Normal to Match Mild	6	265	6	264	99.48	(75.35, 131.33)
	Moderate/Normal to Match Moderate	6	251	6	262	104.28	(78.28, 138.92)
	Severe/Normal to Match Severe	5	284	5	301	105.94	(81.86, 137.12)

† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.

Source: Table 13 of Study 2693-CL-0008

Reviewer's comments:

- Compared to respective normal renal function groups, severe renal impairment had marginal effects on fezolinetant's PK exposure (GMR: 118% for AUCinf; 90% for AUClast; and 106% for Cmax; with all 90% CI including 100%).
- Compared to respective normal renal function groups, mild and moderate impairment groups had similar Cmax but lower AUClast (GMR: 81% for Mild; 69% for Moderate; with all 90% CI including 100%).
- Statistical analysis based on AUCinf may not be as robust as AUClast because AUCinf could not be accurately calculated for 4 participants and therefore excluded from the analyses. More details can be found in response to IR dated 09/02/22 (SN 0011) and 10/03/22 (SN0019).

Plasma PK of ES259564 (the major metabolite)

Results of the statistical assessment of the effect of renal impairment on the PK of ES259564 were provided in Table 36.

Table 36. Statistical Assessment of the Effect of Renal Impairment on Plasma Pharmacokinetics of ES259564

Parameter	Comparison (Test/Reference)	Reference		Test		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
		n	Geometric LS Mean	n	Geometric LS Mean		
AUC_{inf} (h•ng/mL)	Mild/Normal to Match Mild	6	1700	6	1780	104.84	(86.22, 127.47)
	Moderate/Normal to Match Moderate	6	1490	6	2610	174.78	(118.41, 257.99)
	Severe/Normal to Match Severe	5	1520	5	7270	478.79	(347.67, 659.35)
AUC_{last} (h•ng/mL)	Mild/Normal to Match Mild	6	1670	6	1720	103.29	(84.09, 126.87)
	Moderate/Normal to Match Moderate	6	1460	6	2590	177.14	(120.02, 261.44)
	Severe/Normal to Match Severe	5	1490	5	7140	478.56	(347.93, 658.22)
C_{max} (ng/mL)	Mild/Normal to Match Mild	6	166	6	188	113.58	(85.03, 151.71)
	Moderate/Normal to Match Moderate	6	127	6	222	174.90	(124.87, 244.97)
	Severe/Normal to Match Severe	5	127	5	293	231.06	(154.61, 345.31)

All enrolled participants who received at least 1 dose of investigational product for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter (pharmacokinetic analysis set).

Assessment based on an analysis of covariance performed on natural logarithmic-transformed parameters with renal function as a fixed effect and age and body mass index as covariates.

Normal participants may have been enrolled to match more than 1 impaired participant in different impairment groups; these participants were not re-treated.

CI: confidence interval; LS: least squares

† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.

Source: Table 15 of Study 2693-CL-0008

Reviewer's comments:

- Compared to respective normal renal function groups,
    - mild renal impairment had marginal effects on ES259564 exposure (GMR: 105% for AUCinf; 103% for AUClast; and 114% for Cmax; with all 90% CI including 100%).
    - moderate renal impairment group had 70% increase in ES259564 exposure (GMR: 175% for AUCinf; 177% for AUClast; and 175% for Cmax; with all 90% CI above 100%).
    - sever renal impairment group had 2-5-fold increase in ES259564 exposure (GMR: 479% for AUCinf; 479% for AUClast; and 231.0% for Cmax; with all 90% CI above 100%).
- The CLR of ES259564 progressively decreased with increased severity of renal impairment. Compared to their respective match participants with normal renal function, participants with

renal impairment had lower mean ES259564 CLR (9.56 vs 10.4 L/h for mild, 6.98 vs 13.0 L/h for moderate, and 1.61 vs 13.1 L/h for severe renal impairment groups).

4.3.8. Study 2693-CL-0012 Effect of Food on the Pharmacokinetics of Fezolinetant

Title: A Phase 1 Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Fezolinetant in Healthy Female Participants

Primary Objective: This study evaluated the effect of food on the pharmacokinetics of a single oral dose of fezolinetant to-be-marketed formulation under fasted and fed conditions in healthy female participants.

Study design:

This was a randomized, open-label, 2-period, 2-sequence, single dose crossover study in healthy female participants. Sixteen participants (i.e., 8 participants per sequence) were randomized to 1 of 2 sequences according to Table 37 below.

Table 37 Sequences and Study Drug Assignments (2693-CL-0012)

Sequence	n	Period 1	Period 2
1	8	Fezolinetant (fed)	Fezolinetant (fasted)
2	8	Fezolinetant (fasted)	Fezolinetant (fed)

Participants received a single oral administration of a 45 mg fezolinetant tablet (to-be-marketed formulation) under fed or fasted condition on day 1 of each period. The 2 treatment periods were separated by a 5-day washout period. Pharmacokinetic samples were collected at multiple time points up to 72 hours postdose (i.e., 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours postdose).

Subject Disposition: A total of 16 healthy female subjects were randomized, and 16 subjects completed the study. Data from all subjects were included in the analyses of safety and PK.

Safety Results:
No deaths, serious adverse events or treatment-emergent adverse events (TEAEs) that led to withdrawal of treatment were reported during the conduct of this study. The frequency of all TEAEs reported during the study was similar between fasting and fed conditions. Overall, 14 mild TEAEs were reported for 6 (37.5%) participants during the study with 3 participants under the fed condition and 5 participants under the fasted condition.

PK Results:

PK parameters of fezolinetant and its metabolite, ES259564, in fasting and fed conditions are summarized below (Table 38 and Table 39).

Table 38 Fezolinetant Plasma Pharmacokinetic Parameters

Fezolinetant Plasma Pharmacokinetic Parameters

Parameter Category/Statistics	Fasted	Fed
AUCinf (h•ng/mL)		
n	9†	9†
Mean (SD)	2870 (962)	2760 (994)
%CV	33.5	35.9
Median	3070	2600
Min - Max	1770 - 4500	1870 - 4590
AUClast (h•ng/mL)		
n	16	16
Mean (SD)	2590 (877)	2470 (845)
%CV	33.8	34.3
Median	2310	2240
Min -Max	1260 - 4410	1310 - 4570
Cmax (ng/mL)		
n	16	16
Mean (SD)	453 (153)	343 (112)
%CV	33.8	32.8
Median	467	312
Min - Max	207 - 810	225 - 589
tmax (h)		
n	16	16
Median	1.49	2.04
Min - Max	0.500 - 4.00	0.500 - 8.03

All randomized participants who received at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter (pharmacokinetic analysis set).
CV: coefficient of variation; Max: maximum; Min: minimum; SD: standard deviation.
† AUCinf values from 7 participants were not reported and thus not included in the statistical assessment due to undefined elimination phase. AUClast including all evaluable participants, as well as AUCinf excluding these 7 participants, provided consistent bioequivalence results. Refer to [Study 2693-CL-0012, End-of-Text Table 9.4.2.1] for details.
Source: Study 2693-CL-0012, End-of-Text Table 9.4.2.1

Table 39 ES259564 Plasma Pharmacokinetic Parameters

Parameter Category/Statistics	Fasted	Fed
AUCinf (h•ng/mL)		
n	16	16
Mean (SD)	2100 (389)	2090 (344)
%CV	18.5	16.5
Median	2020	2150
Min, Max	1640, 2960	1520, 2700
AUClast (h•ng/mL)		
n	16	16

Mean (SD)	2090 (387)	2070 (345)
%CV	18.5	16.7
Median	2010	2120
Min, Max	1610, 2930	1500, 2680
Cmax (ng/mL)		
n	16	16
Mean (SD)	263 (84.1)	217 (58.0)
%CV	32.0	26.7
Median	247	223
Min, Max	145, 425	119, 301
tmax (h)		
n	16	16
Median	2.00	3.00
Min, Max	0.517, 4.00	1.02, 8.03

All randomized participants who received at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
CV: coefficient of variation; Max: maximum; Min: minimum
Source: End-of-Text Table 9.4.2.2

Statistical analysis of food effects on exposure of fezolinetant and its metabolite, ES259564, in fasting and fed conditions are summarized below (Table 40 and Table 41).

Table 40 Statistical Assessment of Food Effect on Fezolinetant

Parameter	Fasted		Fed		Geometric LS Mean Ratio (%)†	90% CI of Ratio
	n	Geometric LS Mean	n	Geometric LS Mean		
AUCinf (h•ng/mL)	9‡	2630	9‡	2540	96.57	(86.38, 107.96)
AUClast (h•ng/mL)	16	2460	16	2350	95.53	(89.93, 101.49)
Cmax (ng/mL)	16	428	16	328	76.70	(62.03, 94.83)

All randomized participants who received at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with period and food condition as fixed effects and participant as a random effect.
CI: confidence interval; LS: least squares
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
‡ AUCinf values from 7 participants were not reported and thus not included in the statistical assessment due to undefined elimination phase. Refer to [End-of-Text Table 9.4.2.1] for details.
Source: End-of-Text Table 9.4.3.1

Table 41 Statistical Assessment of Food Effect on ES259564

	Fasted	Fed		

Parameter	n	Geometric LS Mean	n	Geometric LS Mean	Geometric LS Mean Ratio (%)†	90% CI of Ratio
AUCinf (h•ng/mL)	16	2070	16	2060	99.51	(96.85, 102.25)
AUClast (h•ng/mL)	16	2050	16	2040	99.43	(96.73, 102.20)
Cmax (ng/mL)	16	251	16	210	83.60	(74.91, 93.31)

All randomized participants who received at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with period and food condition as fixed effects and participant as a random effect.
CI: confidence interval; LS: least squares
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
Source: End-of-Text Table 9.4.3.2

The geometric LS mean ratio and 90% CI for the AUCinf and AUClast of fezolinetant and ES259564 fell within the 80 to 125% boundary when comparing fed and fasted conditions. Whereas a high-fat meal reduced fezolinetant Cmax (geometric LS mean ratio of 76.70%; 90% CI [62.03, 94.83]) and ES259564 Cmax (geometric LS mean ratio of 83.6%; 90% CI [74.91, 93.31]). The median tmax of fezolinetant was also delayed by 30 minutes (from 1.49 hours to 2.04 hours) and by 1 hour for ES259564.

Conclusions:
Therefore, following a single 45 mg dose of fezolinetant to healthy female participants, a high-fat, high-calorie meal did not affect fezolinetant AUCinf and AUClast compared to under fasted conditions.
The high-fat, high-calorie meal decreased Cmax (< 20%) of fezolinetant and delayed the time to reach Cmax (by ~ 30 minutes) compared to under fasted conditions.
The decrease in Cmax and delay in tmax with food is not clinically relevant, thus fezolinetant can be administered with or without food.

Reviewer comments: The applicant's conclusion is acceptable.

4.3.9. Drug-drug Interaction with Fluvoxamine and Smoking (Study 2693-CL-0006)

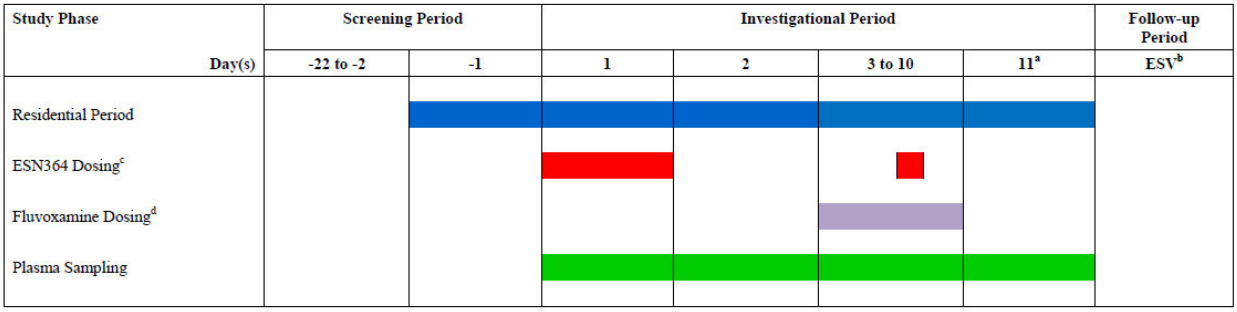
Since fezolinetant is extensively metabolized by the CYP1A2 enzyme, phase 1 Study 2693-CL-0006 was conducted to assess the effect of multiple doses of fluvoxamine, a strong inhibitor of CYP1A2, and smoking, a CYP1A2 inducer, on the single dose PK of fezolinetant in healthy postmenopausal women.

Title: A Phase 1 Study to Assess the Effect of Multiple Doses of Fluvoxamine and Smoking on the Single Dose Pharmacokinetics of fezolinetant in Healthy Postmenopausal Female Subjects (2693-CL-0006)

Primary objectives: To evaluate the effect of concomitant administration of fluvoxamine, a strong cytochrome P450 (CYP)1A2 inhibitor, on the pharmacokinetics of a single oral dose of fezolinetant in healthy postmenopausal female subjects

Secondary Objectives: To evaluate the effect of smoking on the pharmacokinetics of fezolinetant with and without concomitant administration of fluvoxamine; To evaluate the effect of concomitant administration of fluvoxamine on the pharmacokinetics of fezolinetant in smokers and nonsmokers; To evaluate the safety and tolerability of a single oral dose of fezolinetant alone and in combination with fluvoxamine

Study Design: This study had an open-label, single sequence design. A total of 18 participants, 9 of which were smokers, were enrolled into the study. See the flow chart below for illustration.



On day 1, a single dose of 30 mg fezolinetant was administered in the morning. On day 3 in the evening and on day 10 in the morning, a single oral dose of 50 mg fluvoxamine was administered. On days 4 to 9, multiple oral doses of 50 mg fluvoxamine were administered bid with a 12-hour interval. On day 7 (fifth day of fluvoxamine dosing), the single dose of 30 mg fezolinetant was administered simultaneously with the morning dose of fluvoxamine. Smokers were instructed to smoke their usual number of cigarettes per day.

Subject Disposition: A total of 18 healthy postmenopausal female subjects were randomized, and 16 subjects completed the study. Data from all subjects were included in the analyses of safety and PK.

4.3.9.1 Effect of Fluvoxamine (CYP1A2 Inhibitor)

PK results:

The results showed that when fezolinetant was co-administered with fluvoxamine, a strong CYP1A2 inhibitor, there was a 9.39-fold increase (90% CI: 788.06%, 1119.91%) in AUCinf and a 1.82-fold increase (90% CI: 161.79%, 203.93%) in Cmax of fezolinetant (Table 42).

Table 42 Statistical Assessment of the Effect of Fluvoxamine on the Pharmacokinetics of Fezolinetant (co-administered)

Parameter	Fezolinetant Alone		Fezolinetant + Fluvoxamine		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
	n	Geometric LS Mean	n	Geometric LS Mean		
Cmax (ng/mL)	18	233	18	424	181.64	(161.79, 203.93)
AUCinf (h•ng/mL)	18	941	18	8840	939.44	(788.06, 1119.91)

All participants who took at least 1 dose of study drug and for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with treatment as a fixed effect and participant as a random effect.
CI: confidence interval; LS: least squares; n: number of participants.
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
Source: Study 2693-CL-0006, End-of-Text Table 12.4.3.1

There was an increase in the t1/2 of fezolinetant (4 hr vs 22. 4 hr) but no substantial changes in tmax.

For the metabolite, co-administration of fluvoxamine resulted in a ~80% reduction of ES259564 Cmax, but a slightly increase (1.08-fold) of AUCinf (90% CI: 102.81%, 113.39%) (Table 43).

Table 43 Study 2693-CL-0006: Statistical Assessment of the Effect of Fluvoxamine on the Pharmacokinetics of ES259564

Parameter	Fezolinetant Alone		Fezolinetant + Fluvoxamine		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
	n	Geometric LS Mean	n	Geometric LS Mean		
Cmax (ng/mL)	18	239	18	48.0	20.10	(17.06, 23.68)
AUCinf (h•ng/mL)	18	1680	18	1810	107.97	(102.81, 113.39)

All participants who took at least 1 dose of study drug and for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with treatment as a fixed effect and participant as a random effect.
CI: confidence interval; ES259564: fezolinetant metabolite; LS: least squares; n: number of participants.
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
Source: Study 2693-CL-0006, End-of-Text Table 12.4.3.2

4.3.9.2 Effect of Smoking (CYP1A2 Inducer)

Smoking is considered as a potent CYP1A2 induction factor. The pharmacokinetic parameters of fezolinetant and ES259564 after fezolinetant administration alone and after fezolinetant co-administration with fluvoxamine in smokers and nonsmokers are summarized below (Table 44).

Table 44 Study 2693-CL-0006: Pharmacokinetic Parameters of Fezolinetant And ES259564 After Fezolinetant Administration Alone and After Fezolinetant Co-Administration With Fluvoxamine In Smokers And Nonsmokers

Parameter	Fezolinetant			ES259564		
	Smokers (n = 9)	Nonsmokers (n = 9)	Total (n = 18)	Smokers (n = 9)	Nonsmokers (n = 9)	Total (n = 18)
Fezolinetant Alone						
C_{max} (ng/mL)	207	282	244	281	211	246
AUC_{inf} (h•ng/mL)	670	1400	1040	1540	1880	1710
CL/F (L/h)	47.1	22.9	35.0	NA	NA	NA
$t_{½}$ (h)	3.23	4.79	4.01	7.61	6.41	7.01
t_{max} (h)	1.00	1.00	1.00	1.50	1.50	1.50

V_z/F (L)	213	151	182	NA	NA	NA
MPR	NA	NA	NA	2.29	1.35	1.82
Fezolinetant + Fluvoxamine						
C_{max} (ng/mL)	407	458	432	63.2	41.0	52.1
AUC_{inf} (h•ng/mL)	7060	13200	10100	1780	1920	1850
CL/F (L/h)	5.04	2.80	3.92	NA	NA	NA
$t_{½}$ (h)	16.0	28.8	22.4	16.5	30.1	23.3
t_{max} (h)	1.50	1.50	1.50	12.0	8.00	12.0
V_z/F (L)	101	96.2	98.8	NA	NA	NA
MPR	NA	NA	NA	0.285	0.169	0.227

Data are the arithmetic means, except tmax, which is the median.
CV: coefficient of variation; Max: maximum; Min: minimum: MPR: metabolite to parent ratio; NA: not applicable
Source: End-of-Text Tables 12.4.2.1 and 12.4.2.2

Statistical analysis of exposure of fezolinetant demonstrate when fezolinetant was administered alone, fezolinetant AUCinf in smokers decreased by about a half with LS mean ratio of 48.29% (90% CI: 39.14%, 59.58%) to non-smoker, while Cmax decreased ~30 % with a geometric LS mean ratio of 71.74% (90% CI: 57.04%, 90.22%) to non-smoker (Table 45).

Table 45 Study 2693-CL-0006: Statistical Assessment of the Effect of Smoking on Fezolinetant After Administration Alone and After Co-administration with Fluvoxamine

Treatment Parameter	Nonsmoker		Smoker		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
	n	Geometric LS Mean	n	Geometric LS Mean		
Fezolinetant Alone						
Cmax (ng/mL)	9	276	9	198	71.74	(57.04, 90.22)
AUCinf (h•ng/mL)	9	1350	9	654	48.29	(39.14, 59.58)
Fezolinetant + Fluvoxamine						
Cmax (ng/mL)	9	450	9	399	88.65	(74.98, 104.81)
AUCinf (h•ng/mL)	9	12000	9	6490	53.92	(36.83, 78.96)

Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with smoking status as a fixed effect.
CI: confidence interval; LS: least squares; n: number of participants.
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
Source: Study 2693-CL-0006, End-of-Text Table 12.4.3.5

For the metabolite ES259564, statistical analysis demonstrated when fezolinetant was administered alone, the Cmax geometric LS mean ratio for smokers versus nonsmokers was 130.20% (90% CI: 109.43, 154.92) and AUCinf geometric LS mean ratio was 81.84% (90% CI: 70.34, 95.22) (Table 46).

Table 46 Study 2693-CL-0006: Statistical Assessment of the Effect of Smoking on the Pharmacokinetics of ES259564 After Fezolinetant Administration Alone and After Co-administration with Fluvoxamine

Smoking Status / Parameter	Nonsmoker		Smoker		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
	n	Geometric LS Mean	n	Geometric LS Mean		
Fezolinetant Alone						
C_{max} (ng/mL)	9	209	9	273	130.20	(109.43, 154.92)
AUC_{inf} (h•ng/mL)	9	1860	9	1520	81.84	(70.34, 95.22)
Fezolinetant + Fluvoxamine						
C_{max} (ng/mL)	9	38.6	9	59.7	154.45	(113.69, 209.84)
AUC_{inf} (h•ng/mL)	9	1880	9	1750	93.12	(77.32, 112.15)

CI: confidence interval; ES259564: fezolinetant metabolite; LS: least squares; n: number of participants.
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
Source: Study 2693-CL-0006, End-of-Text Table 12.4.3.6

Conclusion:

- Co-administration of fezolinetant with fluvoxamine resulted in increased fezolinetant exposure and t½, with no change in tmax, due to decreases in both CL/F and Vz/F. The magnitude of exposure increase (9.39-fold increase in AUCinf and 1.82-fold increase in Cmax) was similar in smokers and nonsmokers. These results were consistent with inhibition of fezolinetant metabolic clearance following co-administration of fluvoxamine.
- Following fezolinetant administration, ES259264 exhibited elimination-rate limited kinetics. Co-administration of fezolinetant with fluvoxamine resulted in a large decrease in ES259564 Cmax (geometric LS mean ratio 20.10%), a small increase in AUCinf (geometric LS mean ratio 107.97%) and a large increase of t½ plus a decrease in the MPR. These changes were similar whether the subject was a smoker or nonsmoker. The addition of fluvoxamine appears to slow the rate of formation of the metabolite and slow its metabolic clearance.
- Smoking resulted in decreased fezolinetant exposure (geometric LS mean ratio 48.29% for AUCinf and 71.74% for Cmax) with similar decreases observed when fezolinetant was co-administered with fluvoxamine. Both CL/F and Vz/F increased with smoking leading to a decrease in fezolinetant t½. The increase in CL/F and decrease in t½ were consistent with smoking increasing CYP1A2 activity. The increase in Vz/F can be explained by increased first pass metabolism leading to a decrease in oral bioavailability.
- When fezolinetant was administered alone in smokers, ES259564 Cmax slightly increased (1.30-fold), AUCinf slightly decreased (geometric LS mean ratio 81.84%), while the MPR increased. These results were of the same magnitude when fezolinetant was administered in combination with fluvoxamine. These results are consistent with smoking increasing the fraction of parent converted to metabolite, but not affecting the amount of the metabolite.

Reviewer comments: The applicant's conclusion for impact of CYP1A2 inhibitor (fluvoxamine) and inducer (smoking) to exposure of fezolinetant is reasonable.

4.3.10. Phase 2 Dose-finding Study ESN364-HF-205

Title: A Randomized, Placebo-Controlled, Double-Blind, Dose-Ranging, Phase 2b Study to Investigate the Efficacy of ESN364 in Postmenopausal Women Suffering From Vasomotor Symptoms (Hot Flashes)

Primary Objective:

The primary objective of this study was to evaluate the effect of different doses and dosing regimens of ESN364 on frequency and severity of VMS (hot flashes).

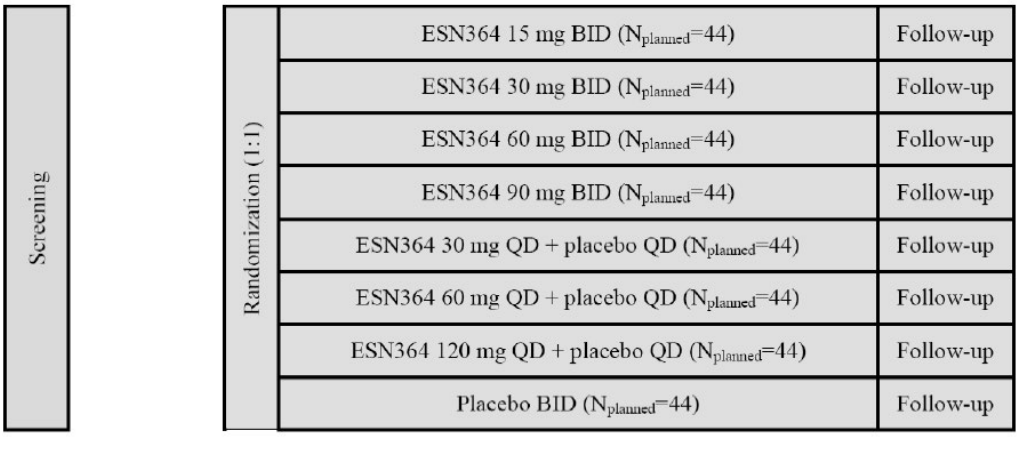
There were 4 co-primary efficacy endpoints:

- 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

Study Design:

This was a 12-week, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, multicenter study to assess the efficacy of ESN364 in postmenopausal women with VMS (hot flashes). A schematic overview of the study design was provided in Figure 6.

Figure 15. Overview of Study ESN364_HF_205



a. Screening was to be performed up to 35 days prior to randomization, with a minimum of 7 days to allow for baseline data collection of vasomotor symptom frequency and severity. V = visit.

PK Assessment:

Pharmacokinetic samples were taken at week 4 (visit 3) predose and 1 (± 30 min), 3 (± 30 min), 5 (-1 h/30 min), and 7 hours (-1 h/+2 h) postdose as well as predose at week 12 (visit 5).

PD Assessment:

Venous blood samples were collected for pharmacodynamic assessments at day 1 (visit 2), week 4 (visit 3), week 8 (visit 4), week 12 (visit 5)/early termination (ET), and at the follow-up visit (week 15 [visit 6]). The Week 4 PD sample was taken at the same time as the 3-hour postdose PK sample.

Subject Disposition:

A total of 356 patients were randomized to treatment (including placebo). Among them, 287 patients (80.6%) completed the study and (19.4%) discontinued treatment. See Table 47 for more details. Discontinuations due to adverse events of ALT or AST increase were observed in 2 patients at 60 mg BID, and 1 patient each at 90 mg BID, 60 mg QD and 120 mg QD.

Table 47. Patient Classification: All Randomized Subjects

		ESN364 BID			
Analysis Set	Placebo (n = 44)	15 mg (n = 45)	30 mg (n = 44)	60 mg (n = 45)	90 mg (n = 44)
Randomized	44 (100.0%)	45 (100.0%)	44 (100.0%)	45 (100.0%)	44 (100.0%)
Safety analysis set†	43 (97.7%)	45 (100.0%)	43 (97.7%)	45 (100.0%)	44 (100.0%)
Full analysis set‡	43 (97.7%)	45 (100.0%)	43 (97.7%)	45 (100.0%)	42 (95.5%)
Per protocol set: week 4§	42 (95.5%)	38 (84.4%)	39 (88.6%)	37 (82.2%)	34 (77.3%)
Per protocol set: week 12¶	37 (84.1%)	37 (82.2%)	36 (81.8%)	29 (64.4%)	30 (68.2%)
Treatment discontinuation	7 (15.9%)	5 (11.1%)	6 (13.6%)	12 (26.7%)	12 (27.3%)

	ESN364 QD			
Analysis Set	30 mg (n = 45)	60 mg (n = 45)	120 mg (n = 44)	Total (n = 356)
Randomized	45 (100.0%)	45 (100.0%)	44 (100.0%)	356 (100.0%)
Safety analysis set†	43 (95.6%)	45 (100.0%)	44 (100.0%)	352 (98.9%)
Full analysis set‡	43 (95.6%)	44 (97.8%)	44 (100.0%)	349 (98.0%)
Per protocol set: week 4§	38 (84.4%)	40 (88.9%)	36 (81.8%)	304 (85.4%)
Per protocol set: week 12¶	31 (68.9%)	36 (80.0%)	34 (77.3%)	270 (75.8%)
Treatment discontinuation	11 (24.4%)	9 (20.0%)	7 (15.9%)	69 (19.4%)

† All randomized patients who received at least 1 dose of study drug.

‡ All randomized patients who received at least 1 dose of study drug and had baseline and postbaseline efficacy evaluation.

§ All randomized patients from the Full Analysis Set who had measurement of the primary efficacy endpoint available at week 4, ≥ 85% interactive diary compliance during the 4-week treatment period and treatment compliance > 85% between randomization and week 4.

¶ All randomized patients from the Full Analysis Set who had measurement of the primary efficacy endpoint available at week 12, ≥ 85% interactive diary compliance during the 12-week treatment period and treatment compliance > 85% between randomization and week 12.

Sources: Table 12.1.1.2, Table 12.1.1.3

Results

Efficacy results:

Primary analysis of change from baseline in frequency and severity of VMS at Week 4 and Week 12 were presented in Table 48 and Table 49.

Table 48. Primary Analysis of Change in the Mean Frequency of Moderate and Severe VMS per 24 h from Baseline to Week 4 and Week 12: Full Analysis Set

Analysis Visit	Treatment Group	n	Change from Baseline	Difference from Placebo		
			LS Mean (SE)	LS Mean (SE)	95% CI	P-value
Week 4	Placebo (n = 43)	42	-4.2 (0.65)	NA	NA	NA
	ESN364 15 mg BID (n = 45)	40	-6.1 (0.61)	-1.9 (0.84)	(-3.56, -0.25)	0.0240 *
	ESN364 30 mg BID (n = 43)	41	-7.2 (0.64)	-3.0 (0.84)	(-4.68, -1.38)	0.0004 *
	ESN364 60 mg BID (n = 45)	40	-7.0 (0.62)	-2.8 (0.84)	(-4.44, -1.14)	0.0010 *
	ESN364 90 mg BID (n = 42)	37	-7.7 (0.65)	-3.5 (0.84)	(-5.20, -1.89)	< 0.0001 *
	ESN364 30 mg QD (n = 43)	40	-6.5 (0.65)	-2.3 (0.84)	(-4.00, -0.68)	0.0058 *
	ESN364 60 mg QD (n = 44)	43	-7.2 (0.61)	-3.0 (0.82)	(-4.65, -1.41)	0.0003 *
	ESN364 120 mg QD (n = 44)	42	-6.6 (0.63)	-2.4 (0.84)	(-4.06, -0.76)	0.0042 *
Week 12	Placebo (n = 43)	37	-5.3 (0.58)	NA	NA	NA
	ESN364 15 mg BID (n = 45)	38	-7.2 (0.54)	-1.8 (0.75)	(-3.30, -0.35)	0.0154 *
	ESN364 30 mg BID (n = 43)	37	-7.5 (0.56)	-2.1 (0.74)	(-3.60, -0.67)	0.0043 *
	ESN364 60 mg BID (n = 45)	31	-7.6 (0.55)	-2.3 (0.75)	(-3.76, -0.83)	0.0023 *
	ESN364 90 mg BID (n = 42)	31	-8.0 (0.58)	-2.6 (0.75)	(-4.09, -1.16)	0.0005 *
	ESN364 30 mg QD (n = 43)	33	-7.4 (0.58)	-2.1 (0.75)	(-3.52, -0.58)	0.0064 *
	ESN364 60 mg QD (n = 44)	36	-7.9 (0.54)	-2.6 (0.74)	(-4.04, -1.15)	0.0005 *
	ESN364 120 mg QD (n = 44)	36	-7.4 (0.57)	-2.1 (0.75)	(-3.52, -0.59)	0.0063 *

Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (Full Analysis Set).

Note: Baseline was the average frequency of 24 h vasomotor symptom from 7 non-missing days prior to day 1. The LS means, standard errors, confidence intervals, and P-values come from an ANCOVA model with change from baseline as the dependent variable and treatment group, pooled center, smoking status as factors and baseline measurement, baseline weight as covariates. For subjects in the efficacy analysis populations with missing primary efficacy endpoints, multiple imputation by fully conditional specification methods were used.

NA: not applicable; VMS: vasomotor symptoms.

* P-values from the model < 0.05.

Source: Table 7 of CSR for Study ESN364-HF-205

Table 49. Primary Analysis of Change in the Mean Severity of Moderate and Severe VMS per 24 h from Baseline to Week 4 and Week 12: Full Analysis Set

Analysis Visit	Treatment Group	n	Change from Baseline	Difference from Placebo		
			LS Mean (SE)	LS Mean (SE)	95% CI	P-value
Week 4	Placebo (n = 43)	42	-0.3 (0.15)	NA	NA	NA
	ESN364 15 mg BID (n = 45)	40	-0.8 (0.14)	-0.5 (0.20)	(-0.84, -0.07)	0.0215 *
	ESN364 30 mg BID (n = 43)	41	-0.9 (0.15)	-0.6 (0.20)	(-1.01, -0.24)	0.0017 *
	ESN364 60 mg BID (n = 45)	40	-1.2 (0.14)	-0.8 (0.20)	(-1.21, -0.44)	< 0.0001 *
	ESN364 90 mg BID (n = 42)	37	-1.3 (0.15)	-1.0 (0.20)	(-1.37, -0.59)	< 0.0001 *
	ESN364 30 mg QD (n = 43)	40	-0.7 (0.15)	-0.4 (0.20)	(-0.81, -0.04)	0.0322 *
	ESN364 60 mg QD (n = 44)	43	-0.9 (0.14)	-0.6 (0.19)	(-0.99, -0.23)	0.0017 *
	ESN364 120 mg QD (n = 44)	42	-1.0 (0.15)	-0.7 (0.20)	(-1.08, -0.31)	0.0004 *
Week 12	Placebo (n = 43)	37	-0.8 (0.16)	NA	NA	NA
	ESN364 15 mg BID (n = 45)	38	-1.0 (0.15)	-0.3 (0.21)	(-0.67, 0.16)	0.2324
	ESN364 30 mg BID (n = 43)	37	-1.1 (0.16)	-0.4 (0.21)	(-0.80, 0.04)	0.0736
	ESN364 60 mg BID (n = 45)	31	-1.3 (0.16)	-0.6 (0.21)	(-0.98, -0.15)	0.0080 *
	ESN364 90 mg BID (n = 42)	31	-1.4 (0.17)	-0.6 (0.21)	(-1.07, -0.22)	0.0028 *
	ESN364 30 mg QD (n = 43)	33	-0.9 (0.16)	-0.2 (0.21)	(-0.58, 0.26)	0.4647
	ESN364 60 mg QD (n = 44)	36	-1.3 (0.15)	-0.5 (0.21)	(-0.92, -0.10)	0.0160 *
	ESN364 120 mg QD (n = 44)	36	-1.1 (0.16)	-0.4 (0.21)	(-0.78, 0.06)	0.0901

Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (Full Analysis Set).

Note: Baseline was the average severity of 24 h vasomotor symptom from 7 non-missing days prior to day 1. The LS means, standard errors, confidence intervals, and P-values come from an ANCOVA model with change from baseline as the dependent variable and treatment group, pooled center, smoking status as factors and baseline measurement, baseline weight as covariates. For subjects in the efficacy analysis populations with missing primary efficacy endpoints, multiple imputation by fully conditional specification methods were used.

VMS: vasomotor symptoms. NA: not applicable.

* P-values from the model < 0.05.

Source: Table 8 of CSR for Study ESN364-HF-205

Reviewer's comments:

- All 4 of co-primary endpoints were significantly different from placebo for the 90 mg BID, 60 mg BID and 60 mg QD dose groups.
- All ESN364 dose groups were significantly different from placebo with respect to mean change in the frequency of moderate to severe VMS at both weeks 4 and 12.
    - The improvement in frequency of moderate to severe VMS relative to placebo at weeks 4 and 12 was greater than 2, indicative of a clinically relevant improvement, for all dose groups except 15 mg BID.
- All groups were significantly different from placebo with respect to mean change in the severity of moderate to severe VMS from baseline to week 4, but only 60 mg BID, 90 mg BID and 60 mg QD demonstrated significance with respect to mean change in severity at week 12.

PK results:

PK data from this Phase 2 study were analyzed, together with data from other studies, in the population PK analysis.

PD results:

- **LH:** LH levels showed a small mean and median decrease from baseline in the placebo group. In the ESN364 groups, there was a mean and median decrease from baseline at all postbaseline time points, particularly at 3 hours postdose at week 4. The decrease appears to be dose-related and persisted through week 12. However, the very low numbers of patients with 3-hour postdose samples at later weeks hinders accurate analysis at weeks 8 and 12 (n = 0, 1, or 2).
- **FSH:** All treatment groups showed a small mean and median decrease from baseline in FSH levels during the treatment period including the placebo group. There was no treatment- or dose-related effects. One patient in the 30 mg BID group had an adverse event of blood FSH decreased.
- **Estradiol (E2):** Patients with an estradiol level below the limit of quantification (73.4 pmol/L), were recorded as having a result at half the limit of quantification. Since a large proportion of patients in all treatment groups had levels recorded as this, the summary statistics are skewed, and the median value was 36.70 pmol/L, for all treatment groups at all post baseline time points. For the mean change from baseline, the interpatient variability was large, and there were no clear trends or differences from placebo.
- **SHBG:** There were no clinically meaningful changes in SHBG levels over the course of the study in any treatment group, and no difference from placebo.

4.4. Physiologically based Pharmacokinetic Modeling and Simulation Review

EXECUTIVE SUMMARY

The objective of this review is to evaluate the adequacy of the Applicant's Physiologically based Pharmacokinetic (PBPK) analysis to predict the DDI liability of fezolinetant as a victim of CYP1A2-mediated interaction by moderate and weak CYP1A2 inhibitors.

The Division of Pharmacometrics has reviewed the PBPK submission (Reports 2693-pk-0005, 2693-pk-0014 and modeling files), and responses to FDA's requests for information (dated 9/2/22 and 10/6/22) to conclude the following:

- The PBPK modeling analysis was considered adequate to predict the effect of moderate and weak CYP1A2 inhibitors on the exposure of 45 mg fezolinetant
    - coadministration of the moderate CYP1A2 inhibitor mexiletine (200 mg three times a day (TID) or 400 mg TID) is expected to increase the Cmax and AUC of fezolinetant 1.4- to 1.6-fold and 3.4- to 4.6- fold, respectively.

- coadministration of the weak CYP1A2 inhibitor cimetidine (400 mg twice daily (BID) or 300 mg four times a day (QID)) is expected to increase the Cmax and AUC of fezolinetant 1.3- to 1.4-fold and 1.6- to 2.0-fold, respectively.

Methods

Model Development

The PBPK analyses were performed using the software Simcyp® version 21 release 1. The PBPK model of fezolinetant was developed based on physicochemical properties, preclinical, and clinical PK data.

The absorption of fezolinetant for the tablet formulation, under fasted and fed state, was described using the Advanced Dissolution, Absorption and Metabolism (ADAM) model. Human jejunum effective permeability (Peff) of fezolinetant was determined by estimating the transcellular passive permeability (Ptrans,0) using the Mechanistic Passive Regional Permeability Predictor (MechPeff) model. A passive permeability value of 101.9 x 10-6 cm/s was estimated using in vitro Caco-2 cells permeability data [2693-ME-0011] and analysis in SIVA 3.

The in vitro Papp values of fezolinetant at 2, 20 and 200 µM were 27, 28 and 29 x 10-6 cm/s for the apical to basal direction [2693-ME-0011]. Those values were approximately twice that of propranolol (Papp= 13.6 x 10-6 cm/s), suggesting that fezolinetant is a highly permeable compound. In the human mass balance study, unchanged fezolinetant accounted for 0.1 % in feces in 0 to 24-hour post-dose sample [ESN364-CPK-103] suggesting high drug absorption. Weibull functions was used to characterize the fasted and fed dissolution profiles of fezolinetant. The in vitro dissolution data were used to mimic the fasted dissolution profile [CTD Module 3.2.P.5.4], while the fed dissolution profile was optimized based on observed clinical data under fed condition [2693-CL-0012 and ESN364-CPK-101]. There were around 20% decrease in Cmax, 30-min delay in Tmax, and no change in AUC with a high-fat, high calorie meal [2693-CL-0012].

The unbound fraction of fezolinetant in plasma (fup) was 0.49, concentration-independent with albumin as main plasma binding protein [2693-ME-0012]. The blood-to-plasma partitioning ratio was set at 0.9. A full PBPK model was used to characterize the disposition of fezolinetant. The Rodgers and Rowland method was used to predict the volume of distribution at steady state (Vss=0.82 L/kg). In vitro data suggested no evidence for active uptake of fezolinetant by the transporters OATP1B, OATP1A2, OATP2B1 and PEPT1; neither efflux by the transporters MRP2 and MRP3 [2693-ME-0008, ESN364-DDI-004, ESN364-DDI-005 and Tebu-03-25Feb2015].

Metabolic profiles of fezolinetant were obtained from in vitro [2693-ME-0009] and in vivo studies [2693-ME-0006, 2693-ME-0015]. In human hepatocytes, fezolinetant was extensively metabolized, primarily to yield a hydroxylated metabolite ES259564 [CYP0720-R1]. In the human mass balance study [ESN364-CPK-103], ES259564 AUC was approximately 2-fold higher than fezolinetant AUC, with only fezolinetant and ES259564 being detected in plasma. The metabolite-to-parent ratio (MPR) ranged from 0.7 to 1.8. ES259564 was considered 20-fold less potent against NK3 receptors than parent with no significant off-target activities.

In vitro, three approaches to reaction phenotyping (assays with recombinant human CYP enzymes, human liver microsomes and chemical inhibitors) implicated CYP1A2 as the primary catalyzing enzyme to the formation of ES259564 from fezolinetant and minor contributions from CYP2C9 and CYP2C19 [2693-ME-0009]. Clinically, co-administration of the strong CYP1A2 inhibitor fluvoxamine (50 mg BID) increased the AUCinf and Cmax of fezolinetant (single 30 mg dose) by 9.4-fold and 1.8-fold, respectively, and decreased the mean MPR from 1.8 to 0.23 [2693-CL-0006].

The contribution of CYP1A2 to fezolinetant clearance was optimized to 92% (metabolic fmCYP1A2=0.9) based on the clinical DDI effect of fluvoxamine in non-smoking women. The intrinsic clearance of CYP1A2 (Clint, CYP1A2) and additional hepatic clearance (HLM Clint) were calculated by retrograde analysis using the apparent clearance (CL/F) value of 14.5 L/h reported in the study 2693-CL-007 (control cohort). The renal clearance of fezolinetant was set to 0.2 L/h, based on the reported value in this study.

Additional comments:

- High variability of CL/F (inter-study and inter-subject within each study) was reported. The CL/F of fezolinetant was estimated to be 10.8 L/h for a typical nonsmoking woman receiving the tablet formulation in the phase 2 and 3 studies, and the inter-subject variability (%CV) of CL/F was estimated to be 46% in postmenopausal female participants with VMS, based on a population PK analysis [2693-PK-0010]. In addition, the reported mean CL/F ranged from 12.4 L/h in premenopausal and menopausal nonsmoking women receiving 45 mg fezolinetant [2693-CL-0010] to 22.9 L/h in the clinical DDI study with fluvoxamine in the control group of healthy postmenopausal nonsmoking women receiving 30 mg fezolinetant [2693-CL-0006]. This CL/F variability was not readily explained by menopausal status, age, or dose (<120 mg), and bioavailability was not expected to be a significant factor (considering fezolinetant solubility and permeability/absorption profile).

Neither fezolinetant or metabolite ES259564 showed significant reversible or time-dependent inhibition towards the CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4, in vitro [CYP0720 R2F]. Weak to null induction liability of fezolinetant and metabolite towards CYP1A2, CYP2B6 and CYP3A4 was reported in vitro [CYP0720 R2F].

Model Application

The PBPK analysis was used to predict the PK of fezolinetant following 45 mg single dose (SD) in the presence of the following CYP1A2 inhibitors:

- Moderate CYP1A2 inhibitor mexiletine (200 mg TID or 400 mg TID)
- Weak CYP1A2 inhibitor cimetidine (300 mg QID or 400 mg BID)

The software's library compound models for fluvoxamine and cimetidine were used in the simulations for the respective DDIs. The Applicant developed a PBPK model for mexiletine. The default PBPK model of cimetidine did not include the parameter of CYP1A2 reversible inhibition constant (Ki).

In response to FDA's request to information (dated 9/2/22), the Applicant provided a verification of the ability of the PBPK analysis to predict CYP1A2-mediated DDI by cimetidine and mexiletine. Database and literature search were conducted for in vitro CYP1A2 IC50/Ki values of cimetidine and mexiletine, and clinical DDI studies (in non-smokers) between cimetidine or mexiletine and CYP1A2 substrates. DDI simulations were conducted for the CYP1A2 substrates caffeine, theophylline (IV and oral), and zolpidem (default software's compound library models) using the reported lowest and highest in vitro IC50/Ki values for each CYP1A2 inhibitor. Simulated results were compared to reported AUC or clearance (CL) change in the presence of the CYP1A2 inhibitors. Several-fold reduction of the in vitro values were required to adequately describe the observed inhibitory DDI effect; thus, in vivo optimized values for CYP1A2 Ki were determined for cimetidine and mexiletine.

Additional comments:

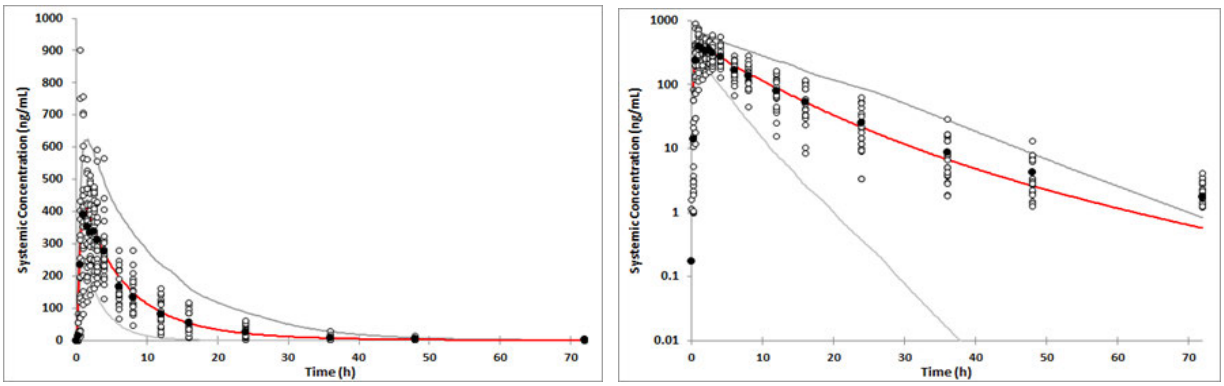
- For cimetidine, all the predicted/observed ratios for the AUC or CL changes with the optimized CYP1A2 Ki value (3.5 µM) fell into a 0.8-1.25 range, except for one clinical study out of 18 studies. For mexiletine, a poor CYP1A2 predictive performance was determined using a 0.8-1.25 range: the predicted/observed ratios fell outside the range in 3 out of 5 studies. Nonetheless, all predicted/observed ratios fell within a 0.5-1.50 range. The Reviewer noted the submitted validation analysis for mexiletine was considered sufficient to assess the effect of a moderate CYP1A2 inhibitor on fezolinetant PK based on magnitude of the estimated DDI effect and regulatory decision for risk management of DDI in the prescribing information (i.e., avoid use with moderate CYP1A2 inhibitor).

Results

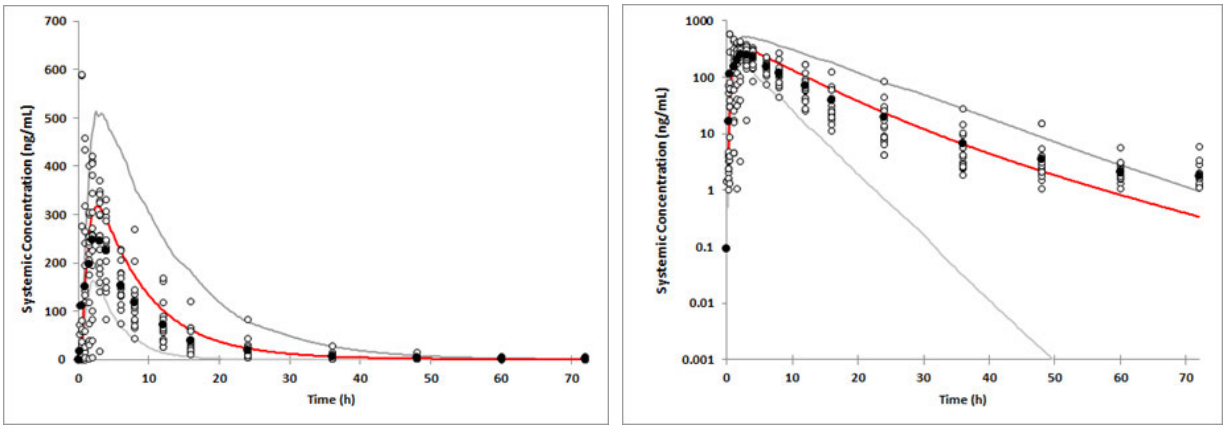
1. Can the PBPK model adequately describe the PK profiles of fezolinetant?

Yes, the PBPK model of fezolinetant described well the observed PK profile in women receiving single and multiple doses of fezolinetant under fasting and fed conditions [Studies ESN364-CPK-101, 2693-CL-0006, -0007, -0008, -0010 and -0012] (Figure 1 and Table 1). The percent prediction errors (%PE) for AUC and Cmax were equal or less than 30% for all clinical studies used in the model validation, except for study 2693-CL-0006 (control cohort). A higher apparent clearance was reported in this study and the reason for this observation could not be identified by the Applicant (refer to Methods section: 'additional comments' for further discussion).

Figure 1. Predicted and observed plasma concentration-time profiles of fezolinetant



Linear (left panel) and log-linear (right panel) PK profiles of 45 mg SD dosing of fezolinetant in fasted women. Individual and mean data from Study 2693-CL-0010 (circles). Solid red line: mean for the predicted population (N = 220, 22 x 10 trials); grey lines: 5th-95th concentration-time percentiles. (Source: Simulation output file "asp2693_t09_pk07.xlxs").



Linear (left panel) and log-linear (right panel) PK profiles of 45 mg SD dosing of fezolinetant in women under fed state. Individual and mean data from Study 2693-CL-0012 (circles). Solid red line: mean for the predicted population (N = 160, 16 x 10 trials); grey lines: 5th-95th concentration-time percentiles. (Source: Simulation output file "asp2693_t09_pk09.xlxs").

Table 1. Predicted and observed PK parameters of fezolinetant following single and multiple doses

Fezolinetant Dosage [Study]	**Cmax (ng/mL)**			**AUC (ng/mL.h)**		
	Obs	**Pred**	**%PE**	**Obs**	**Pred**	**%PE**
20 mg Day 21 [ESN364-CPK-101, fed]	185	163	-12	1130	1470	30
30 mg SD [2693-CL-0006, non-smoker, fasted]	282	329	17	1400	2680	91
30 mg SD [2693-CL-0007, control cohort 1, fasted]	358	294	-18	2300	2440	6

30 mg SD [2693-CL-0007, control cohort 2, fasted]	384	294	-23	2340	2440	4
30 mg SD [2693-CL-0008, control cohort 1, fasted]	270	298	10	2220	2420	9
30 mg SD [2693-CL-0008, control cohort 2, fasted]	260	298	15	2200	2420	10
30 mg SD [2693-CL-0008, control cohort 3, fasted]	286	298	4	2470	2420	-2
45 mg SD [2693-CL-0010, to-be-market formulation]	506	431	-15	3840	3353	-13
45 mg SD [2693-CL-0010, phase 3 formulation]	527	431	-18	3960	3353	-15
45 mg SD [2693-CL-0012, fasted]	453	439	-3	2870	3354	17
45 mg SD [2693-CL-0012, fed]	343	325	-5	2760	3221	17
60 mg Day 21 [ESN364-CPK-101, fed]	423	401	-5	2880	3740	30

PK parameters are mean values. AUC values represent AUCinf for single dose (SD), expect for AUC24h for Day 21 in the Study ESN364-CPK-101. %PE= [(predicted value – observed value)/observed value] x 100. (Source: Applicant's Response to IR dated 10/6/22, Table 1).

Q2. Can PBPK analyses predict the effect of a CYP1A2 inhibitor on the PK of fezolinetant?

Yes, the PBPK analysis was considered adequate to estimate the DDI liability of fezolinetant as a victim of CYP1A2 inhibition.

The model adequately predicted the interaction effect of the strong CYP1A2 inhibitor fluvoxamine (50 mg BID) on the PK of fezolinetant (30 mg SD) in nonsmoking women [2693-CL-0006]. The predicted geometric mean ratios of Cmax and AUCinf were within 10% of the observed values (Table 2). These results suggest that fezolinetant PBPK model provided a reasonable estimate of the metabolic contribution of CYP1A2 (fmCYP1A2=0.92) to fezolinetant clearance at single dose in vivo.

Table 2. Predicted and observed Cmax and AUC changes of fezolinetant in the presence of the strong CYP1A2 inhibitor fluvoxamine

DDI Scenario	Cmax ratio (90%CI)		AUCinf ratio (90%CI)	
	Observed	Predicted	Observed	Predicted
fezolinetant 30 mg SD + fluvoxamine 50 mg BID	1.63 (1.38 - 1.94)	1.48 (1.44 - 1.53)	8.89 (6.91 - 11.4)	8.57 (8.13 – 9.42)

PK data are geometric mean ratios. Cmax and AUC ratios are expressed as with/without inhibitor. Observed: Study 2693-CL-0006. (Source: Applicant's Response to IR dated 10/6/22, Table 2).

The model was used to predict the interaction effect of moderate and weak CYP1A2 inhibitors on fezolinetant 45 mg SD, under both fasted and fed conditions. The predicted geometric mean ratios of Cmax and AUC of fezolinetant in the presence of mexiletine (moderate CYP1A2 inhibitor) or cimetidine (weak CYP1A2 inhibitor) are summarized in Table 3.

Table 3. PBPK predicted Cmax and AUC ratios for fezolinetant in the presence of CYP1A2 inhibitors

CYP1A2 Inhibitor	Fezolinetant (45 mg SD) PK in the presence of CYP1A2 inhibitors

Dosing Regimen	Cmax Ratio (90% CI)	AUCinf Ratio (90% CI)
Mexiletine 400 mg TID – fasted	1.41 (1.38, 1.45)	4.61 (4.39, 4.84)
Mexiletine 400 mg TID – fed	1.59 (1.54, 1.64)	4.55 (4.33, 4.78)
Mexiletine 200 mg TID – fasted	1.36 (1.33, 1.39)	3.43 (3.27, 3.59)
Mexiletine 200 mg TID – fed	1.50 (1.47, 1.54)	3.38 (3.24, 3.54)
Cimetidine 300 mg QID - fasted	1.30 (1.27, 1.32)	2.01 (1.96, 2.05)
Cimetidine 300 mg QID - fed	1.33 (1.30, 1.35)	1.91 (1.87, 1.95)
Cimetidine 400 mg BID – fasted	1.32 (1.29, 1.35)	1.75 (1.71, 1.79)
Cimetidine 400 mg BID - fed	1.36 (1.33, 1.39)	1.61 (1.58, 1.64)

PK data are geometric mean ratios and 90% confidence interval. Cmax and AUC ratios are expressed as with/without inhibitor. Simulations were conducted using the population model "Sim-Healthy Volunteers", with weight distribution adjusted to give mean weight = 74 kg. N=10 x 10 trials, proportion of females=1, age range 40-65 years. Abbreviations: BID: twice daily; TID: three times a day; QID: four times a day (Source: Applicant's Response to IR dated 10/6/22, Table 11).

Additional comments:

- The Applicant demonstrated that the predicted magnitude of DDI did not change significantly with multiple-dose administration of fezolinetant in the presence of an inhibitor compared to the predicted DDI of single dose administration of fezolinetant. These results are in line with the short half-life and minimal accumulation of fezolinetant.
- In vitro assays [2693-ME-0009] determined that fezolinetant is primarily metabolized by CYP1A2, with minor contributions of CYP2C9 and CYP2C19. The clinical interaction effect of the strong CYP1A2 inhibitor fluvoxamine [2693-CL-0006] was used to optimize the percentage contribution of CYP1A2 to fezolinetant metabolism in vivo. However, the Applicant acknowledged that fluvoxamine is an inhibitor of several CYP isoforms, including the ones determined to be involved in fezolinetant metabolism in vitro (CYP1A2, CYP2C9 and CYP2C19). Thus, by assigning the magnitude of the effect of fluvoxamine being only mediated by CYP1A2 inhibition, the current PBPK analysis seemed to represent the maximal effect of CYP1A2 inhibition on the clearance of fezolinetant. The DDI predictions with the CYP1A2 inhibitors should be interpreted with caution.

Conclusions

The PBPK modeling analysis was used to predict the effect of moderate and weak CYP1A2 inhibitors on the PK of fezolinetant and serve as the regulatory basis for recommendations for management of DDI risk in the prescribing information.

The PBPK modeling analysis was considered adequate to predict the effect of moderate and weak CYP1A2 inhibitors on the exposure of 45 mg fezolinetant:

- coadministration of the moderate CYP1A2 inhibitor mexiletine (200 mg TID or 400 mg TID) is expected to increase the Cmax and AUC of fezolinetant 1.4- to 1.6-fold and 3.4- to 4.6-fold, respectively.
- coadministration of the weak CYP1A2 inhibitor cimetidine (400 mg BID or 300 mg QID) is expected to increase the Cmax and AUC of fezolinetant 1.3- to 1.4-fold and 1.6- to 2.0-fold, respectively.

4.5 Pharmacometrics Review

Population PK Analysis

Executive Summary

The FDA's Assessment: In general, the applicant's population PK and exposure response analyses on efficacy and safety are considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

The Applicant's Position:

General Information	
Objectives of PPK Analysis	Characterize the fezolinetant concentration-time profile in healthy women, postmenopausal women with vasomotor symptoms (VMS), women with polycystic ovarian syndrome (PCOS), and women with uterine fibroids (UF); assess the impact of pre-defined covariate effects on fezolinetant PK parameters; and generate individual predicted PK parameters and/or exposure predictions for subsequent exposure-response analyses.
Studies Included	14 clinical studies including eight phase 1, four phase 2, and two phase 3 studies were used to develop the population pharmacokinetic model. **Phase I studies** included single and multiple ascending dose studies in healthy non-Asian subjects (ESN364-CPK-101 and ESN364-CPK-102) as well as healthy subjects from China (2693-CL-0030) and Japan (2693-CL-0020). In addition, a drug-drug interaction study evaluating the impact of a strong CYP1A2 inhibitor and smoking status on fezolinetant pharmacokinetics

		(2693-CL-0006) was also included. Finally, studies assessing formulation differences between hard gelatin capsules and between phase 3 tablets (2693-CL-0009) and the to-be-marketed tablet and the phase 3 tablet formulations (2693-CL-0010) as well as a food effect study (2693-CL-0012) assessing the impact of a high-fat breakfast on fezolinetant pharmacokinetics were also included. **Phase 2 studies** included three proof-of-concept studies in women with VMSv (ESN364_HF_204), polycystic ovarian syndrome (ESN364-PCO-201), or uterine fibroids (ESN364-UF-02) as well as a dose ranging study in women with VMS related to menopause (ESN364_HF_205). **Phase 3 studies** (2693-CL-0301 and 2693-CL-0302) included pharmacokinetic data from postmenopausal women with VMS.
Dose(s) Included		Doses from 3 to 900 mg (single dose) and 20 to 720 mg qd (multiple dose); dose proportional from 20 to 60 mg qd.
Population Included		Healthy volunteers, participants with Uterine Fibroids, participants with Polycystic Ovarian Syndrome; and participants with VMS (female only, n=1488)
Population Characteristics (Applicant - Table 8)	General	Age: median 54 yr (range: 19-65) Weight: median 73.0 kg (range: 42.0-126.0) Sex: 1488 (100%) female Race: 1152 (77%) White, 272 (18%) Black, 42 (3%) Asian, 22 (2%) Other
	Organ Impairment	Dedicated Hepatic Impairment study (0007) was not included in the PopPK analyses. Dedicated Renal Impairment study (0008) was not included in the PopPK analyses. Note that there is an error in classifying

		patients into normal and mild renal impairment categories as shown in Table 8. The regular cutoff in eGFR of 90 ml/min between normal and mild renal impairment was not used.
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and below level of quantitation (BLQ)		No. of patients: 1488 No. of PK samples measurable: 11577 N (%) BLQ: 1480 (11.3%)
Sampling Schedule	Rich or Sparse Sampling	Extensive PK sampling designs (i.e., phase 1) and those with sparse designs (i.e., phase 2 and phase 3) (See Table 1 in the popPK report).
	In ITT Population	NA
Covariates Evaluated		Covariates of interest were added simultaneously in order to evaluate a full model. Covariates were pre-specified in accordance with ICH guidelines and selected based on clinical utility and mechanistic plausibility. Body weight: CL/F, Vc/F Age: ka, CL/F, Vc/F Race: CL/F, Vc/F Creatinine clearance: CL/F Study Phases: CL/F Formulation: ka, F Pre-menopause: CL/F, Vc/F Food: ka The intended to be evaluated covariates:

		Caffeine: CL/F CYP1A2 Clinical Inhibitors: CL/F CYP2C9 Clinical Inhibitors: CL/F CYP2C19 Clinical Inhibitors: CL/F Concomitant CYP1A2 inhibitors and CYP2C9 inhibitors were not evaluated because only a small number of subjects received one of these medications. In addition, baseline caffeine intake was not evaluated because this information was not collected in several studies. Finally, the investigation of the impact of CYP2C19 inhibitors was not evaluated in the full model, but rather following backward elimination since there is generally more uncertainty in the quality of data from concomitant medications compared to standard demographic variables. Current smoking status was included in the base model as a pre-specified structural covariate.
	Time-varying	*NA*

Final Model	**Summary**	**Acceptability** **[FDA's comments]**
Software and Version	NONMEM® (version 7.4)	Acceptable
Model Structure	A two-compartment model with Erlang distribution transit compartment (n=6) absorption and first-order elimination adequately characterized the fezolinetant concentration-time data.	Acceptable
Model Parameter Estimates	Applicant - Table 14	Acceptable

Uncertainty and Variability (Relative Standard Error [RSE], IIV, Shrinkage, Bootstrap)	Parameters were generally estimated with good precision (RSE <20%) except for ABW on $V2_{ADC}$, and AST on METDM4. (Applicant - Table 9 and 11)	
BLQ for Parameter Accuracy	The impact of concentrations below the limit of quantitation on fezolinetant PK parameters was also assessed during base model development. Attempts to incorporate the left censored BLQ measurements using the M3 method were unsuccessful; however, models utilizing the M2 method with the YLO option indicated similar estimates for key parameters, overall, with larger estimates of residual variability. As such, advanced methods to handle BLQ data were not explored further and data below the LLOQ was excluded from the analysis.	Acceptable
Goodness of Fit (GOF), Visual Predictive check (VPC)	Applicant-Best Model Goodness-of-Fit Plots and Figure 11-18 for VPC	Acceptable
Significant Covariates and Clinical Relevance	Applicant - Figure 9 and 10	Acceptable
Analysis Based on Simulation (optional)		
Labeling Language	**Description**	**Acceptability** **[FDA's comments]**
12.3 PK	Distribution	Acceptable with minor changes.

	The mean apparent volume of distribution (Vz/F) of fezolinetant is 189 L. <u>Elimination</u> The apparent clearance at steady-state of fezolinetant is 10.8 L/h. (b) (4) <u>Specific Populations</u> (b) (4)	

Applicant - Table 8: Summary of Key Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study

Covariate	Study														
	2	6	9	10	12	20	30	101	102	201	204	205	301	302	Total
Age (years)															
N	16	18	16	22	16	12	16	18	28	41	41	286	483	475	1,488
N Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean(SD)	41.8 (7.6)	54.5 (5.0)	55.6 (5.7)	52.1 (10.7)	33.6 (8.0)	42.9 (14.8)	33.1 (5.8)	33.8 (8.2)	37.5 (9.5)	26.7 (4.3)	53.3 (4.0)	54.5 (4.5)	54.4 (5.0)	54.3 (5.0)	52.3 (8.3)
Median (Min,Max)	43.0 (29.0, 52.0)	55.0 (45.0, 64.0)	55.5 (46.0, 64.0)	55.0 (24.0, 64.0)	32.0 (22.0, 46.0)	44.0 (23.0, 62.0)	33.0 (25.0, 43.0)	36.0 (20.0, 45.0)	35.5 (22.0, 53.0)	27.0 (19.0, 41.0)	54.0 (44.0, 60.0)	54.5 (41.0, 65.0)	54.0 (40.0, 65.0)	54.0 (40.0, 65.0)	54.0 (19.0, 65.0)
Body Weight (kg)															
N	16	18	16	22	16	12	16	18	28	41	41	286	483	475	1,488
N Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean(SD)	69.3 (12.0)	65.5 (8.9)	68.2 (10.0)	71.6 (11.9)	70.9 (12.8)	53.8 (6.6)	53.9 (4.4)	66.8 (13.2)	67.3 (8.4)	80.7 (19.1)	69.7 (13.1)	75.7 (12.9)	75.1 (13.2)	75.0 (13.7)	74.2 (13.7)
Median (Min,Max)	70.0 (51.0, 103.0)	64.7 (54.4, 92.6)	66.8 (52.2, 81.4)	68.6 (55.9, 100.3)	67.7 (54.8, 97.2)	51.6 (44.8, 67.8)	52.6 (47.5, 62.8)	64.7 (53.4, 99.6)	66.2 (55.3, 88.2)	77.0 (52.3, 126.0)	67.0 (49.0, 117.0)	74.5 (45.5, 117.7)	74.2 (42.0, 121.2)	73.1 (45.0, 125.0)	73.0 (42.0, 126.0)
Height (cm)															
N	16	18	16	22	16	12	16	18	28	41	41	286	482	475	1,487
N Missing	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Mean(SD)	165.2 (5.4)	167.2 (8.7)	163.8 (5.5)	164.9 (6.8)	164.8 (4.1)	157.7 (5.1)	157.7 (5.0)	166.5 (8.0)	167.1 (4.7)	168.9 (6.6)	165.9 (5.3)	163.0 (7.0)	162.8 (6.5)	163.3 (6.5)	163.4 (6.7)
Median (Min,Max)	165.5 (151.0, 174.0)	166.5 (154.0, 189.0)	164.5 (150.0, 175.0)	163.5 (154.0, 181.0)	165.0 (156.0, 171.0)	158.2 (149.0, 167.0)	157.7 (147.8, 167.0)	164.7 (155.5, 179.2)	167.5 (158.1, 178.0)	170.0 (157.0, 186.0)	165.0 (152.0, 176.0)	163.0 (145.0, 204.0)	162.6 (144.8, 180.3)	163.0 (142.2, 182.0)	163.0 (142.2, 204.0)
Body Mass Index (kg/m2)															
N	16	18	16	22	16	12	16	18	28	41	41	286	482	475	1,487
N Missing	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Mean(SD)	25.4 (3.7)	23.4 (2.2)	25.5 (3.9)	26.4 (3.3)	26.1 (4.3)	21.7 (2.8)	21.7 (1.6)	24.0 (3.8)	24.1 (2.5)	28.3 (6.6)	25.3 (4.8)	28.5 (4.4)	28.3 (4.5)	28.1 (4.7)	27.7 (4.7)
Median (Min,Max)	24.7 (19.2, 34.0)	23.4 (18.6, 27.5)	25.6 (19.2, 30.6)	26.8 (19.6, 32.6)	25.1 (19.2, 33.0)	21.2 (17.6, 26.3)	21.7 (19.1, 24.1)	22.3 (20.4, 35.1)	23.5 (20.2, 29.0)	26.7 (20.5, 43.6)	23.9 (19.1, 43.2)	28.2 (18.6, 38.7)	28.0 (18.0, 37.9)	27.6 (18.0, 38.0)	27.4 (17.6, 43.6)
Creatinine Clearance (mL/min)															
N	16	18	16	22	16	12	16	18	28	41	41	286	483	475	1,488
N Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table continued on next page

Covariate	Study														
	2	6	9	10	12	20	30	101	102	201	204	205	301	302	Total
Mean(SD)	107.3 (25.6)	94.8 (10.6)	88.2 (13.4)	107.3 (23.9)	134.0 (24.6)	106.9 (29.7)	108.7 (14.4)	121.7 (24.7)	122.0 (27.2)	146.9 (43.5)	98.8 (21.6)	106.1 (23.3)	100.6 (24.3)	102.2 (25.4)	104.5 (26.4)
Median(Min, Max)	108.5 (65.9, 151.3)	95.2 (76.3, 117.6)	90.8 (61.0, 102.9)	105.2 (72.7, 187.6)	135.1 (98.3, 179.7)	103.7 (72.9, 151.4)	108.9 (83.7, 135.9)	115.7 (83.5, 196.0)	118.9 (83.4, 186.0)	140.9 (68.3, 274.2)	97.2 (54.5, 150.0)	105.6 (55.3, 181.0)	97.7 (49.0, 174.9)	99.1 (50.5, 211.1)	101.1 (49.0, 274.2)
Sex, n (%)															
Female	16 (100%)	18 (100%)	16 (100%)	22 (100%)	16 (100%)	12 (100%)	16 (100%)	18 (100%)	28 (100%)	41 (100%)	41 (100%)	286 (100%)	483 (100%)	475 (100%)	1,488 (100%)
Menopause Status, n (%)															
Pre-menopause	16 (100%)	0 (0%)	0 (0%)	4 (18%)	16 (100%)	6 (50%)	16 (100%)	18 (100%)	27 (96%)	41 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	144 (10%)
Post-menopause	0 (0%)	18 (100%)	16 (100%)	18 (82%)	0 (0%)	6 (50%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	41 (100%)	286 (100%)	483 (100%)	475 (100%)	1,344 (90%)
Race, n (%)															
White	9 (56%)	18 (100%)	8 (50%)	11 (50%)	4 (25%)	0 (0%)	0 (0%)	15 (83%)	27 (96%)	28 (68%)	41 (100%)	213 (74%)	399 (83%)	379 (80%)	1,152 (77%)
Black	5 (31%)	0 (0%)	8 (50%)	11 (50%)	11 (69%)	0 (0%)	0 (0%)	2 (11%)	1 (4%)	1 (2%)	0 (0%)	68 (24%)	71 (15%)	94 (20%)	272 (18%)
Asian	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (100%)	16 (100%)	1 (6%)	0 (0%)	1 (2%)	0 (0%)	1 (0%)	9 (2%)	1 (0%)	42 (3%)
American Indian Alaskan Native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (0%)	3 (1%)	1 (0%)	6 (0%)
Native Hawaiian Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)	4 (0%)
Unknown	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (24%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (1%)
Smoking Status, n (%)															
Non-smoker	9 (56%)	9 (50%)	16 (100%)	22 (100%)	16 (100%)	7 (58%)	15 (94%)	18 (100%)	28 (100%)	0 (0%)	0 (0%)	187 (65%)	340 (70%)	302 (64%)	969 (65%)
Past Smoker	5 (31%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	57 (20%)	84 (17%)	81 (17%)	229 (15%)
Current Smoker	2 (12%)	9 (50%)	0 (0%)	0 (0%)	0 (0%)	4 (33%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	42 (15%)	59 (12%)	92 (19%)	208 (14%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	41 (100%)	41 (100%)	0 (0%)	0 (0%)	0 (0%)	82 (6%)

Table continued on next page

Covariate	Study														
	2	6	9	10	12	20	30	101	102	201	204	205	301	302	Total
Renal Function Category, n (%)															
Normal	11 (69%)	12 (67%)	9 (56%)	17 (77%)	16 (100%)	7 (58%)	14 (88%)	17 (94%)	26 (93%)	38 (93%)	27 (66%)	210 (73%)	302 (63%)	306 (64%)	1,012 (68%)
Mild	5 (31%)	6 (33%)	7 (44%)	5 (23%)	0 (0%)	5 (42%)	2 (12%)	1 (6%)	2 (7%)	3 (7%)	13 (32%)	74 (26%)	170 (35%)	164 (35%)	457 (31%)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	2 (1%)	11 (2%)	5 (1%)	19 (1%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ESRD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Study Number Index: 2=ESN364-UF-02, 6=2693-CL-0006, 9=2693-CL-0009, 10=2693-CL-0010, 12=2693-CL-0012, 20=2693-CL-0020, 30=2693-CL-0030, 101=ESN364-CPK-101,

102=ESN364-CPK-102, 201=ESN364-PCO-201, 204=ESN364_HF_204, 205=ESN364_HF_205, 301=2693-CL-0301, 302=2693-CL-0302

SD = standard deviation, Min = minimum, Max = maximum

Creatinine clearance was calculated using the Cockroft-Gault equation.

Source: MSTask14_Blind/script/report-2693-pk-0010-data-summary-section5.1.html

Source provided in the Population PK report.

Applicant - Table 14: Parameter Estimates for the Best Model in Derived Analysis Dataset 3

Parameter [a]	Notation	Estimate (%SEM)
Fixed Effects		
ktr – Known Meal Status [log 1/hr]	θ1	2.698 [2.9]
CL [log L/hr]	θ2	2.382 [0.7]
Vc [log L]	θ3	4.562 [0.3]
Q [log L/hr]	θ4	0.853 [4.0]
Vp [log L]	θ5	4.540 [4.1]
[redacted]		(b) (4)
Current Smoker on CL [log fraction]	θ12	0.414 [9.6]
Unknown Smoking Status on CL [log fraction]	θ13	0.077 [74.1]
Change in CL at Time=0 for Study 2693-CL-0020 [log fraction]	θ14	0.345 [7.5]
Half-Life for Rate of Decline of CL for 2693-CL-0020 [log hr]	θ15	4.960 FIX
Meal Status = Fed on ktr [log fraction]	θ16	-1.071 [5.3]
ktr - Unknown Meal Status [log 1/hr]	θ17	3.194 [4.0]
Body Weight on Vc [power]	θ25	0.938 [5.1]
Race = Black on Vc [log fraction]	θ26	0.094 [24.2]
Study 2693-CL-0006 on CL [log fraction]	θ30	0.486 [24.8]
Phase 1 studies on CL [log fraction]	θ31	0.166 [27.2]
Box-Cox Parameter	θ32	-0.347 [14.8]
Dose on ktr [power]	θ33	-0.150 [29.3]
Interindividual Variability		
IIV ktr – Meal Status Known	2	0.238 [17.3]

	ω1	
IIV CL	2 ω2	0.213 [4.5]
IIV Vc	2 ω4	0.023 [15.5]
IIV Vp	2 ω5	3.654 [15.8]
IIV ktr – Meal Status=Unknown	2 ω6	1.077 [13.1]
Residual Variability		
RV Phase 1/2 - Proportional [sd]	θ6	0.383 [1.8]
RV Phase 1/2 - Proportional – Time > 3.5 hr [sd]	θ7	0.253 [1.4]
RV Phase 3 - Proportional [sd]	θ8	0.396 [1.9]
RV Phase 3 - Proportional – Time > 3.5 hr [sd]	θ9	0.557 [1.8]

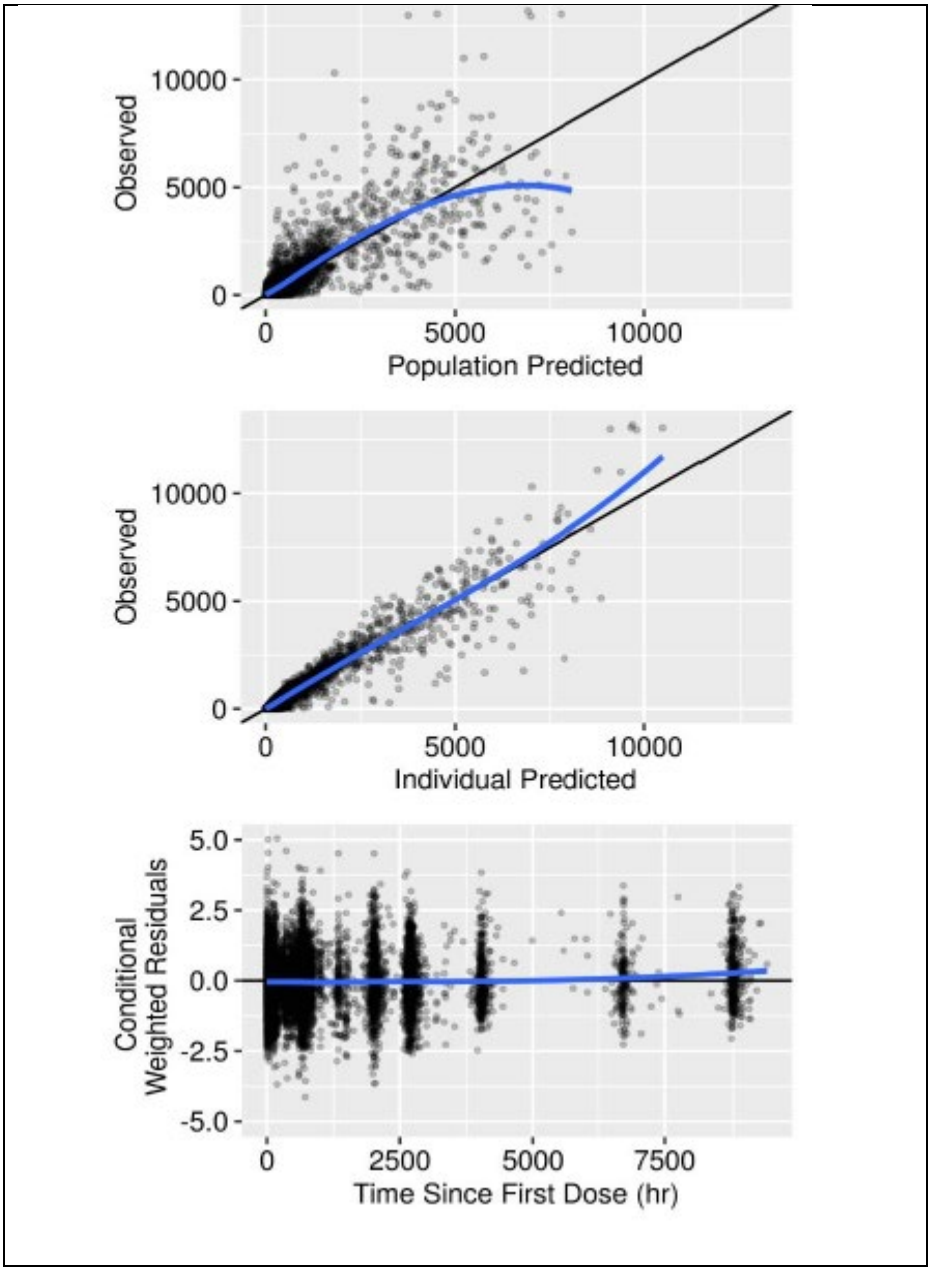
a Parameters represent typical values in which the reference individual is a white, non-smoker with a body weight of 70 kg receiving 90 mg of the tablet formulation in the fasted state in the phase 2 or phase 3 studies

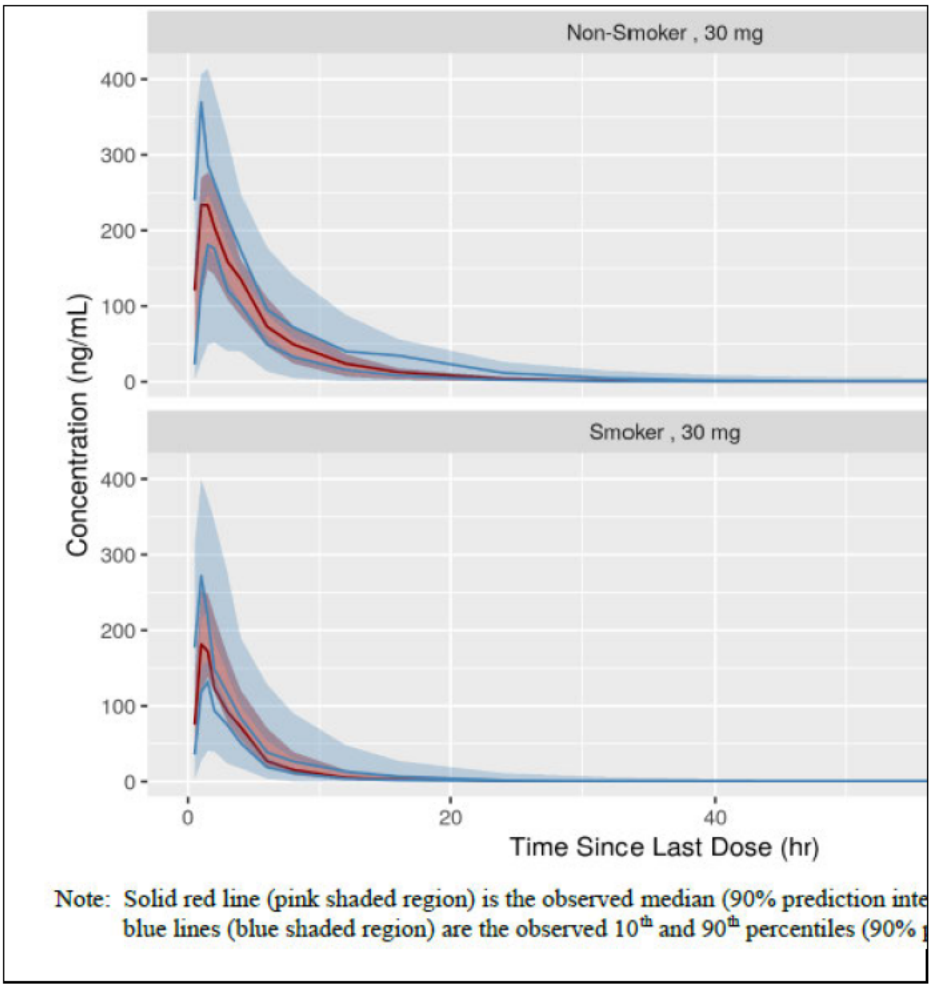
Source: MSTask14_Blind/deliv/table/parms-best-model-full3035-dad3.csv

Code: MSTask14_Blind/script/report-2693-PK-0010-best-model-parameter-summary.Rmd

Source provided in the Population PK report.

Applicant – Adapted from Best Model Goodness-of-Fit Plots (Section 9, PopPK report) and from Figure 11 (study 2693-CL-0006)





Note: Solid red line (pink shaded region) is the observed median (90% prediction inte
blue lines (blue shaded region) are the observed 10th and 90th percentiles (90% p

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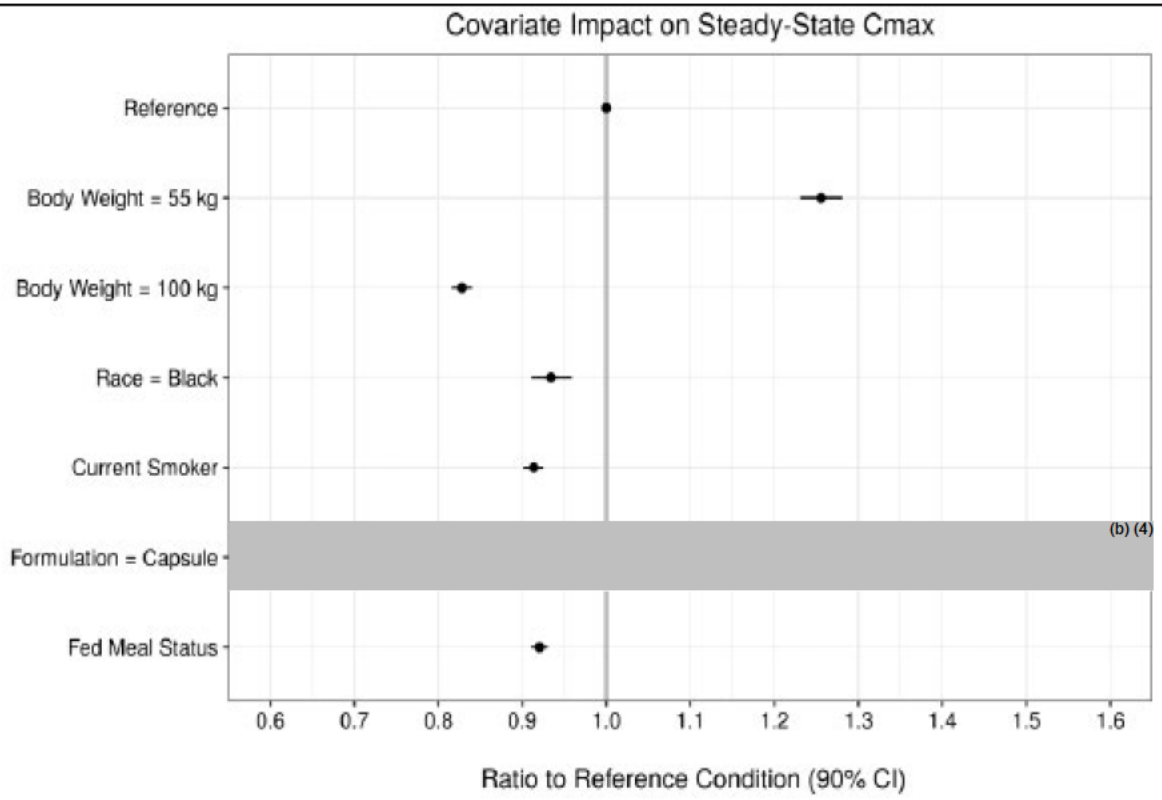
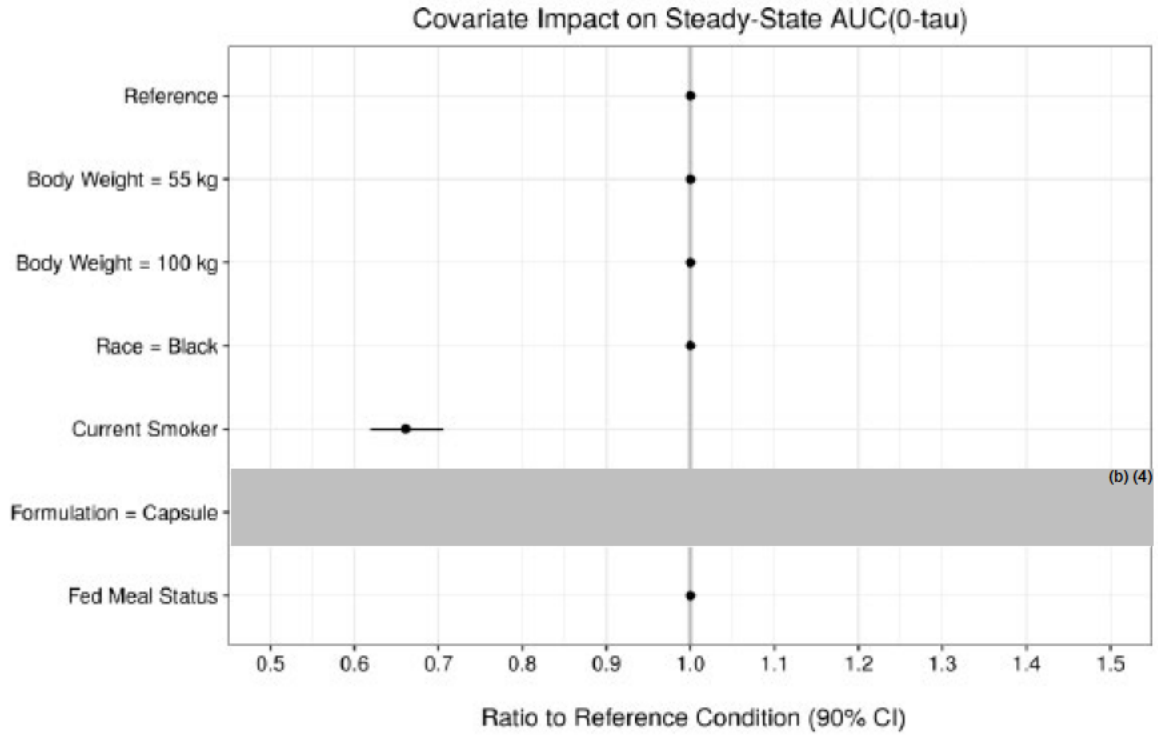
Source provided in the Population PK report.

Applicant – Figure 9 and 10: Impact of Significant Covariates on Exposure (Cmaxss and AUC(0-tau)ss)



Reference Subject: white, non-smoker with a body weight of 75 kg administered 45 mg once daily doses of the tablet formulation in the fasted state.



Reference Subject: white, non-smoker with a body weight of 75 kg administered 45 mg once daily doses of the tablet formulation in the fasted state.

The FDA's Assessment:

The applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives.

PPK Review Issues

There are no PPK review issues.

Reviewer's Independent Analysis

The applicant's analyses were verified by the reviewer, with no significant discordance identified. We further verified the steady-state AUCs of fezolinetant in participants with normal, mild, and moderate renal impairment from the phase 3 studies (2693-CL-0301 and 2693-CL-0302) predicted based on the population PK analysis. We noticed that the cutoff value between normal and mild was set as 80 instead of 90 ml/min with respect to eGFR. After correcting the error, the total exposure of fezolinetant in participants with mild or moderate renal impairment was similar to the exposures in participants with normal renal function, as shown in [Sponsor Table 5 in the IR response dated 9/29/2022] and [Sponsor Figure 1 in the IR response dated 9/29/2022].

Sponsor Table 5: Predicted AUC (Mean, Range) for Participants Based on Renal Function in Phase 3 Studies (PopPK Analysis)

DOSE (mg)	RENCAT	N	MEAN_AUC (ng.h/mL)	MEDIAN_AUC (ng.h/mL)	SD_AUC (ng.h/mL)	MIN_AUC (ng.h/mL)	MAX_AUC (ng.h/mL)	CV_AUC
30	Normal	201	2803	2690	1360.9	802	9276	48.6
30	Mild	267	2594	2397	1232.8	774	10904	47.5
30	Moderate	7	2393	2096	942.9	1234	4298	39.4
45	Normal	199	4159	3930	1886.6	1269	11325	45.4
45	Mild	275	4097	3863	1712.3	1348	12689	41.8
45	Moderate	9	4061	3402	1487	2516	7308	36.6

AUCss: AUC0-24 at steady state; CV: coefficient of variation; N: number of participants; PopPK: population pharmacokinetics.

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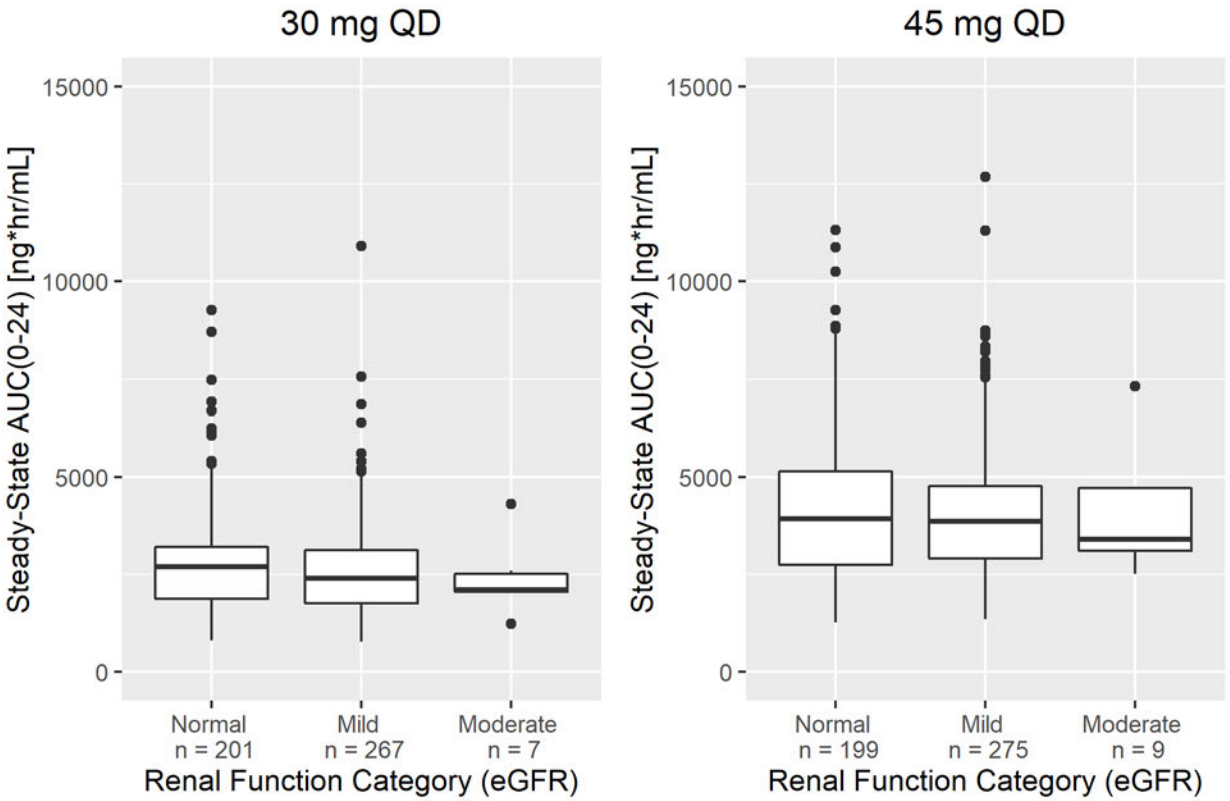
Sponsor Figure 1: The Distribution of Fezolinetant AUC at 30 mg and 45 mg in Postmenopausal Women with VMS and in Female Participants with Mild and Moderate Renal Impairment.



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Exposure-Response Analysis

ER (efficacy) Executive Summary

The FDA's Assessment:

The applicant's exposure response analyses on efficacy are considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

ER (efficacy) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	Characterize the relationship between fezolinetant exposure and both the frequency and severity of hot flashes in postmenopausal women; and Assess the impact of covariate effects on the frequency and severity of hot flashes, as well as the impact they may have on the relationship between fezolinetant exposure and hot flashes.
Study Included	Phase 3 studies 2693-CL-0301 and 2693-CL-0302
Endpoints	Primary: hot flash frequency Secondary: hot flash severity
No. of Patients (total, and with individual PK)	A total of 83284 daily hot flash diary records from 342 placebo subjects and 639 fezolinetant treated subjects, with at least one measurable pharmacokinetic (PK) concentration, were included in the analysis. Subjects were postmenopausal females ranging from 40-65 years of age. Subjects were predominantly Caucasian, non-smokers. Seventeen percent of subjects were African American and 16% of subjects were current smokers. Per our IR request dated 10/18/2022, participants receiving concomitant treatment with the anti-viral drug,

		acyclovir, were inadvertently excluded from the data set due to a mismatch in the searched term, “ACYCLOVIR”, and the standardized medication name, “ACICLOVIR”.	
Population Characteristics (Applicant - Table 1)	General	Age: median 54.0 yr (min, max: 40.0, 65.0) Body Mass Index: median 27.8 (min, max: 18.0, 38.0) Sex: 1022 (100%) female Race: 828 (81%) White, 174 (17%) Black, 4 (0.4%) American Indian, 10 (1%) Asian, 6 (0.6%) Other	
	Pediatrics (if any)	Not applicable	
Dose(s) Included		30 mg QD and 45 mg QD	
Exposure Metrics Explored (range)		Individual predicted steady-state AUC(0-τ) was selected to drive exposure-response relationships instead of integrating fezolinetant concentration in each count interval.	
Covariates Evaluated		• Continuous Covariates: Age, Body mass index, Baseline average hot flash frequency, Time since onset of hot flashes (in months), Time since onset of amenorrhea (in months). • Categorical Covariates: Oophorectomy status, Race (Non-black vs. black), Smoking status (Non-smokers, Smokers)	
Final Model Parameters		**Summary**	
Model Structure		<u>Frequency endpoints</u>: Non-linear mixed effect frequency model (Poisson distribution model): $$P(Y_{ij} = N) = \frac{\lambda_{ij}{}^{N}}{N!} \cdot e^{-\lambda_{ij}}$$ where λ_{ij} is an estimated function, containing fixed and random effects, and represents the expected number of hot flashes within a particular time interval.	Acceptable

	The two frequency models and the severity model each included separate components for baseline, placebo effects (i.e., non-drug effects), and fezolinetant drug effects. A temporal delay was estimated between fezolinetant exposure and maximum effects on hot flash frequency and severity. This delay was quantitated using a simple exponential model whereby the effective AUC (EAUC) increases over time until the steady-state AUC(0-τ) is achieved. $$EAUC_{ij} = \begin{cases} 0 & if\ t_{ij} \le 0 \\ AUC_{SS}(0-\tau)_i \cdot \left(1 - \exp\left(-exp\left(\theta_{ke0}\right) \cdot t_{ij}\right)\right) & if\ t_{ij} > 0 \end{cases}$$ t_{ij} represents time in days relative to the first day of active treatment for the ith subject on the jth day, $AUCss(0-\tau)_i$ is the individual predicted steady-state AUC in the ith subject, and $EAUC_{ij}$ is the effective AUC in the ith subject on the $_j$th day. <u>Severity endpoints</u>: Multinomial model The total number of hot flashes into the number of mild, moderate, and severe hot flashes in each 24-hour interval for prediction of the hot flash severity endpoint.	
Model Parameter Estimates	Applicant - Table 8, and 12	Acceptable
Model Evaluation	Applicant - Figure 12,13,14, 21, 22,23, 24 and 25	
Covariates and Clinical Relevance	No intrinsic or extrinsic covariates which included age, BMI, race, smoking status,	.

	time since onset of hot flashes, time since amenorrhea, and oophorectomy status were identified as important predictors of hot flash frequency or severity.	
Simulation at different dose levels	The mean (90% confidence interval) placebo-corrected change from baseline reduction in moderate and severe hot flash frequency at week 12 was predicted to be -2.01 (-2.70, -1.40) and -2.38 (-3.04, -1.65) for the 30 mg and 45 mg treatment groups, respectively. The mean (90% confidence interval) placebo-corrected change from baseline in hot flash severity at week 12 was predicted to be -0.24 (-0.27, -0.20) and -0.27 (-0.31, -0.24) for the 30 mg and 45 mg treatment groups using Observed Total Hot Flash Frequency, respectively.	Acceptable
Visualization of E-R relationships	Applicant - Figure 11, 19 and 20	Acceptable
Overall Clinical Relevance for ER	Fezolinetant exposure was predictive of both the frequency and severity of hot flashes. Increasing fezolinetant exposure decreased hot flash frequency and reduced the proportion of hot flashes that were severe.	Acceptable
Labeling Language	**Description**	**Acceptability** **[FDA's comments]**
	NA	NA

Applicant - Table 50: Summary of Baseline Characteristics

	IMGN853-0401	IMGN853-0403	IMGN853-0417	All
	(N = 203)	(N = 242)	(N = 97)	(N = 542)
Age (yr)				
Mean (SD)	62.0 (8.8)	62.8 (10)	61.9 (9.5)	62.4 (9.6)
Median (range)	62.0 (37.0 - 86.0)	64.0 (34.0 - 89.0)	62.0 (35.0 - 85.0)	63.0 (34.0 - 89.0)
Race				
American Indian	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Asian	7 (3.4%)	6 (2.5%)	2 (2.1%)	15 (2.8%)
Black	5 (2.5%)	7 (2.9%)	0 (0.0%)	12 (2.2%)
Others or Not Reported	4 (2.0%)	10 (4.1%)	2 (2.1%)	16 (3.0%)
White	185 (91.1%)	219 (90.5%)	93 (95.9%)	497 (91.7%)
Sex				
Female	197 (97.0%)	242 (100.0%)	97 (100.0%)	536 (98.9%)
Male	6 (3.0%)	0 (0.0%)	0 (0.0%)	6 (1.1%)
Weight (kg)				
Mean (SD)	72.0 (17)	70.1 (16)	67.8 (14)	70.4 (16)
Median (range)	69.3 (46.4 - 136)	67.0 (36.1 - 125)	67.0 (41.8 - 124)	68.3 (36.1 - 136)
Body surface area (m^2)				
Mean (SD)	1.77 (0.19)	1.73 (0.18)	1.72 (0.17)	1.74 (0.18)
Median (range)	1.74 (1.41 - 2.46)	1.72 (1.28 - 2.32)	1.69 (1.38 - 2.26)	1.72 (1.28 - 2.46)
Body mass index (kg/m^2)				
Mean (SD)	27.1 (6.0)	27.1 (6.0)	25.9 (5.1)	26.9 (5.9)
Median (range)	25.9 (16.9 - 53.7)	26.0 (15.0 - 50.1)	25.8 (16.5 - 46.0)	25.9 (15.0 - 53.7)
Lean body mass (kg)				
Mean (SD)	46.3 (6.4)	44.7 (6.1)	44.4 (5.7)	45.2 (6.2)
Median (range)	45.4 (33.8 - 74.8)	44.3 (31.8 - 65.0)	43.8 (33.4 - 62.3)	44.7 (31.8 - 74.8)
Ideal body weight (kg)				
Mean (SD)	54.8 (6.0)	52.8 (5.9)	53.7 (5.9)	53.7 (6.0)
Median (range)	54.3 (41.7 - 75.0)	52.2 (38.5 - 70.3)	52.9 (39.5 - 71.8)	53.8 (38.5 - 75.0)
Adjusted ideal body weight (kg)				
Mean (SD)	61.7 (8.4)	59.7 (8.1)	59.3 (7.6)	60.4 (8.2)
Median (range)	60.5 (45.2 - 96.7)	59.1 (42.8 - 87.1)	58.5 (44.8 - 83.4)	59.5 (42.8 - 96.7)
Alkaline phosphatase (IU/L)				
Mean (SD)	113 (1.1e+02)	99.8 (61)	126 (1.2e+02)	109 (95)
Median (range)	90.0 (11.0 - 1.24e+03)	84.8 (30.0 - 573)	96.0 (48.0 - 799)	89.0 (11.0 - 1.24e+03)

	IMGN853-0401	IMGN853-0403	IMGN853-0417	All
Alanine aminotransferase (*IU/L*)				
Mean (SD)	26.4 (19)	20.9 (16)	21.9 (18)	23.1 (18)
Median (range)	23.0 (4.00 - 154)	17.0 (6.00 - 166)	17.0 (2.00 - 107)	19.0 (2.00 - 166)
Aspartate aminotransferase (*IU/L*)				
Mean (SD)	27.9 (19)	24.6 (14)	25.8 (16)	26.1 (17)
Median (range)	22.0 (11.0 - 159)	21.0 (8.00 - 124)	21.0 (10.0 - 108)	21.0 (8.00 - 159)
Albumin (*g/dL*)				
Mean (SD)	3.74 (0.52)	4.08 (0.41)	3.81 (0.49)	3.90 (0.49)
Median (range)	3.80 (2.00 - 5.00)	4.10 (2.60 - 5.30)	3.90 (2.60 - 4.60)	4.00 (2.00 - 5.30)
Creatinine (*μmol/L*)				
Mean (SD)	78.6 (25)	69.9 (17)	70.0 (20)	73.2 (21)
Median (range)	70.7 (35.4 - 177)	67.0 (40.0 - 141)	66.0 (35.0 - 131)	69.0 (35.0 - 177)
Creatinine clearance (*mL/min*)				
Mean (SD)	81.1 (31)	85.2 (31)	84.5 (31)	83.6 (31)
Median (range)	75.9 (27.5 - 211)	81.5 (31.3 - 217)	78.2 (32.0 - 232)	78.6 (27.5 - 232)
Soluble FOLR1 Missing & Imputed				
No	10 (4.9%)	173 (71.5%)	77 (79.4%)	260 (48.0%)
Yes	193 (95.1%)	69 (28.5%)	20 (20.6%)	282 (52.0%)
Soluble FOLR1 (pmol/L)				
Mean (SD)	42.8 (36)	85.5 (1.7e+02)	307 (1.1e+03)	109 (4.8e+02)
Median (range)	40.4 (12.0 - 551)	40.4 (8.39 - 1.47e+03)	40.7 (11.9 - 9.21e+03)	40.4 (8.39 - 9.21e+03
Target FOLR1 Expression Category				
High	81 (39.9%)	142 (58.7%)	97 (100.0%)	320 (59.0%)
Low	44 (21.7%)	0 (0.0%)	0 (0.0%)	44 (8.1%)
Medium	40 (19.7%)	100 (41.3%)	0 (0.0%)	140 (25.8%)
Unknown	9 (4.4%)	0 (0.0%)	0 (0.0%)	9 (1.7%)
Very Low	29 (14.3%)	0 (0.0%)	0 (0.0%)	29 (5.4%)
Baseline Tumor Sum of Diameters Missing & Imputed				
No	188 (92.6%)	242 (100.0%)	88 (90.7%)	518 (95.6%)
Yes	15 (7.4%)	0 (0.0%)	9 (9.3%)	24 (4.4%)
Investigator Assessed Baseline Tumor Sum of Diameters (mm)				
Mean (SD)	69.3 (50)	69.4 (51)	59.3 (51)	67.6 (51)
Median (range)	55.0 (10.0 - 294)	56.0 (10.0 - 271)	44.0 (10.0 - 351)	55.0 (10.0 - 351)

Source provided in the ER report.

Applicant - Table 8 and 12: Parameter Estimates for Best Moderate and Severe Hot Flash Frequency and Severity Model

Best Frequency Model

Parameter Description	Notation	Estimate	SE
Fixed Effects [a]			
Baseline rate $Y_{j-1}=0$ (θ_{base}) [log 1/d]	θ_1	2.037	0.011
Scale (θ_{scale}) [log]	θ_2	3.805	0.056
Shape (θ_{shape}) [log]	θ_3	-0.276	0.034
Markov slope (θ_{markov}) [log $1/Y_{j-1}$]	θ_4	-3.389	0.029
Fractional change in rate during baseline period ($\theta_{basetime}$) [log frac/d]	θ_5	0.01	0.001
Post-baseline drift (θ_{drift}) [log 1/d]	θ_6	-4.395	0.062
Effective exposure to achieve half of maximum drug effect (θ_{auc50}) [log ng*hr/mL]	θ_7	10.668	0.294
ke0 (θ_{ke0}) [log 1/d]	θ_8	-1.90	0.104
Random Effects			
IIV on baseline (ω^2-base)	$\omega_{1,1}$	0.045	0.002
Covariance (ω-base, ω-AUC50)	$\omega_{2,1}$	0.09	0.038
IIV on AUC50 (ω^2-AUC50)	$\omega_{2,2}$	9.943	1.427
Covariance (ω-base, ω-scale)	$\omega_{3,1}$	0.039	0.009
Covariance (ω-auc50, ω-scale)	$\omega_{3,2}$	-0.43	0.32
IIV on scale (ω^2-scale)	$\omega_{3,3}$	1.214	0.094
Covariance (ω-base, ω-shape)	$\omega_{4,1}$	0.003	0.007
Covariance (ω-auc50, ω-shape)	$\omega_{4,2}$	-1.234	0.206
Covariance (ω-scale, ω-shape)	$\omega_{4,3}$	0.243	0.045
IIV on scale (ω^2-shape)	$\omega_{4,4}$	0.666	0.048

IIV = interindividual variability

[a] Log transformed parameters were estimated for model parameters that were constrained to be positive

Best Severity Model

Parameter Description	Notation	Estimate	SE
Fixed Effects [a]			
$\beta_{k=2}$ [logit]	θ_1	4.297	0.113
$\beta_{k=3}$ [log logit]	θ_2	1.578	0.023
Maximum placebo effect (θ_{pmax}) [logit]	θ_3	-0.968	0.013
Placebo half-life (θ_{phl}) [log d]	θ_4	2.527	0.033
Maximum drug effect (θ_{emax}) [logit]	θ_5	-0.912	0.05
Effective exposure to achieve half of maximum drug effect (θ_{auc50}) [log ng*hr/mL]	θ_6	6.615	0.259
ke0 (θ_{ke0}) [log 1/d]	θ_7	-0.74	0.201
Box-cox transformation IIV $\beta_{k=2}$ (θ_{box})	θ_8	0.165	0.008
Random Effects			
IIV on $\beta_{k=2}$ (ω^2-$\beta_{k=2}$)	$\omega_{1,1}$	10.623	0.723
Covariance (ω -$\beta_{k=2}$, ω -$\beta_{k=3}$)	$\omega_{1,2}$	1.356	0.108
IIV on $\beta_{k=3}$ (ω^2-$\beta_{k=3}$)	$\omega_{2,2}$	0.47	0.024

IIV = interindividual variability

[a] Log transformed parameters were estimated for model parameters that were constrained to be positive

Source provided in the ER report.

Applicant - Table 1 in IR response on 8/22/2022: Comparison of Model Parameter Estimates for Original and Simplified Severity Models

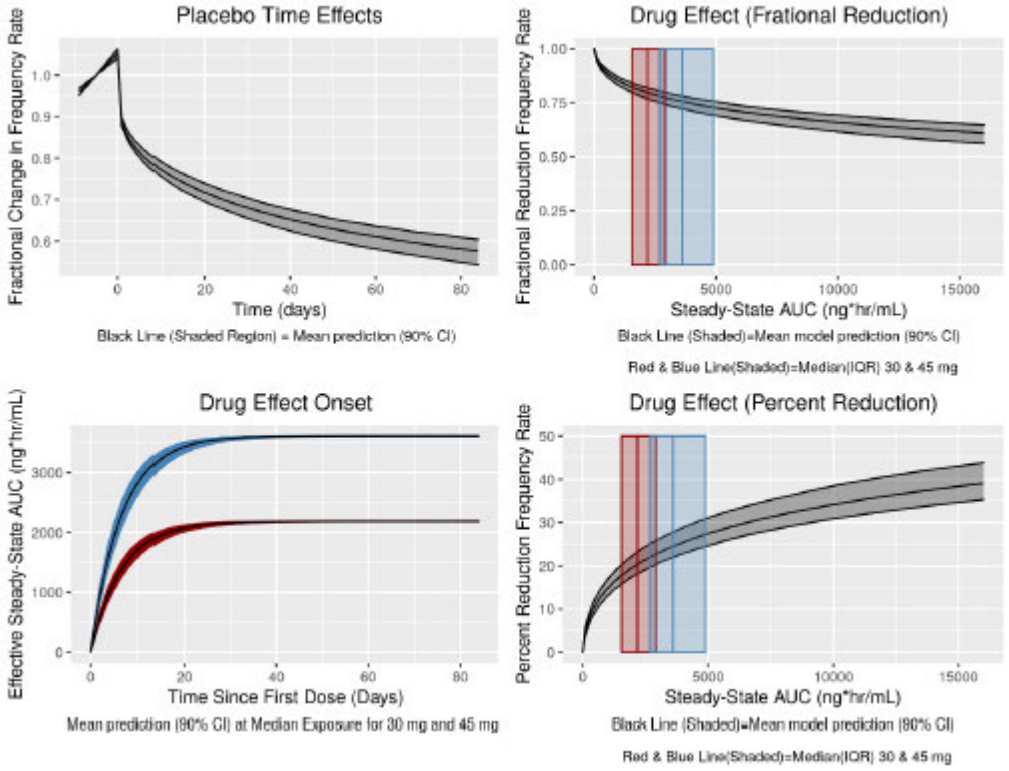
Parameter Description	Notation	Original Run112d_mod NM 7.4.4 Estimate (SE)	Simplified Run109_mod NM 7.4.4 Estimate (SE)	Simplified Run9999_mod NM 7.5.0 Estimate (SE)
Fixed Effects [a]				
$\beta_{k=2}$ [logit]	θ_1	4.297 (0.113)	3.66 (0.0726)	3.66 (0.0723)
$\beta_{k=3}$ [log logit]	θ_2	1.578 (0.023)	1.46 (0.00174)	1.46 (0.00174)
Maximum placebo effect (θ_{pmax}) [logit]	θ_3	-0.968 (0.013)	-0.907 (0.0117)	-0.907 (0.0117)
Placebo half-life (θ_{phi}) [log d]	θ_4	2.527 (0.033)	2.49 (0.0322)	2.49 (0.0322)
Maximum drug effect (θ_{emax}) [logit]	θ_5	-0.912 (0.05)	-1.00 (0.0442)	-1.00 (0.0442)
Effective exposure to achieve half of maximum drug effect (θ_{auc50}) [log ng*hr/mL]	θ_6	6.615 (0.259)	7.11 (0.147)	7.11 (0.147)
ke0 (θ_{ke0}) [log 1/d]	θ_7	-0.74 (0.201)	-0.623 (0.153)	-0.623 (0.153)
Box-cox transformation IIV $\beta_{k=2}$ (θ_{box})	θ_8	0.165 (0.008)	0.175 (0.00974)	0.175 (0.00972)
Random Effects				
IIV on $\beta_{k=2}$ (ω^2-$\beta_{k=2}$)	$\omega_{1,1}$	10.623 (0.723)	NE	NE
Covariance (ω -$\beta_{k=2}$, ω -$\beta_{k=3}$)	$\omega_{1,2}$	1.356 (0.108)	NE	NE
IIV on $\beta_{k=3}$ (ω^2-$\beta_{k=3}$)	$\omega_{2,2}$	0.47 (0.024)	NE	NE
IIV on β_k (ω^2-β_k)	$\omega_{1,1}$	NE	4.66 (0.247)	4.66 (0.247)
Objective Function Value		4169163.918	4264042.849	4264042.849

[a] Log transformed parameters were estimated for model parameters that were constrained to be positive

NE = not estimated

Applicant - Figure 11, 19 and 20: Illustration of Baseline and Post-Baseline Placebo-time Effects and Drug Effect Components of Moderate and Severe Hot Flash Frequency and Severity Model

Frequency Model



Severity Model

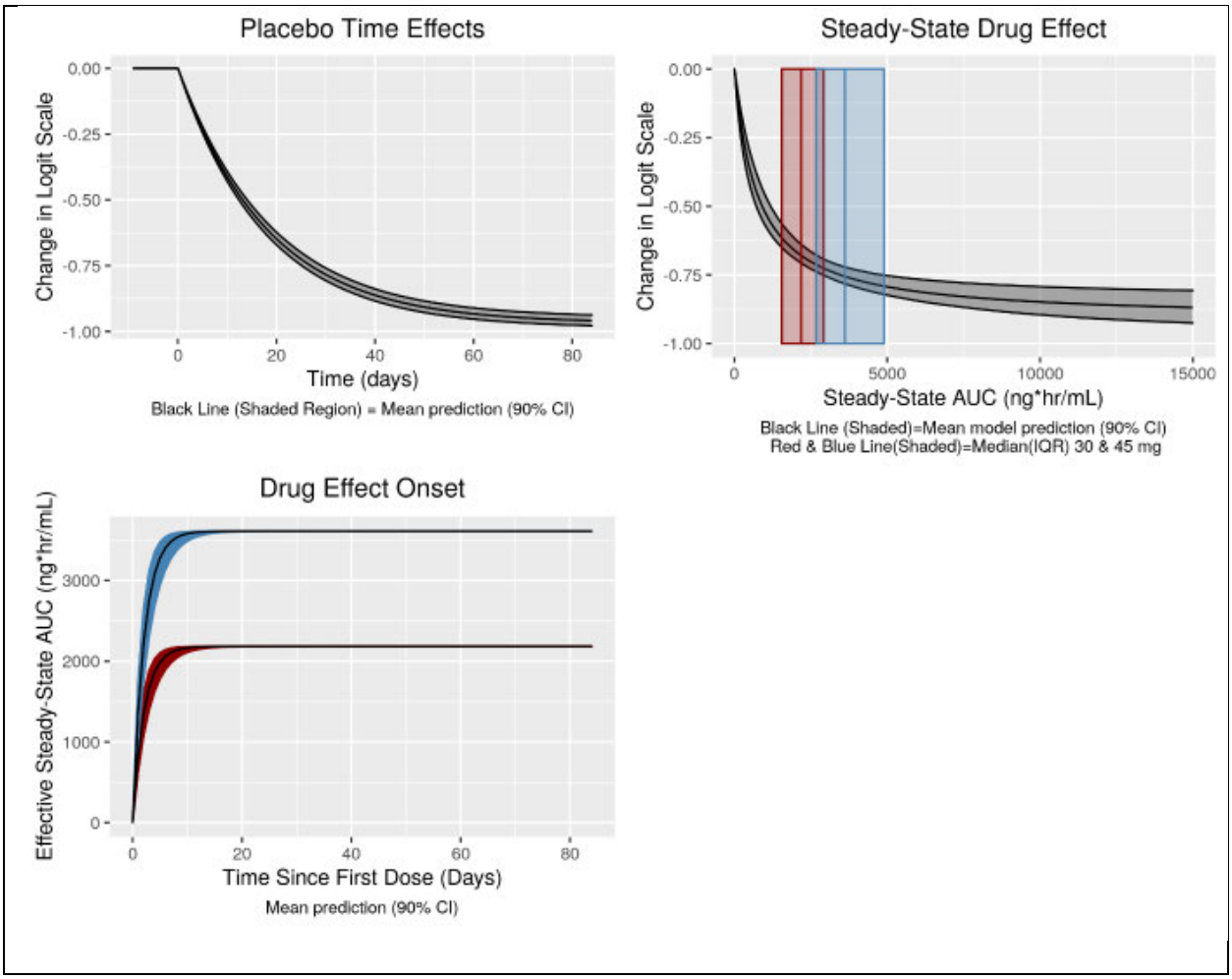
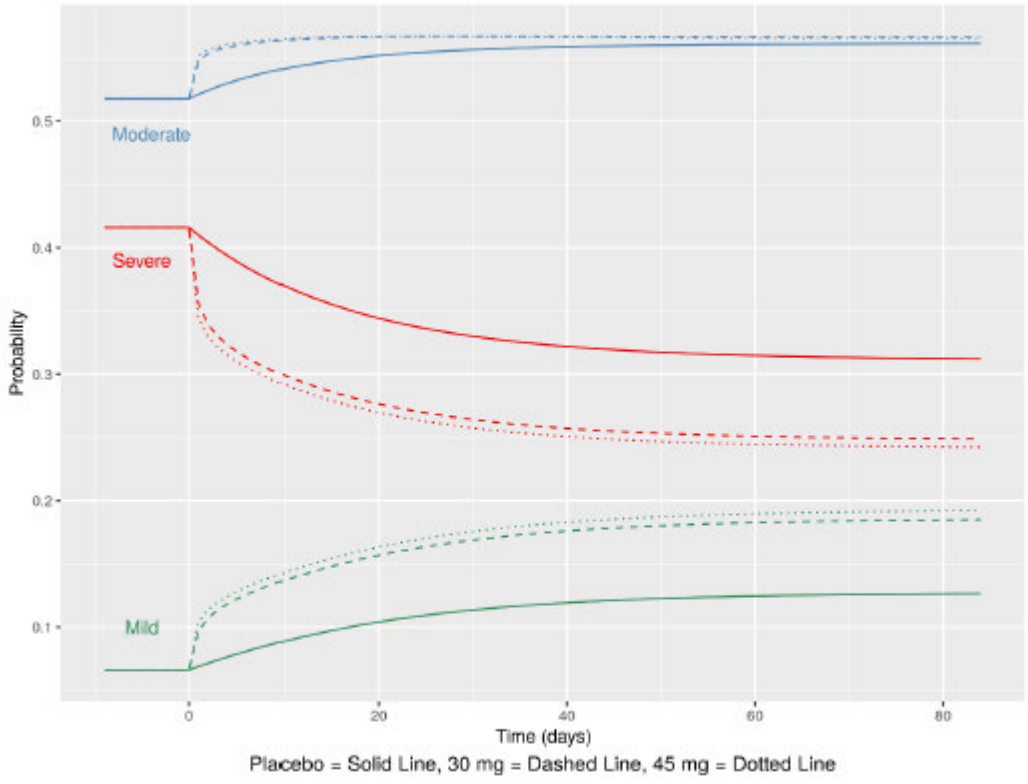


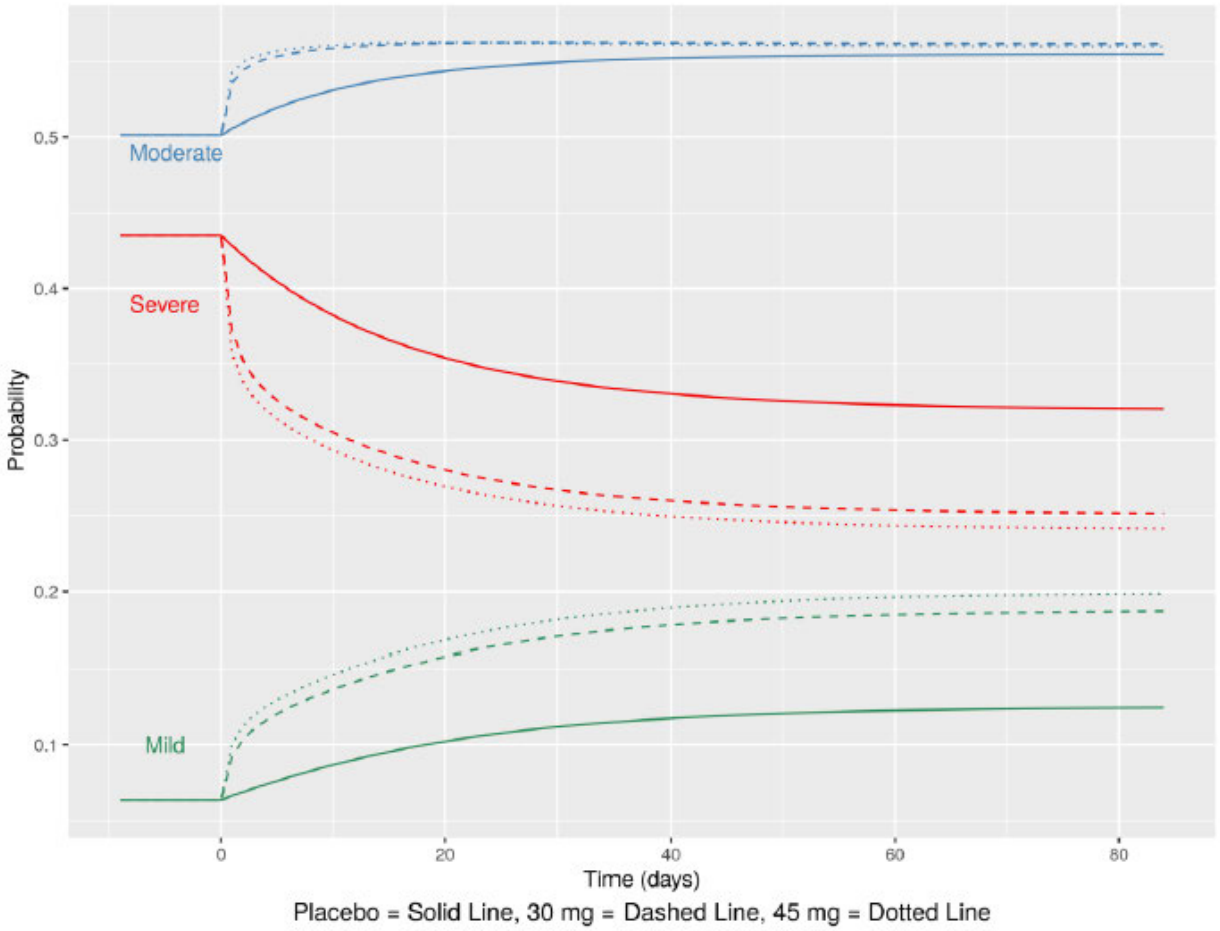
Figure 20 Mean Predicted Probability of Mild, Moderate, and Severe Hot Flashes



Note: Green lines represent probability of mild hot flash, blue lines represent probability of moderate hot flash, and red lines represent probability of severe hot flash. Solid lines represent probability for placebo, dashed lines represent probability at median exposure for 30 mg dose group, and dotted lines represent probability at median exposure for 45 mg dose group.

Source provided in the ER report.

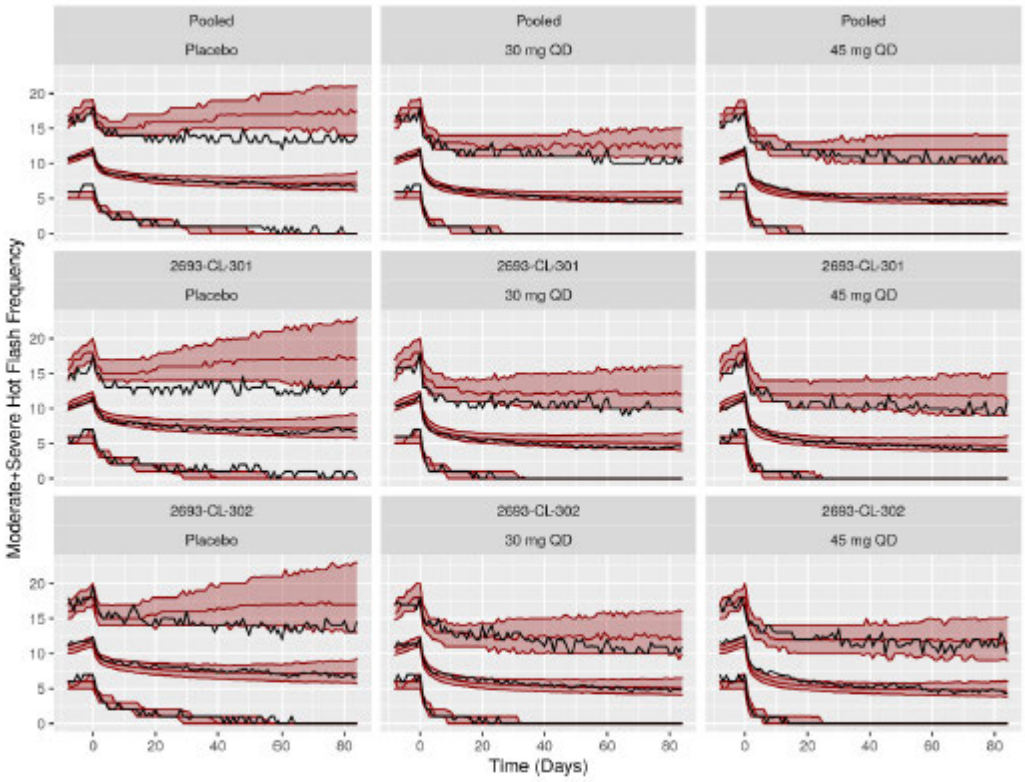
Applicant - Figure 1 in IR response dated 8/31/2022: Mean Predicted Probability of Mild, Moderate, and Severe Hot Flashes for Simplified Model (Run109_mod.txt)



Note: Green lines represent probability of mild hot flash, blue lines represent probability of moderate hot flash, and red lines represent probability of severe hot flash. Solid lines represent probability for placebo, dashed lines represent probability for 30 mg dose group, and dotted lines represent probability for 45 mg dose group.

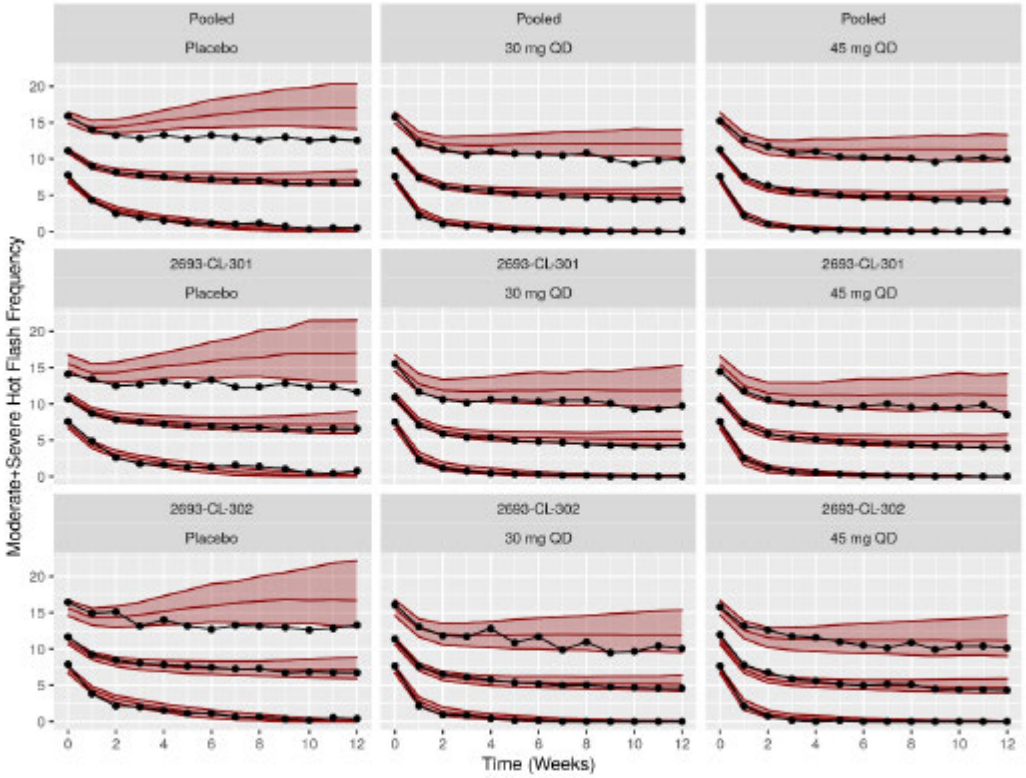
Applicant - Figure 12, 13 and 14: Visual Predictive Check for Placebo-Corrected Change from Baseline (Average (Daily)) Moderate and Severe Hot Flash Frequency for the Best Model

Figure 12 Visual Predictive Check for Daily Moderate and Severe Hot Flash Frequency for the Best Model



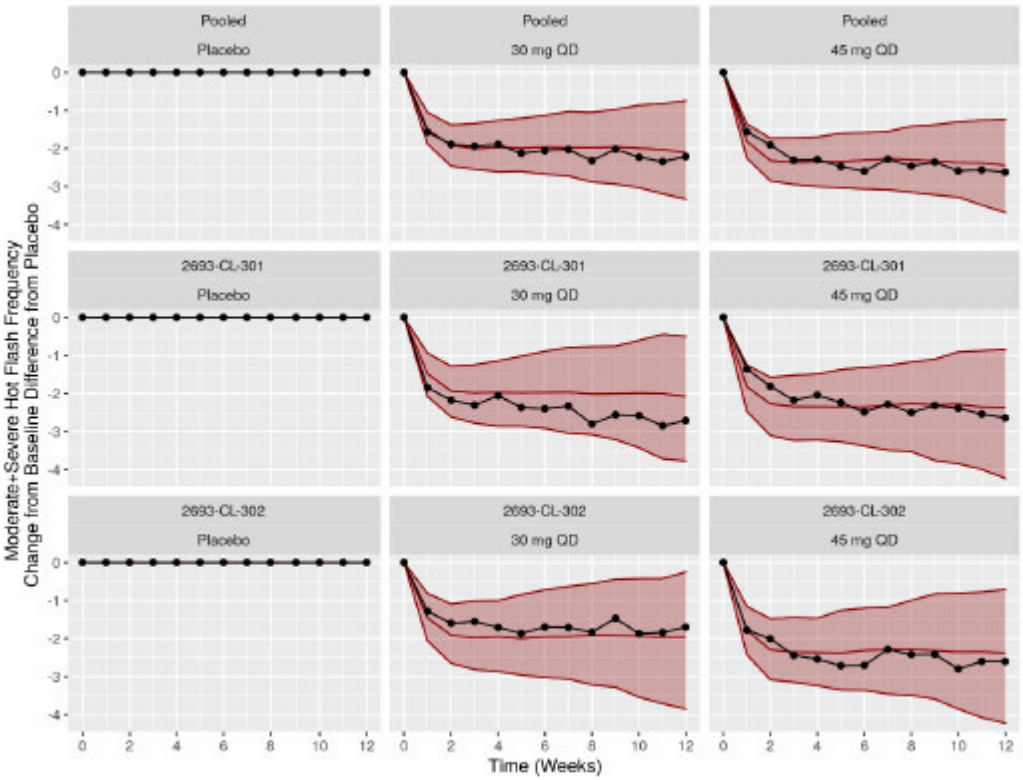
Note: Solid black lines represent the observed mean (middle), 10th (bottom), and 90th (top) percentiles for daily moderate and severe hot flash frequency. The pink shaded regions represent the simulated 90% prediction interval for the mean (middle), 10th (bottom), and 90th (top) percentiles and the solid red line represents the median simulated value for each of the mean, 10th, and 90th percentiles.

Figure 13 Visual Predictive Check for Average Daily Moderate and Severe Hot Flash Frequency for the Best Model



Note: Solid black lines with solid black circles represent the observed mean (middle), 10th (bottom), and 90th (top) percentiles for average daily moderate and severe hot flash frequency by week. The pink shaded regions represent the simulated 90% prediction interval for the mean (middle), 10th (bottom), and 90th (top) percentiles and the solid red line represents the median simulated value for each of the mean, 10th, and 90th percentiles.

Figure 14 Visual Predictive Check for Placebo-Corrected Change from Baseline Average Daily Moderate and Severe Hot Flash Frequency

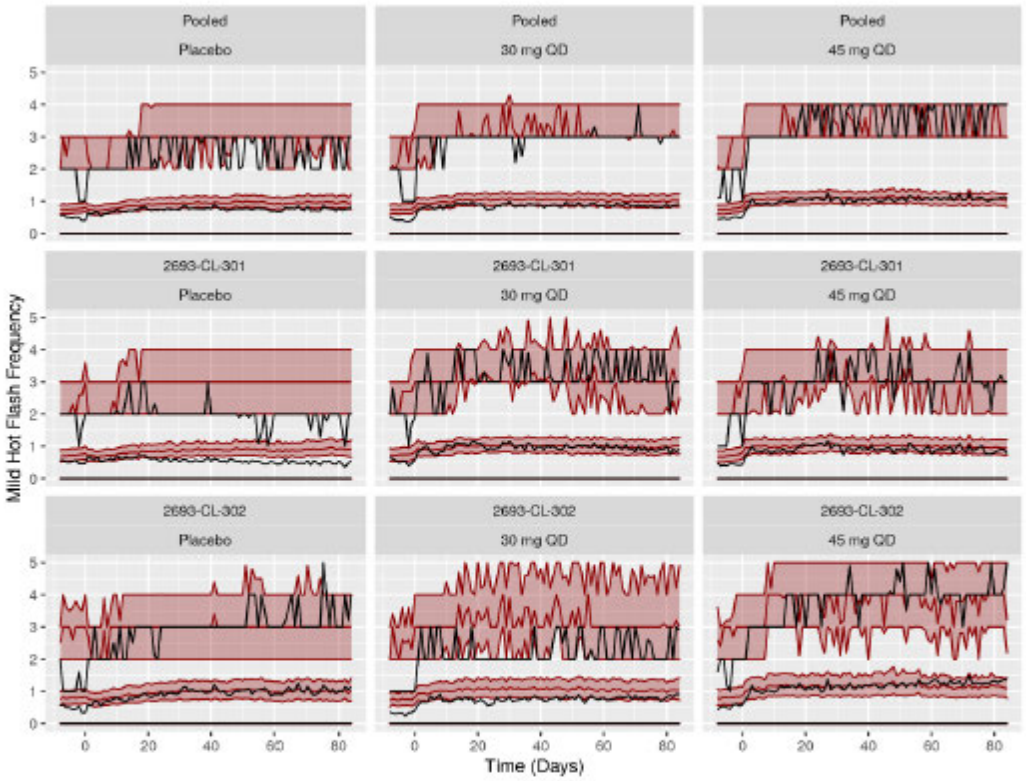


Note: Solid black lines with solid black circles represent the observed mean for average daily moderate and severe hot flash frequency by week. The pink shaded region represents the 90% prediction interval and the solid red line represents the median simulated value.

Source provided in the ER report.

Applicant - Figure 21, 22, 23, 24 and 25: Visual Predictive Check for the Best Severity Model

Figure 21 Visual Predictive Check for Daily Mild Hot Flash Frequency for Best Severity Model



Note: Solid black lines represent the observed mean (middle), 10th (bottom near zero), and 90th (top) percentiles for daily hot flash frequency. The pink shaded regions represent the simulated 90% prediction interval for the mean (middle), 10th (bottom near zero), and 90th (top) percentiles and the solid red line represents the median simulated value for each of the mean, 10th, and 90th percentiles. Note that both observed and simulated values are near zero for the 10th percentile.

Figure 22 Visual Predictive Check for Daily Moderate Hot Flash Frequency for Best Severity Model

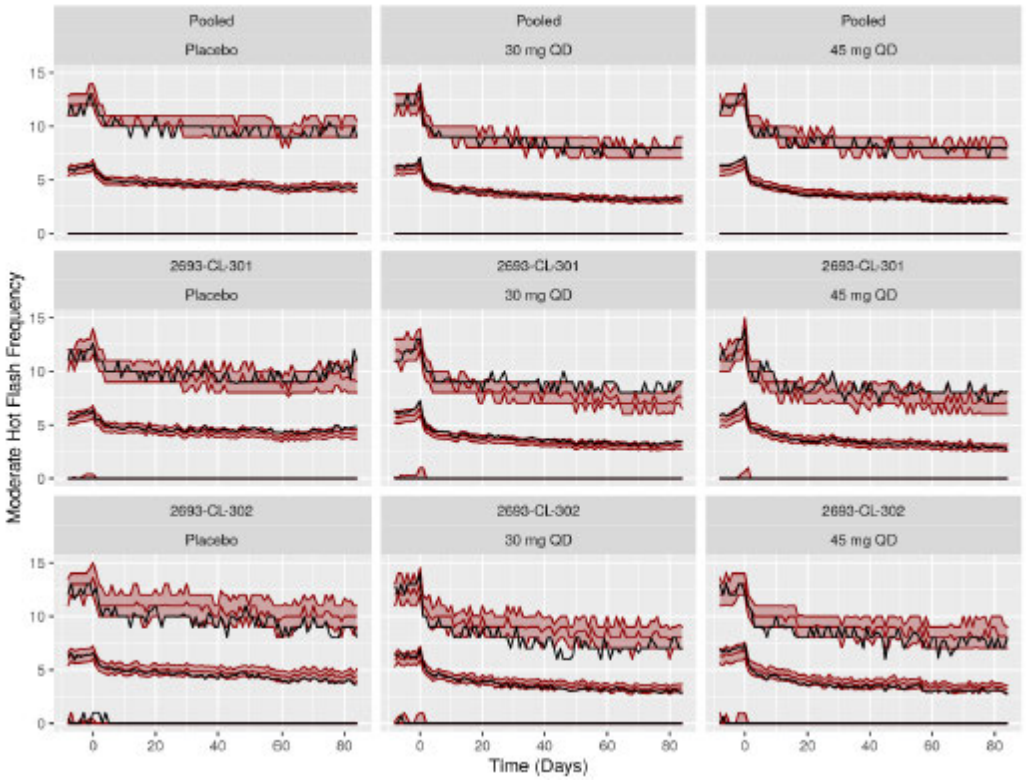
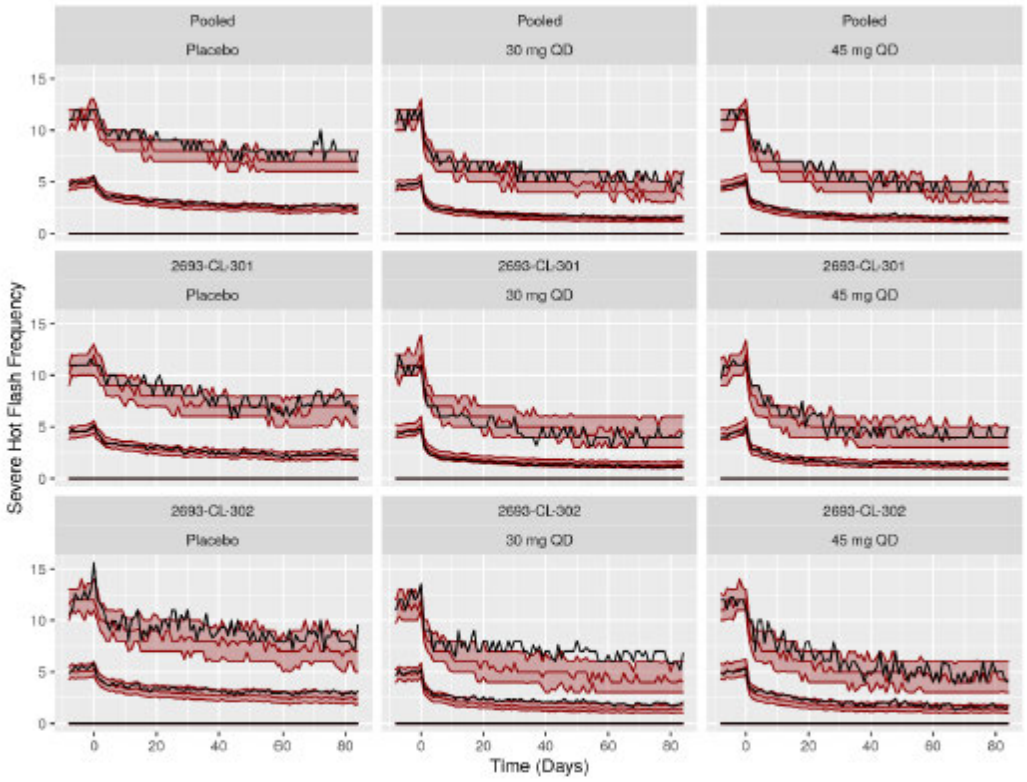
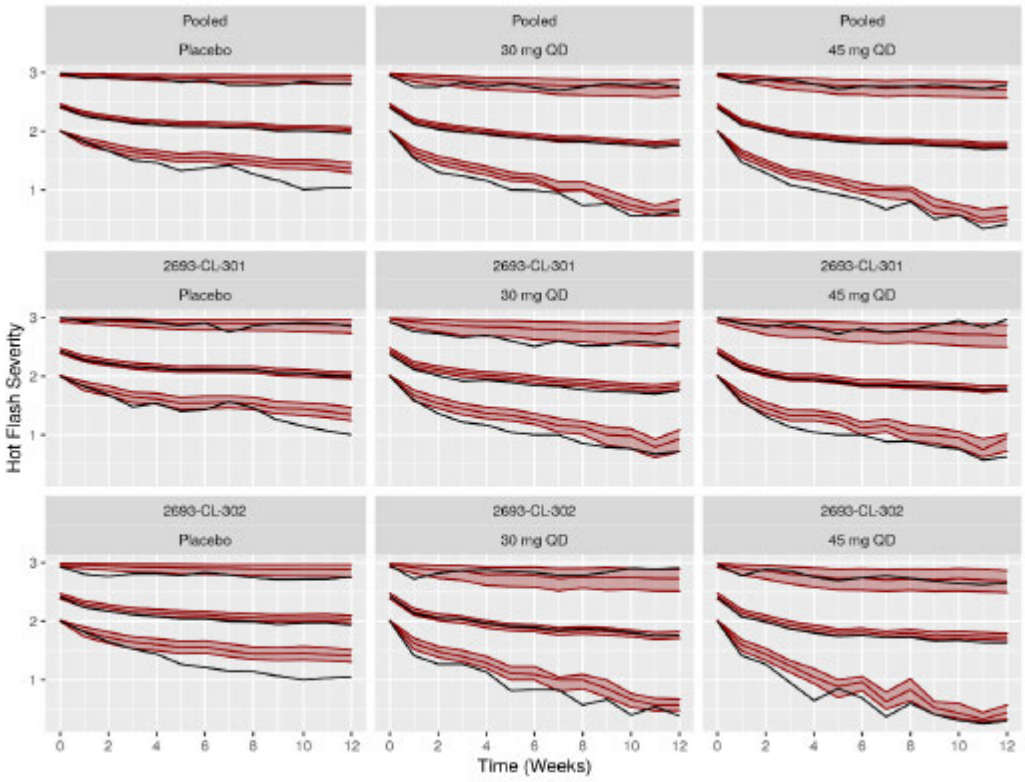


Figure 23 Visual Predictive Check for Daily Severe Hot Flash Frequency for Best Severity Model



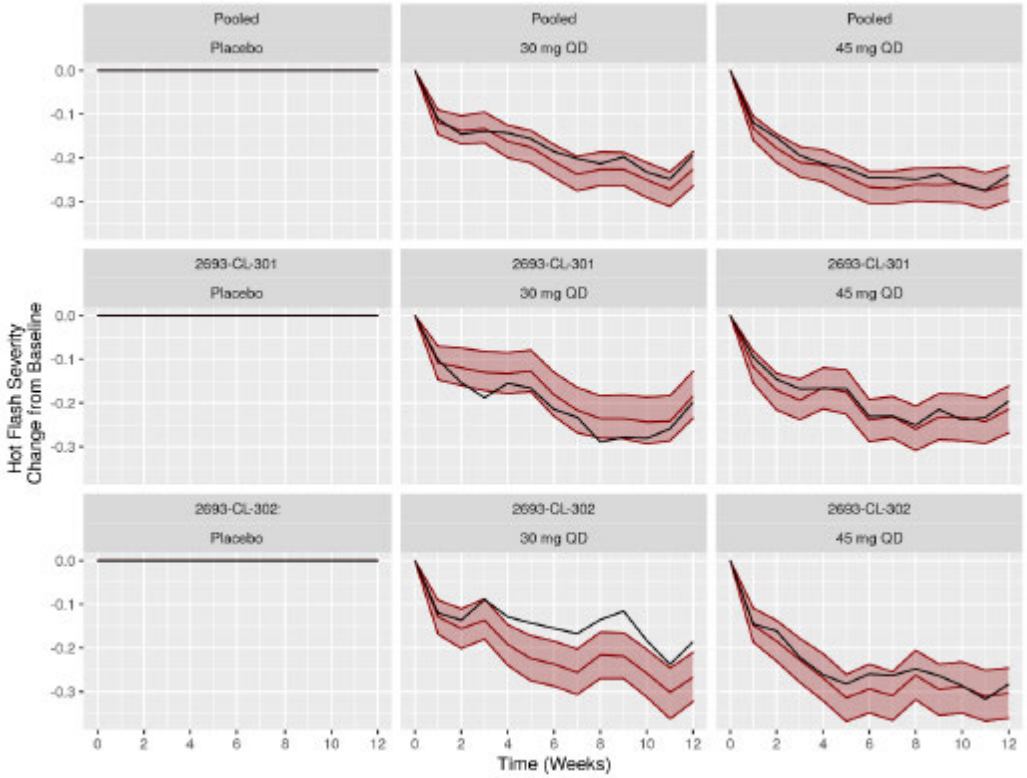
Note: Solid black lines represent the observed mean (middle), 10th (bottom near zero), and 90th (top) percentiles for daily mild hot flash frequency. The pink shaded regions represent the simulated 90% prediction interval for the mean (middle), 10th (bottom near zero), and 90th (top) percentiles and the solid red line represents the median simulated value for each of the mean, 10th, and 90th percentiles. Note that both observed and simulated values are near zero for the 10th percentile.

Figure 24 Visual Predictive Check for Average Severity for Best Severity Model



Note: Solid black lines represent the observed mean (middle), 10th (bottom), and 90th (top) percentiles for average hot flash severity. The pink shaded regions represent the simulated 90% prediction interval for the mean (middle), 10th (bottom), and 90th (top) percentiles and the solid red line represents the median simulated value for each of the mean, 10th, and 90th percentiles.

Figure 25 Visual Predictive Check for Change from Baseline Average Severity Difference from Placebo for Best Severity Model



Note: Solid black lines represent the observed mean for average hot flash severity. The pink shaded region represents the 90% prediction interval and the solid red line represents the represents the median simulated value of the mean.

ER (safety) Executive Summary

The FDA's Assessment:

The applicant's exposure response analyses on safety are considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

ER (safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		Characterize the relationship between fezolinetant exposure and the time to event of transaminase elevations and frequency of other adverse events of clinical interest; and Assess the impact of pre-defined covariate effects on the frequency of adverse events.
Studies Included		Planned: phase 3 studies (2693-CL-0301 and 2693-CL- 0302) Pooled: phase 3 studies (2693-CL-0301 and 2693-CL- 0302) and phase 2 studies (ESN364_HF_204 and ESN364_HF_205)
Population Included		Women with vasomotor symptoms (VMS) associated with menopause
Endpoints		Liver transaminases (i.e., ALT or AST elevations greater than 3-times the upper limit of normal (>3x ULN)) as well as biomarkers
No. of Patients (total, and with individual PK)		Planned: N=1022 and pooled: N=1400
Population Characteristics (Applicant - Table 6)	General (pooled)	Age: median 54.0 yr (min, max: 40.0, 65.0) Body Mass Index: median 27.8 (min, max: 18.0, 44.1) Sex: 1022 (100%) female Race: 1123 (80%) White, 251 (18%) Black, 6 (0.0%) American Indian, 12 (1%) Asian, 8 (1%) Other

	Pediatrics (if any)	Not applicable	
Dose(s) Included		Planned: 30 mg QD and 45 mg QD; Pooled: up to 180 mg daily.	
Exposure Metrics Explored (range)		Planned: Individual predicted steady-state AUC(0-τ) and Cmax were explored Pooled: Total daily dose, individual predicted Cavg, and treatment effect (i.e., step function Dose > 0 yes/no).	
Covariates Evaluated		• Continuous Covariates: age, BMI, baseline liver transaminase level • Categorical Covariates: Race, smoking status, diabetes mellitus history (Smoking status was unknown in Study ESN364_HF_204 and not previously identified as predictive of liver transaminase elevations and was therefore not investigated in the pooled dataset.)	
Final Model Parameters		**Summary**	**Acceptability** **[FDA's comments]**
Model Structure		For safety event endpoints: Cox regression model	**Acceptable**
Model Parameter Estimates		Applicant - Table 7 and 8	Acceptable
Model Evaluation		Applicant - Figure IV and 21	Acceptable
Covariates and Clinical Relevance		Of the covariates tested, only baseline ALT and baseline AST were identified as statistically significant covariates. Since baseline ALT and baseline AST were highly correlated and the model with baseline ALT provided a better fit, the model including	Acceptable

	baseline ALT on the hazard rate was used for subsequent illustrations.	
Simulation for Specific Population	NA	NA
Visualization of E-R relationships	Planned: Applicant - Figure 5, 6, 7, and 8 Pooled: Applicant - Figure 22, 23, 24, and 25	Acceptable
Overall Clinical Relevance for ER	• In the phase 3 data from Studies 2693-CL-0301 and 2693-CL-0302 which included daily doses up to 45 mg, model-based time to first event analyses for ALT or AST elevations >3x ULN did not identify fezolinetant exposure as a statistically significant predictor of ALT or AST elevations. Baseline ALT was identified as a statistically significant covariate and predicted an increased rate of post-baseline ALT or AST elevations with increasing baseline ALT values. • In the pooled phase 2 and phase 3 data including total daily doses up to 180 mg, model-based time to first event analyses did identify fezolinetant exposure as a statistically significant predictor of ALT or AST elevations >3x ULN. ALT or AST elevations were predicted to increase with increasing average fezolinetant concentration. Baseline ALT remained a statistically significant covariate and was included in the pooled phase 2 and phase 3 model.	Acceptable.

	Exploratory graphical analysis using data from Studies 2693-CL-0301 and 2693-CL-0302 showed no clear relationship between fezolinetant exposure and pertinent safety endpoints including liver transaminases (i.e., ALT and AST), bone safety biomarkers (i.e., BSAP, CTXI, P1NP), platelets, blood glucose, and creatine kinase (CK). The distribution of safety laboratory measurements were generally similar across treatment groups for all endpoints. Similarly, no clear trends were observed between laboratory safety measurements and individual predicted fezolinetant exposure metrics.	
Labeling Language	**Description**	**Acceptability** **[FDA's comments]**
12.2 Pharmacodynamics	Not applicable	

Applicant - Table 6: Summary of Covariates Evaluated in Model-based Analyses

Table 6 Summary of Covariates Evaluated in Model-based Analyses

Covariate	Summary Statistic	ESN364_ HF_204	ESN364_ HF_205	2693-PK-0301	2693-PK-0302	Total
Age (years)	N	83	322	506	489	1400
	N Missing	0	0	0	0	0
	Mean (SD)	53.5 (4.1)	54.5 (4.7)	54.4 (5.0)	54.3 (5.0)	54.3 (4.9)
	Median (Min,Max)	54.0 (44.0, 64.0)	54.0 (41.0, 65.0)	54.0 (40.0, 65.0)	54.0 (40.0, 65.0)	54.0 (40.0, 65.0)
Body Mass Index (kg/m^2)	N	83	322	505	489	1399
	N Missing	0	0	1	0	1
	Mean (SD)	25.6 (4.9)	28.4 (4.5)	28.3 (4.5)	28.0 (4.7)	28.1 (4.6)
	Median (Min,Max)	24.1 (19.1, 44.1)	28.2 (18.6, 38.7)	28.0 (18.0, 37.9)	27.6 (18.0, 38.0)	27.8 (18.0, 44.1)
Baseline ALT[a] (U/L)	N	83	322	506	489	1400
	N Missing	0	0	0	0	0
	Mean (SD)	21.2 (10.5)	19.9 (10.9)	21.0 (10.8)	21.4 (11.4)	20.9 (11.0)
	Median (Min,Max)	18.0 (8.0, 67.0)	17.0 (6.0, 99.0)	19.0 (6.0, 128)	19.0 (6.0, 93.0)	18.0 (6.0, 128.0)
Baseline AST[a] (U/L)	N	83	322	506	489	1400
	N Missing	0	0	0	0	0
	Mean (SD)	20.8 (4.8)	18.9 (6.7)	20.6 (6.0)	21.4 (7.4)	20.5 (6.7)
	Median (Min,Max)	20.0 (14.0, 41.0)	17.0 (9.0, 49.0)	20.0 (7.0, 54.0)	20.0 (9.0, 72.0)	19.0 (7.0, 72.0)
Race	White (%)	83 (100)	236 (73)	417 (82)	387 (79)	1123 (80)
	Black (%)	0 (0)	79 (25)	74 (15)	98 (20)	251 (18)
	Asian (%)	0 (0)	2 (1)	9 (2)	1 (0)	12 (1)
	American Indian or Alaskan Native (%)	0 (0)	2 (1)	3 (1)	1 (0)	6 (0)
	Other (%)	0 (0)	3 (1)	3 (1)	2 (0)	8 (1)
Smoking History	Current (%)	0 (0)	44 (14)	60 (12)	94 (19)	198 (14)
	Former (%)	0 (0)	63 (20)	89 (18)	84 (17)	236 (17)
	Never (%)	0 (0)	215 (67)	357 (71)	311 (64)	883 (63)
	Unknown (%)	83 (100)	0 (0)	0 (0)	0 (0)	83 (6)
Diabetes Mellitus History	No (%)	81 (98)	321 (100)	469 (93)	449 (92)	1320 (94)
	Yes (%)	2 (2)	1 (0)	37 (7)	40 (8)	80 (6)

Footnotes appear on next page

Applicant - Table 7, 8 and 11: Cox Proportional Hazard Model Parameter Estimates for ALT or AST Elevations >3x ULN for Fezolinetant Exposure

Table 7 **Cox Proportional Hazard Model Parameter Estimates for ALT or AST Elevations >3x ULN for Fezolinetant Exposure in Studies 2693-CL-301 and 2693-CL-0302**

Parameter	Estimate[a]	Standard Error	p-value[b]	Hazard Ratio[a]	Hazard Ratio[a] 95% Confidence Limits
Dose [mg]	0.01264	0.01798	0.4709	1.013	0.980, 1.052
AUC(0-tau) [ng*hr/mL]	9.21573E-06	0.0001103	0.9342	1.00	1.00, 1.00
On-Treatment (Step)	0.25522	0.81164	0.7479	1.291	0.304, 8.770

[a] Estimates and hazard ratios represent the effect of a 1-unit change for continuous covariates

[b] p-value for likelihood ratio

Table 8 **Cox Proportional Hazard Model Parameter Estimates for ALT or AST Elevations >3x ULN for Additional Covariate Effects in Studies 2693-CL-301 and 2693-CL-0302**

Parameter	Estimate [a]	Standard Error	p-value [b]	Hazard Ratio [a]	Hazard Ratio [a] 95% Confidence Limits
Age [yr]	-0.01169	0.04301	0.7861	0.988	0.909, 1.076
Body Mass Index [kg/m^2]	0.01818	0.04598	0.6934	1.018	0.929, 1.114
Current Smokers	-0.59088	0.74181	0.3878	0.554	0.088, 1.898
African American Race	-0.72796	0.74163	0.2782	0.483	0.077, 1.654
History of Diabetes Mellitus	-0.69103	1.02648	0.4538	0.501	0.028, 2.412
Baseline ALT [U/L]	0.03928	0.00727	< 0.0001	1.040	1.023, 1.053
Baseline AST [U/L]	0.06923	0.01560	0.0005	1.072	1.035, 1.101

[a] Estimates and hazard ratios represent the effect of a 1-unit change for continuous covariates

[b] p-value for likelihood ratio

Table 11 **Cox Proportional Hazard Model Parameter Estimates for ALT or AST Elevations > 3x ULN for Fezolinetant Total Daily Dose and Fezolinetant Cavg Model with Baseline ALT**

Model	-2LL	p-value [b]	Parameter	Estimate [a]	Standard Error	Hazard Ratio [a]	Hazard Ratio [a] 95% Confidence Limits
Total Daily Dose	371.477	<0.0001	Dose [mg]	0.01308	0.00387	1.013	1.005, 1.021
			Baseline ALT [U/L]	0.03892	0.00710	1.040	1.023, 1.053
Steady -State Cavg	366.030	<0.0001	Cavg [ng/mL]	0.00238	0.0004411	1.002	1.001, 1.003
			Baseline ALT [U/L]	0.03828	0.00705	1.039	1.023, 1.052

-2LL for models without covariates = 395.706

[a] Estimates and hazard ratios represent the effect of a 1-unit change for continuous covariates

[b] p-value for likelihood ratio, degrees of freedom=2

Source provided in the ER report.

Applicant - Figure 5, 6, 7 and 8: Maximum Post-baseline ALT and Maximum Change from Baseline ALT in Studies 2693-CL-0301 and 2693-CL-0302 Over the 12-week Treatment Period

Figure 5 **Maximum Post-baseline ALT and Maximum Change from Baseline ALT in Studies 2693-CL-0301 and 2693-CL-0302 Over the 12-week Treatment Period**

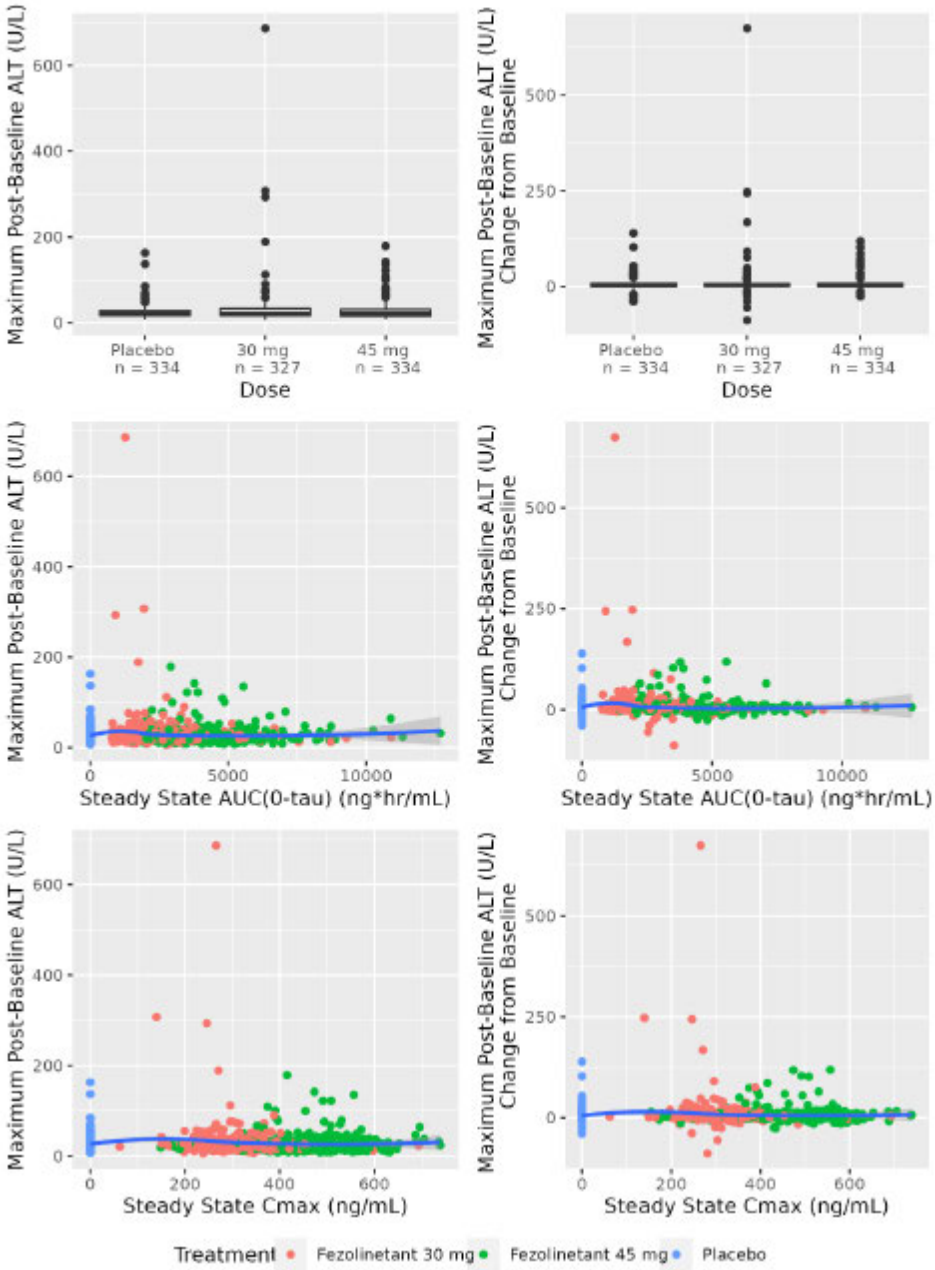


Figure 6 **Maximum Post-baseline AST and Maximum Change from Baseline AST in Studies 2693-CL-0301 and 2693-CL-0302 Over the 12-week Treatment Period**

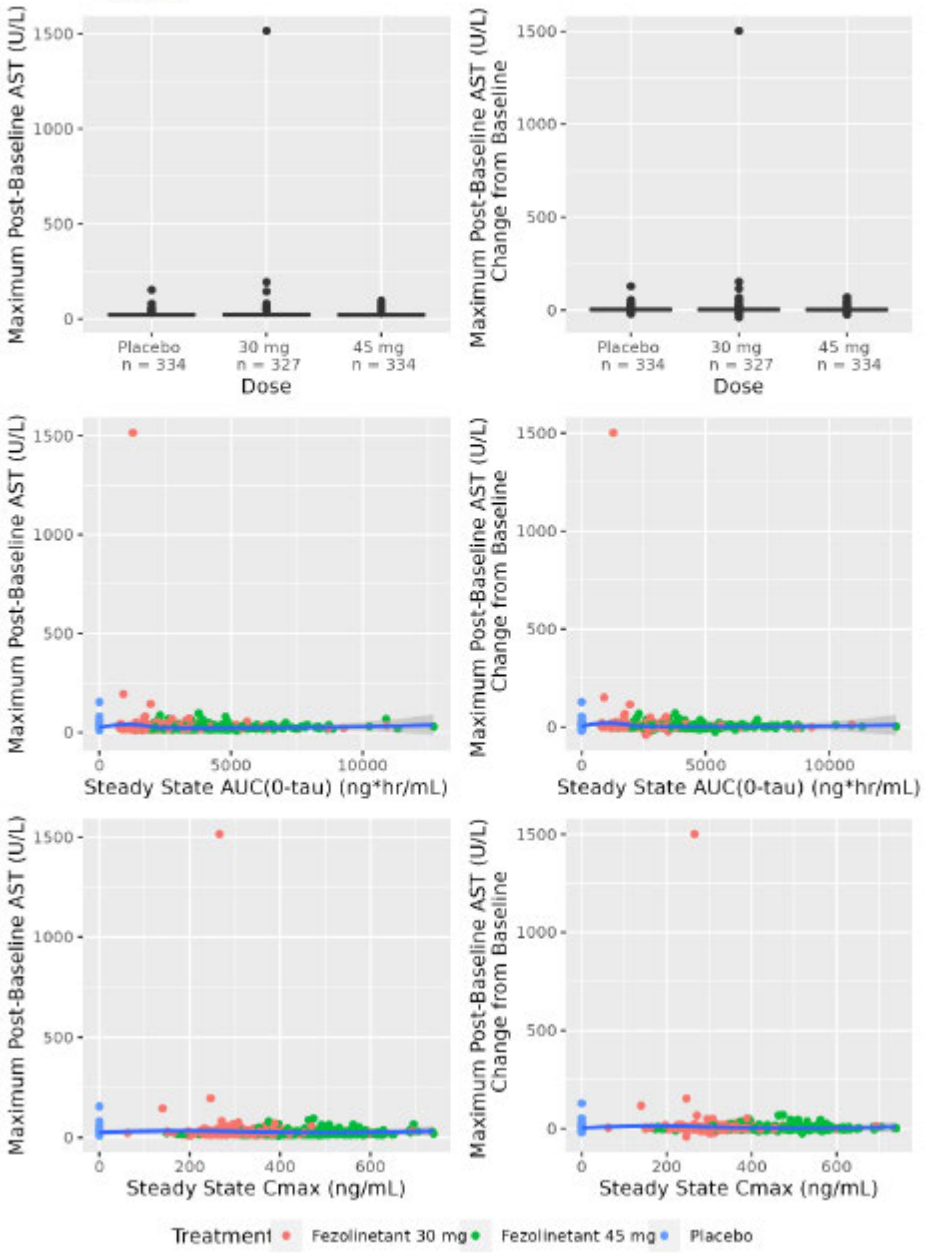


Figure 7 **Maximum Post-baseline ALT and Maximum Change from Baseline ALT in Studies 2693-CL-0301 and 2693-CL-0302 Over the 12-week Treatment Period Excluding ALT Values > 600 U/L**

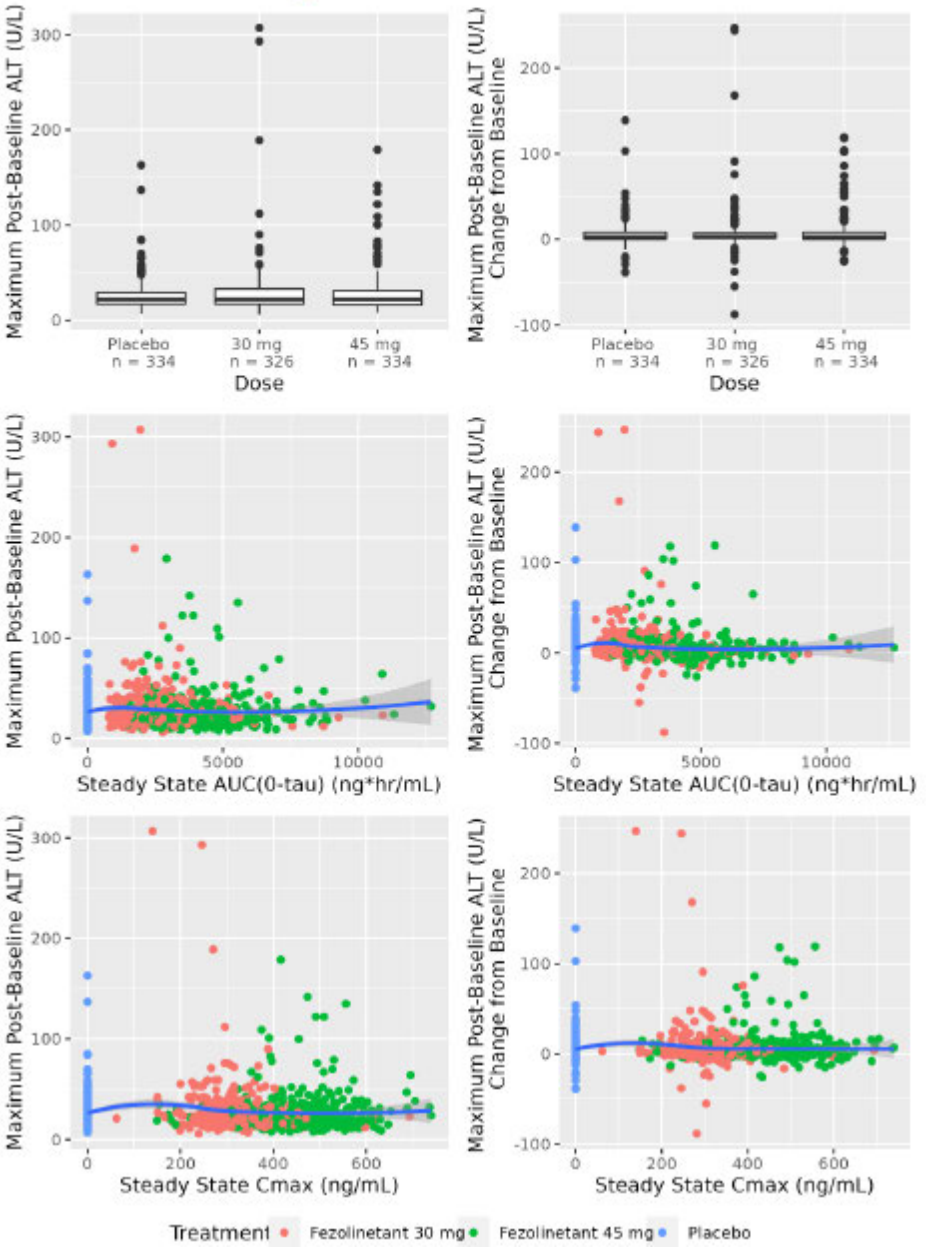
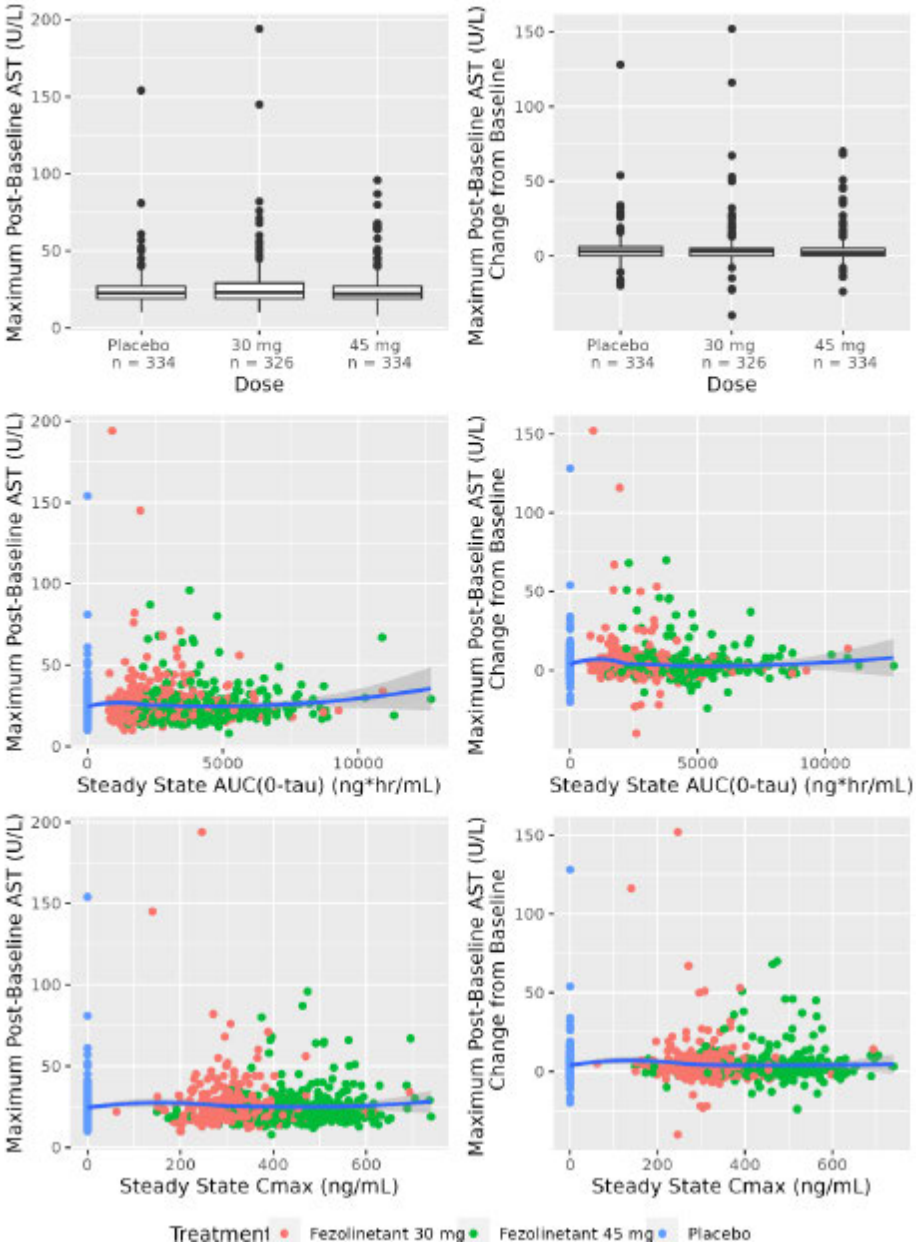


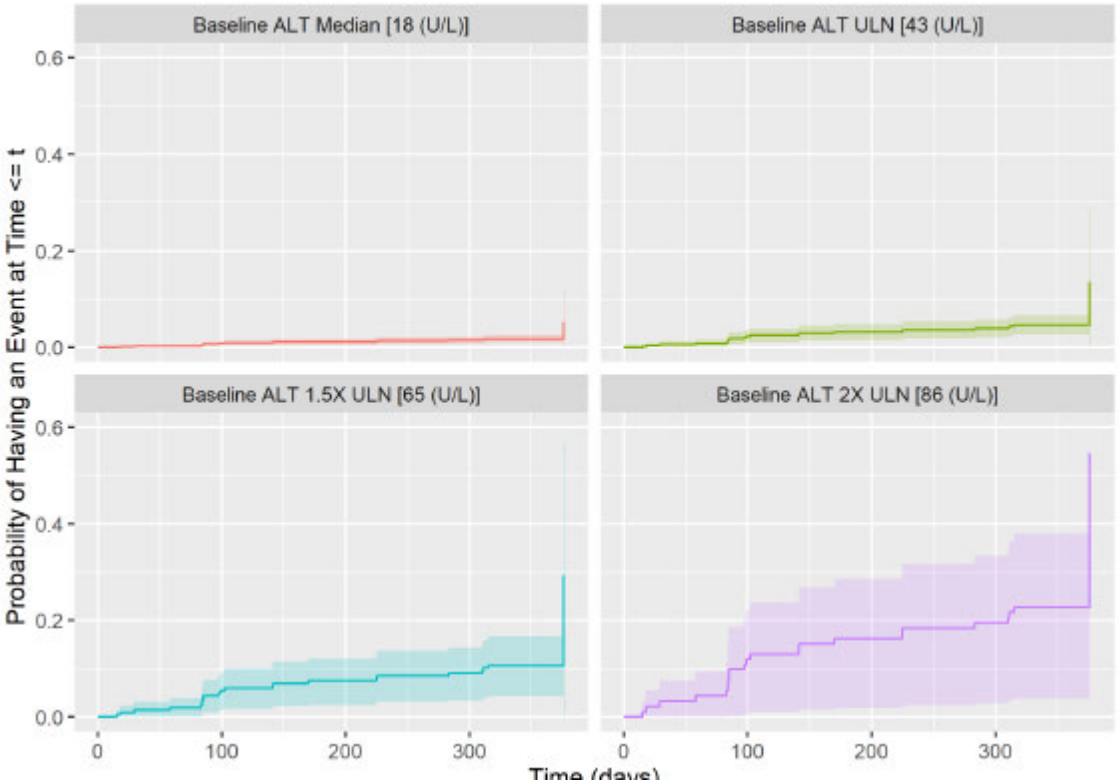
Figure 8 **Maximum Post-baseline AST and Maximum Change from Baseline AST in Studies 2693-CL-0301 and 2693-CL-0302 Over the 12-week Treatment Period Excluding AST Values > 600 U/L**



Source provided in the ER report

Applicant - Figure 21: Predicted Cumulative Distribution Function for Different Baseline ALT Values in Phase 3 Studies 2693-CL-0301 and 2693-CL-0302

Figure 21 Predicted Cumulative Distribution Function for Different Baseline ALT Values in Phase 3 Studies 2693-CL-0301 and 2693-CL-0302



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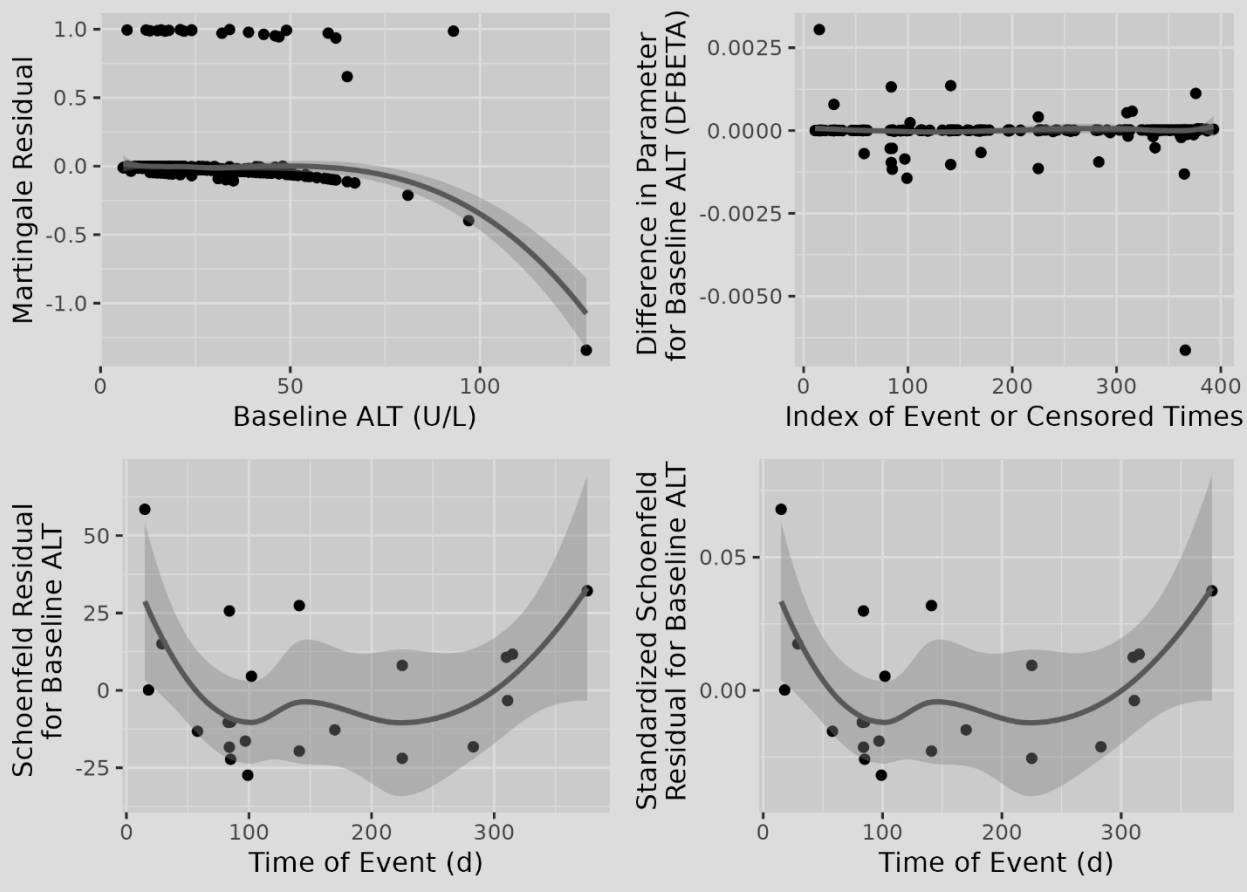
Applicant - Figure IV: Residual Plots for Cox PH Model Including Baseline ALT



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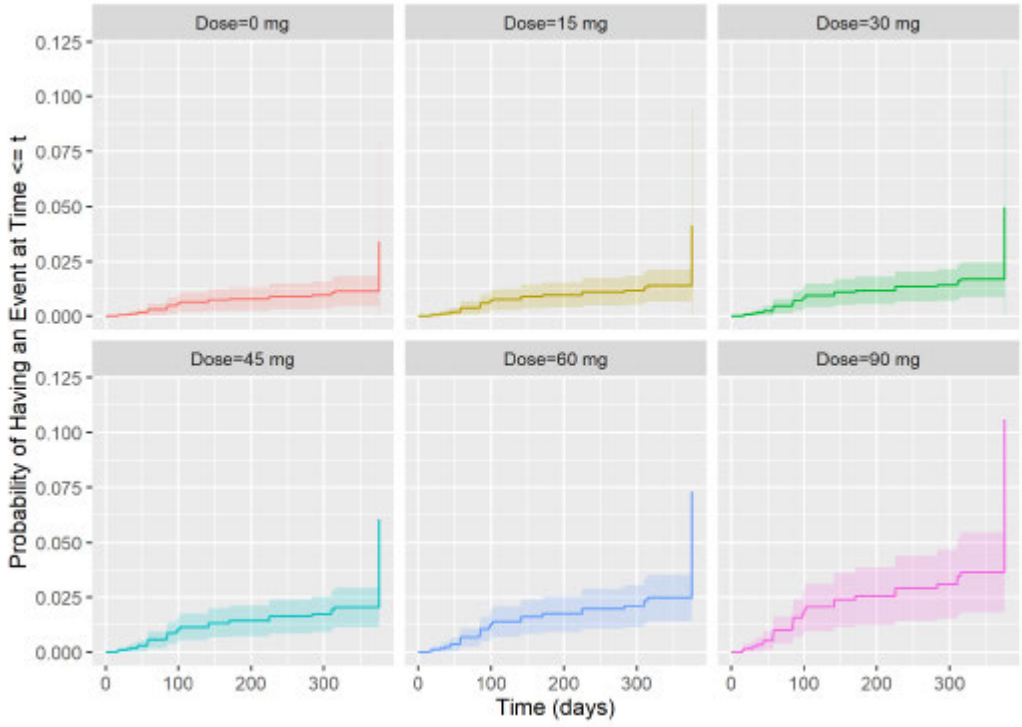
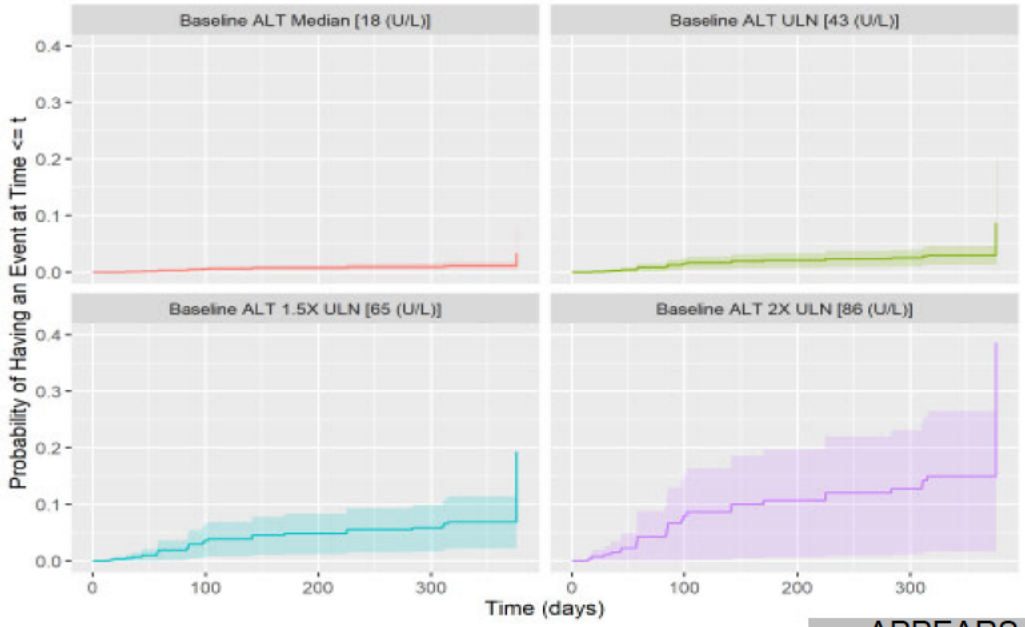
Applicant - Figure 22, 23, 24 and 25: Predicted Cumulative Distribution Function for Total Daily Dose Model with Baseline ALT at Different Fezolinetant Total Daily Dose/Cavg Levels

Figure 22 Predicted Cumulative Distribution Function for Total Daily Dose Model with Baseline ALT at Different Fezolinetant Total Daily Dose Levels



Note: Illustration of fezolinetant total daily dose effects with baseline ALT value of 18 U/L

Figure 23 **Predicted Cumulative Distribution Function for Total Daily Dose Model with Baseline ALT at Different Baseline ALT Values**



Note: Illustration of baseline ALT effects performed at fezolinetant dose level of 0 mg
x-axis limited to improve visualization of central tendency

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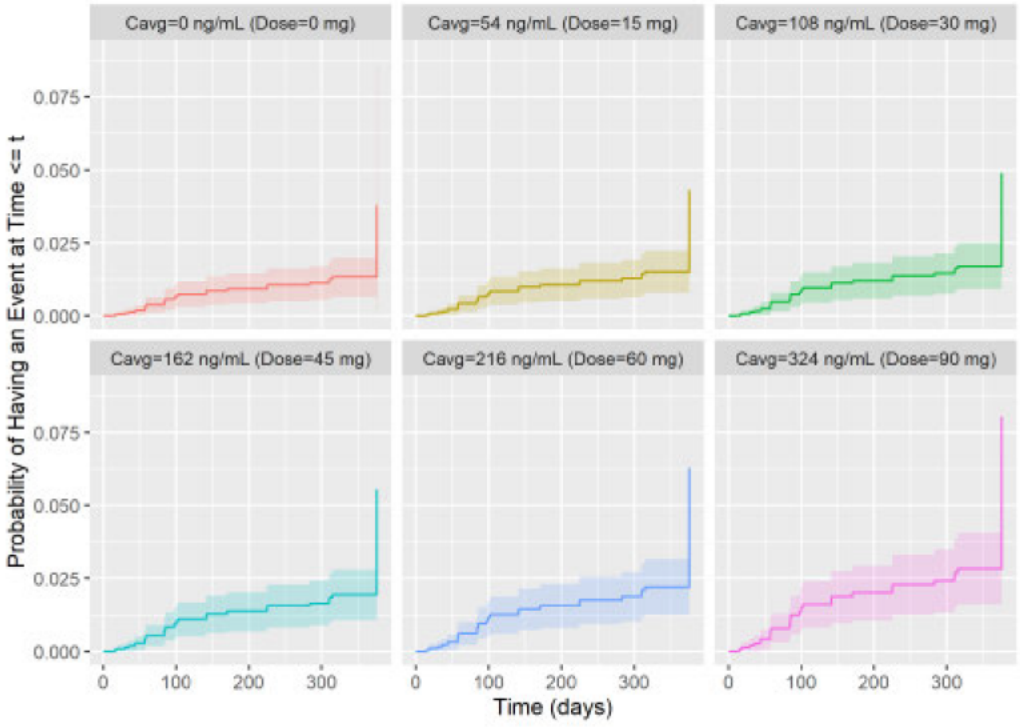
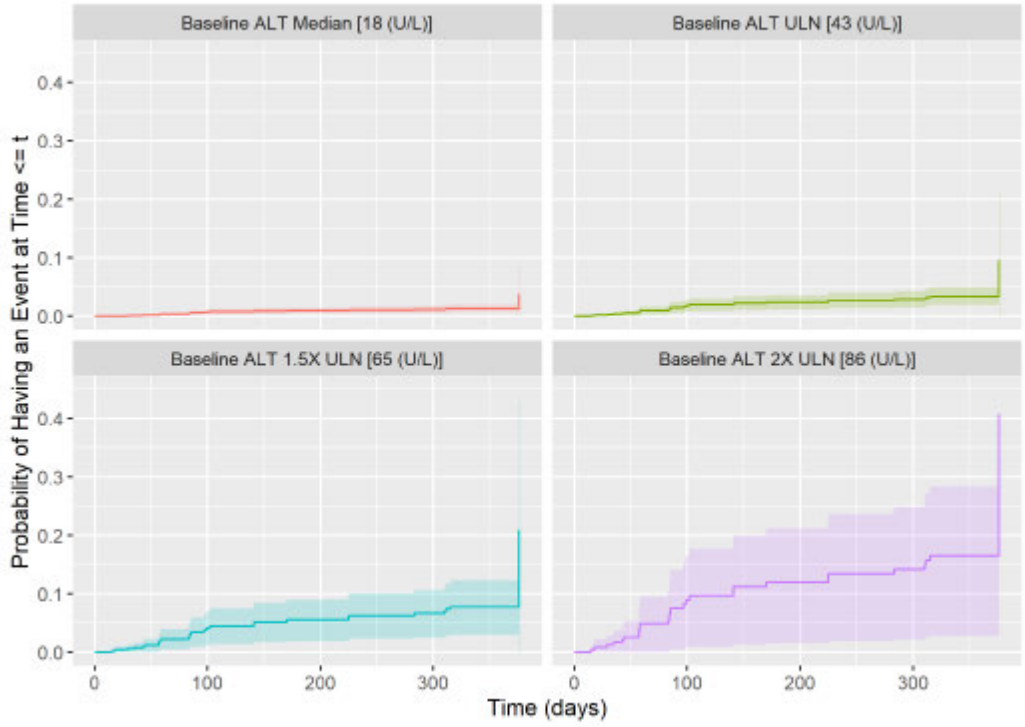
Figure 24 **Predicted Cumulative Distribution Function for Cavg Model with Baseline ALT at Different Steady-State Fezolinetant Cavg Values**



Note: Illustration of fezolinetant Cavg effects performed at baseline ALT value of 18 U/L

Figure 25 Predicted Cumulative Distribution Function for Cavg Model with Baseline ALT at Different Baseline ALT Values



Note: Illustration of baseline ALT effects performed at fezolinetant Cavg value of 0 ng/mL

Source provided in the ER report.

The Reviewer's Assessment:

The applicant's analyses results are considered acceptable for the purpose of supporting analyses objectives.

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/s/

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