CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219469Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 8, 2025

To: Samantha Bell, Regulatory Project Manager, Division of Urology, Obstetrics, and Gynecology (DUOG)

Marcea B. Whitaker, Clinical Reviewer, DUOG

From: Montherson L. Saint Juste, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for LYNKUET® (elinzanetant) capsules, for oral use

NDA: 219469

Background:
In response to DUOG's consult request dated August 6, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for LYNKUET® (elinzanetant).

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 26, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on July 15, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Montherson L. Saint Juste at 301-796-1200 or Montherson.SaintJuste@fda.hhs.gov.

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MONTHERSON L SAINT JUSTE
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 8, 2025
To:	Samantha Bell, BS, BA, RAC Regulatory Project Manager **Division of Urology, Obstetrics, and Gynecology (DUOG)**
Through:	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Montherson L. SaintJuste, PharmD, MS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LYNKUET (elinzanetant)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 219469
Applicant:	Bayer HealthCare Pharmaceuticals Inc.

1 INTRODUCTION

On July 26, 2024, Bayer HealthCare Pharmaceuticals Inc. submitted for the Agency's review an original New Drug Application (NDA) 219469 for LYNKUET (elinzanetant) capsules, for oral use. The purpose of this submission is to seek approval for the proposed treatment of moderate and severe vasomotor symptoms (VMS) associated with menopause.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Urology, Obstetrics and Gynecology (DUOG) on August 6, 2024, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LYNKUET (elinzanetant) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft LYNKUET (elinzanetant) PPI received on July 26, 2024, and received by DMPP and OPDP on September 24, 2025.
- Draft LYNKUET (elinzanetant) Prescribing Information (PI) received on July 26, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 24, 2025.
- Approved VEOZAH (fezolinetant) comparator labeling dated December 16, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
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MONTHERSON L SAINT JUSTE
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MARCIA B WILLIAMS
10/08/2025 12:50:30 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 24, 2025
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 219469
Product Name, Dosage Form, and Strength:	Lynkuet (elinzanetant) capsule, 60 mg
Applicant Name:	Bayer Pharmaceuticals, Inc. (Bayer)
FDA Received Date:	June 13, 2025
TTT ID #:	2024-10453-1
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Bayer Pharmaceuticals, Inc. submitted revised container labels and carton labeling received on June 13, 2025 for Lynkuet. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels and carton labeling for Lynkuet (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

In response to the Agency's container labels and carton labeling recommendations, Bayer Pharmaceuticals, Inc. (Bayer) incorporated most of the Agency's recommendations. However, Bayer did not agree with all the recommendations and provided their rationale for not accepting those recommendations.[b] We find Bayer's rationale acceptable.

Additionally, Bayer made minor editorial changes to the container labels and carton labeling. We find Bayer's changes to be reasonable. We did not identify any new medication error concerns associated with the proposed changes. As such, we have no additional recommendations at this time.

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[a] Patel, R. Label and Labeling Review for Lynkuet (NDA 219469). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 MAY 21. TTT ID: 2024-10453.

[b] Response to FDA's comments on the carton and container labeling dated May 27, 2025 (NDA 219469). Whippany (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2025 JUN 13. Available from: \\CDSESUB1\EVSPROD\nda219469\0029\m1\us\111-information-amendment\response-to-fda-labeling-comments-27may2025.pdf.

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STEPHANIE L DEGRAW
06/24/2025 10:30:31 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 21, 2025
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 219469
Product Name, Dosage Form, and Strength:	Lynkuet (elinzanetant) capsule, 60 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Bayer Pharmaceuticals Inc. (Bayer)
FDA Received Date:	7/26/2024, 10/23/2024, 10/29/2024
TTT ID #:	2024-10453
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 INTRODUCTION

As part of the approval process for Lynkuet (elinzanetant) capsules, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed Lynkuet Prescribing Information (PI), Patient Package Insert (PPI), container labels (trade and sample blister cards), and carton labeling (trade and sample) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219469.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Technical Drawings of the Blister Card	C
Applicant Proposed Prescribing Information Changes (Late-Cycle Meeting)	D

3 DISCUSSION: DOSAGE MODIFICATION

The proposed dosage for Lynkuet is 120 mg (2 capsules) once daily at bedtime. However, during the application review process, the Agency identified the need for a dosage modification for patients on concomitant moderate CYP3A4 inhibitors. The Agency recommended a dosage modification to Lynkuet 60 mg (one capsule) once daily at bedtime for patients concomitantly taking a moderate CYP3A4 inhibitor.

We determined the proposed packaging (five 12-count blister cards supplied in a 60-count carton) (b) (4) once daily dosage modification. Specifically, each blister cell contains two capsules, (b) (4) (b) (4) Both increase the risk of wrong dose and wrong storage medications errors for patients prescribed 60 mg once daily. We provided these concerns with the current labeling, packaging configuration, and blister card design in the Late-Cycle Meeting background package for the Applicant.[a]

On May 6, 2025, the Applicant provided a response for further discussion at the Late-Cycle Meeting,[b] which included additional information regarding the blister card design. Specifically, they noted the "bridge" within each blister cell separating the two capsules. Per the Applicant, the bridge "allows for the removal of only one capsule at a time while maintaining the second

[a] Late-Cycle Meeting Background Package (NDA 219469). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 APR 28. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807b3e93&showAsPdf=true

[b] Bayer Follow-up to the Late-Cycle Meeting Background Package (NDA 219469). Whippany (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2025 MAY 6. Available from: \\CDSESUB1\EVSPROD\nda219469\0027\m1\us\111-information-amendment\bayer-follow-up-response.pdf

capsule within the cavity". See Appendix C for images provided by the Applicant. Additionally, the Applicant provided stability data to support the storage of one capsule within open blister cell, and they have initiated a 7-day open dish storage study. In their response, the Applicant also proposed additional handling instructions for Section 16.2 and Section 17 of the Prescribing Information (PI). See Appendix D for the PI changes proposed by the Applicant.

We further evaluated the proposed labels and labeling based on the recommended dosage, modified dosage, and the Applicant's response. We find the Applicant's response reasonable, and with implementation of additional label and labeling recommendations noted below, find the proposed blister card packaging adequate for patients requiring a dosage modification.

4 CONCLUSION

The proposed Lynkuet Prescribing Information (PI), Patient Package Insert (PPI), container labels (trade and sample blister cards), and carton labeling (trade and sample) may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Urology, Obstetrics, and Gynecology (DUOG) in Section 5 and for Bayer Pharmaceuticals Inc. in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF UROLOGY, OBSTETRICS, AND GYNECOLOGY (DUOG)

A. Prescribing Information

1. Highlights of Prescribing Information

a. Dosage and Administration

i. We recommend expressing the dosage as the total amount in milligrams before the number of capsules. For example, revise the dosage statement to read "The recommended dosage is 120 mg (two 60 mg capsules) orally once daily at bedtime with or without food."

ii. To ensure capsules are administered correctly, we recommend adding additional statements that read "Swallow capsules whole. Do not open, crush, or chew capsules." to reflect the administration information in Section 2.1.

2. Section 2 Dosage and Administration

a. As currently presented, the dosage (i.e., 120 mg) is presented before the proprietary name. To prevent confusion, we recommended revising the dosage statement to "The recommended dosage of LYNKUET is 120 mg…"

b. To ensure all pertinent dosage information is not overlooked and to prevent wrong schedule errors, we recommend adding "at about the same time each day" to the end of the recommended dosage sentence.

c. To ensure capsules are administered correctly and not opened for administration, we recommend modifying the sentence "Do not cut, crush or chew capsules", so it reads "Do not open, crush, or chew capsules."

3. Section 16 How Supplied/Storage and Handling

   a. This section lists (b) (4) (b) (4) the trade carton NDC (the saleable unit) is required in this section. To prevent confusion, we recommend removing (b) (4) (b) (4) and the corresponding (b) (4)

   b. It is not clear how many capsules are supplied in one carton. For clarity, we recommend revising the first bullet in Section 16 to read: 60-count carton containing 5 blister cards (5 x 12 capsules) (NDC 50419-475-05).

   c. As currently presented, the package type terms "blister card" and (b) (4) (b) (4) are both used on labels and labeling. Consistent use of the correct package type term may prevent confusion. We recommend using the package type term "blister card" in Section 16 and across all labels and labeling.

4. Section 17 Patient Counseling

   a. "Important Administration Instructions" includes (b) (4) information (i.e., "… (b) (4) …"). This does not encompass all potential (b) (4) (b) (4) therefore may lead to confusion and (b) (4). Remove (b) (4) See also recommendation 4b below.

   b. The advice under "Important Administration Instructions" states to take Lynkuet "at bedtime" but does not include a specific frequency of administration as stated in Section 2 of the PI. To minimize the risk of wrong frequency of administration errors, we recommend revising the sentence to "Advise patients to take LYNKUET once daily at bedtime…"

   c. To ensure the capsules are administered correctly and not opened for administration, we recommend modifying the second sentence, so it reads "Do not open, crush, or chew capsules."

B. Patient Package Insert (PPI)

1. The phonetic spelling in the PPI ((b) (4)) does not align with the phonetic spelling submitted for the proprietary name review (lin kew et'). Revise the phonetic spelling to lin kew et' to reflect the accurate, intended pronunciation of Lynkuet.

2. The "How should I take LYNKUET?" section of the Patient Information contains (b) (4) Patients should

follow the dosing regimen prescribed by the healthcare provider. We recommend removing [redacted] (b) (4)

3. The "How should I take LYNKUET?" section of the Patient Information states to take Lynkuet "at bedtime" but does not include a specific frequency of administration as stated in Section 2 of the PI. Additionally, this important information is at the end of the sentence and may be overlooked. To minimize the risk of wrong frequency of administration errors, we recommend revising the second bullet to "Take LYNKUET once daily at bedtime about the same time each day.", and adding another bullet underneath about food (i.e., "Take LYNKUET with or without food.").
4. To ensure capsules are administered correctly and not opened for administration, we recommend revising the information in the third bullet under "How should I take LYNKUET" to "Swallow capsules whole with water. Do not open, crush, or chew capsules."
5. For missed doses, the information provided only includes instructions for patients who are taking 120 mg (2 capsules). We recommend revising this information to encompass all dosing scenarios and to align with the PI. For example, "If you miss a dose of LYNKUET at bedtime, take the next dose as scheduled the following day. Do not take two doses on the same day to make up for a missed dose."

C. Applicant Proposed Prescribing Information Changes (Late-Cycle Meeting)

1. The proposed language for Section 16.2 and Section 17, uses the term [redacted] (b) (4) [redacted] (b) (4) However, this does not align with the language used in Section 2 and Section 16. We recommend revising the term [redacted] (b) (4) to "dosage modification (i.e., one 60 mg capsule once daily)" and revising the term [redacted] (b) (4) to "blister card".
2. Storage instructions in Section 16.2 may be improved to prevent patients from misplacing capsules. We recommend revising the 2nd sentence to read (changes in bold) "Store the remaining capsule in the original blister card in the carton until the next dose."
3. Section 17 does not include storage instructions for the capsule remaining in the blister cell. To prevent patients misplacing capsules and wrong storage errors, we recommend adding this information to Section 17. For example (changes in bold),

> Instruct patients requiring a dosage modification (i.e., one 60 mg once daily) to partially peel back the foil covering of the blister cell to expose only one of the two capsules. Instruct patients to store the remaining capsule in the original blister card in the carton until the next dose [see Storage and Handling (16.2)].

6 RECOMMENDATIONS FOR BAYER PHARMACEUTICALS INC.

A. Container (Trade and Sample Blister Card) Labels

1. The container labels include the dosage statement [redacted] Remove this statement from the container labels. However, maintain the statement "60 mg per capsule" on each blister cell to ensure the strength per capsule is clearly identified. Consider enlarging this statement as space allows.

B. Carton Labeling (Trade and Professional Sample)

1. As currently presented, the strength does not have adequate legibility, impacting the readability of this important information. Additionally, the strength per capsule is expressed with an error prone symbol (i.e., | or a vertical bar). Certain abbreviations, acronyms, and symbols should not be used on container labels or carton labeling because they are frequently misinterpreted and can lead to medication errors. We recommend the following regarding the strength:

    a. Improve the readability of the strength. You may consider a different, bolder, and/or larger font, elongating the font height, or other means to achieve this.

    b. Replace the vertical bar with the intended meaning "per".

2. The carton labeling includes the dosage statement [redacted] on the principal display panel (PDP). [redacted] Remove this statement from the trade and sample carton PDP.

3. As currently presented, the package type terms "blister card", [redacted] and "card" are all used on carton labeling. Consistent use of the correct package type term may prevent confusion. We recommend using the package type term "blister card" across all labels and labeling.

4. To ensure the capsules are administered correctly and not opened for administration, we recommend adding the statements "Swallow capsules whole. Do not open, crush, or chew capsules." to the PDP or side panel of the trade and sample carton labeling. To avoid [redacted], the statement [redacted] in the recommended dosage statement may be removed from the side panel (see also recommendation 5 below).

5. The recommended dosage statement on the side panel [redacted]

[redacted] (b) (4) We recommend revising this statement to read "Recommended Dosage: see Prescribing Information."

6. The proposed carton labeling contains the storage statement [redacted] (b) (4) however, this statement is not present in subsection 16.2 of the Prescribing Information. Consistent storage information across all labels and labeling may help to minimize confusion and storage errors. We recommend removing the statement [redacted] (b) (4) from the storage statement on carton labeling as the storage temperature range, excursion temperature range, and USP controlled room temperature statement present on the carton provides sufficient storage condition information.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Lynkuet received on July 26, 2024 from Bayer Pharmaceuticals Inc.

Table 2. Relevant Product Information for Lynkuet	
Initial Approval Date	N/A
Active Ingredient	elinzanetant
Indication	The treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.
Dosage Form	capsule
Strength	60 mg
Route of Administration	oral
Dose and Frequency	120 mg LYNKUET (two 60 mg capsules) orally once daily at bedtime.
How Supplied	Carton of 60 capsules (5 blister cards with 12 capsules per blister card)
Storage	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	Foil blister packaging that includes a (b) (4) layer and is (b) (4) (b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Lynkuet labels and labeling submitted by Bayer Pharmaceuticals Inc.

- Prescribing Information received on October 23, 2024, available from \\CDSESUB1\EVSPROD\nda219469\0007\m1\us\114-labeling\draft\labeling\elinzanetant-uspi-23oct2024-clean.docx
- Patient Package Insert received on July 26, 2024, available from \\CDSESUB1\EVSPROD\nda219469\0001\m1\us\114-labeling\draft\labeling\elinzanetant-patient-package-insert.docx
- Trade and professional sample container labels (blister cards) received on October 29, 2024
- Trade and professional sample carton labeling received on October 29, 2024

B.2 Container Labels and Carton Labeling Images

Trade Container Label (Blister card) Professional Sample Label (Blister card)

(b) (4)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Drug Induced Liver Injury Team

Division of Hepatology and Nutrition (DHN)
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration

NDA	219469
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Elinzanetant
Indication	Vasomotor symptoms of menopause
Applicant	Bayer
Requesting Division	Division of Urology, Obstetrics and Gynecology (DUOG)
Primary Reviewer	Ling Lan, MD, PHD Clinical Analyst, OND/DHN
Secondary Reviewers	Paul H. Hayashi, MD, MPH, Associate Director, OND/DHN
Pharmacology & Non-clinical Reviewer	Edwige Chiogo Vouffo, PharmD, PhD Non-clinical analyst, OND/DHN
Clinical Data Scientist Reviewer	Aaron Waddell, PhD, Expert Consultant, DRT Strategies, Inc., OND/CDER
National Center for Toxicological Research (NCTR) Reviewer	Minjun Chen, PhD, Senior Staff Fellow, Division of Bioinformatics and Biostatistics, NCTR
Reviewer Office of Pharmacoepidemiology	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Paul H. Hayashi, MD, MPH, Associate Director of DILI (DHN)
Assessment Date	May 12, 2025

Context: Elinzanetant (EZN) is an oral, small-molecule drug that inhibits NK-1 and NK-3 receptors. The indication for this NDA is vasomotor symptoms (VMS) of menopause. Activation of the kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the arcuate nucleus in the hypothalamus is thought to cause VMS, and EZN is designed to inhibit KNDy neurons via blockade of the neurons' NK-1 and NK-3 receptors. The Division of Urology and Gynecology (DUOG) first consulted the DHN DILI Team on Sep 21, 2022, regarding non-clinical data suggesting hepatotoxicity risk and elevated liver enzymes seen in phase 1 and 2 trials (IND 129492). The DILI Team considered protocol changes largely adequate and made non-hold recommendations only (Consult note attached). In May 2023, fezolinetant (FZT), another oral NK-3 inhibitor, was approved under NDA 216578 for the same indication as EZN. The DILI Team's consult for that NDA is also attached. FZT was labeled for hepatotoxicity under Warnings and Precautions and then updated with a Box Warning based on post-market cases of DILI leading to jaundice. Shortly after receipt of the EZN NDA (21946) on Jul 26, 2024, DUOG reconsulted the DILI Team for opinion of DILI risk and labeling recommendations in the context of the

non-clinical data supporting a hepatotoxicity risk and the concern for a DILI class effect raised by FZT's hepatotoxicity.

Executive Summary: We did not find clinically significant hepatotoxicity with elinzanetant (EZN). Despite marked non-clinical evidence for hepatotoxicity risk, EZN did not cause substantial DILI in the pivotal trials; there were only two liver injury cases attributable to EZN with more than 50% likelihood across the entire development program. These two DILIs were hepatocellular but relatively modest in severity and recovered fully. There were no cases meeting Hy's law. Nevertheless, by our estimates, only about 1500 women may have received EZN under phase 2 or 3 protocols where exposure times were more than just a few days or weeks. The number of women who may be prescribed this drug post-market is substantially higher, so clinically significant liver injury could still arise in a larger population. Furthermore, the risk tolerance for fatal or life-threating liver injury is low due to the targeted disease, which has substantial morbidity but low risk of mortality. It is unclear why the EZN non-clinical data is more concerning for DILI compared to the non-clinical data for fezolinentant (FZT), another NK inhibitor already marketed. FZT had more severe and frequent DILI in its NDA and has had substantial DILI cases post-market. Thus, based on the FZT experience (possible drug class effect); two hepatocellular DILI cases with EZN, albeit modest severity, and risk to benefit considerations, we conclude that labeling should reflect the potential for hepatocellular DILI in Warnings and Precautions with recommendations for baseline liver blood tests and consideration given for periodic monitoring. Our detailed assessment and full recommendations are in this consult's **Section 5**.

Consultation Sections:

Abbreviations:
ADME: absorption, distribution, metabolism, excretion
ALP or AP: alkaline phosphatase
ALT: alanine aminotransferase
AP: alkaline phosphatase
AST: aspartate aminotransferase
AT: aminotransferase (ALT and/or AST)
BMI: body mass index
CPK or CK: creatine phosphokinase
CT: computerized tomography
CYP: cytochrome P450
DB: direct bilirubin
DDI: drug-drug interaction

DILI: drug-induced liver injury
EZN: Elinzanetant
FAERS: FDA Adverse Events Reporting System
FZT: fezolinetant
GGT: gamma-glutamyl transferase
HAV: hepatitis A virus
HBV: hepatitis B virus
HCV: hepatitis C virus
KNDy: kisspeptin/neurokinin B/dynorphin
IP: investigational product
MASLD: metabolic dysfunction associated steatotic liver disease
NCTR: National Center for Toxicological Research
R-value: ALT/ULN ÷ ALP/ULN
TB: total bilirubin
US: ultrasound
ULN: upper limit of normal
VMS: vasomotor symptoms

1.0 Target Disease and Rationale

1.1 Target Disease: Menopause occurs at a median age of 51.4 years, though early menopause can occur in a woman's 40's or sooner.[1] Over 1 billion women will be older than 50 by 2030, worldwide.[2] While 75-85% may have vasomotor symptoms (VMS) of some degree, perhaps half will be of moderate to severe intensity causing decline in quality of life and daily activities. VMS of menopause are due to changes in gonadal hormones and disruption of the tightly controlled temperature circuit that result in exaggerated heat-loss responses.[3] The estimated number of women in the US alone with this condition is 40-50 million.[4] VMS persist for a median duration of seven years and significant comorbidities have been associated with it including cardiovascular disease, bone disease, and cognitive complaints. Some factors influencing the risk of developing and duration of VMS are lower socioeconomic status, African American race, smoking, decreased mood.[5]

Reproductive hormone changes are relevant to VMS, as higher follicle stimulating hormone, and lower estradiol are drivers of VMS. However, all women experience such hormonal changes with menopause, but not all have VMS, suggesting other factors in VMS pathophysiology.[6] Nevertheless, hormone therapy is the most effective treatment.

[1] UpToDate. Clinical manifestations and diagnosis of menopause - UpToDate (accessed Oct 18, 2021)
[2] World Health Technical Report Series. WHO (1996) DOI:10.13140/RG.2.1.3318.4404
[3]Deecher DC and Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. *Arch Womens Ment Health*. 2007;10(6):247-57. DOI: 10.1007/s00737-007-0209-5
[4] Utian WH (2005) Psychosocial and Socioeconomic Burden of Vasomotor Symptoms in Perimenopause: A Comprehensive Review. Health and Quality of Life Outcomes, 3, 47. http://dx.doi.org/10.1186/1477-7525-3-47
[5] Khan SJ *et al*. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. *Int J Womens Health.* 2023 Feb 14;15:273-287. doi: 10.2147/IJWH.S365808
[6] Thurston RC. Vasomotor symptoms: natural history, physiology, and links with cardiovascular health. *Climacteric*. 2018 Apr;21(2):96-100. doi: 10.1080/13697137.2018.1430131

It can reduce symptom frequency and intensity by as much as 90%.[7] Limitations to VMS's hormonal therapy are substantial, though. They include contraindications for women with coronary artery disease, stroke, and unprovoked venous thromboembolism. Also, uterine bleeding and breast pain are prominent adverse effects of hormonal therapy.[8] Thus, the need for medications with better safety profiles and fewer contraindications remains.

1.2 Rationale for Drug Use: EZN is under development as an oral, gelatin capsule at the recommended dose of 120 mg (two 60 mg capsules daily).[9] It is the first dual, selective, non-hormonal neurokinin 1 and 3 (NK-1, NK-3) receptor antagonist that blocks both NK-1 and NK-3 signaling on kisspeptin/neurokinin B/dynorphin (KNDy) neurons.[10] These neurons are involved in thermoregulation with activation leading to sweating, vasodilation, and heat dissipation, all typical components of VMS. Estradiol has a modulatory effect on KNDy activity thus helping to prevent VMS prior to menopause. However, with menopause-associated decline in estradiol, KNDy neurons are less inhibited, thus precipitating VMS (**Figure 1**). This mechanism underlies a rationale to develop drugs that inhibit KNDy neurons by blocking NK-1 and NK-3. [11] The Applicant cites animal studies that support this pathophysiologic pathway and control of hot flashes using NK3 receptor antagonism. Early clinical reports suggest that infusion of neurokinin-B (NK-B) can induce hot flashes.[12]

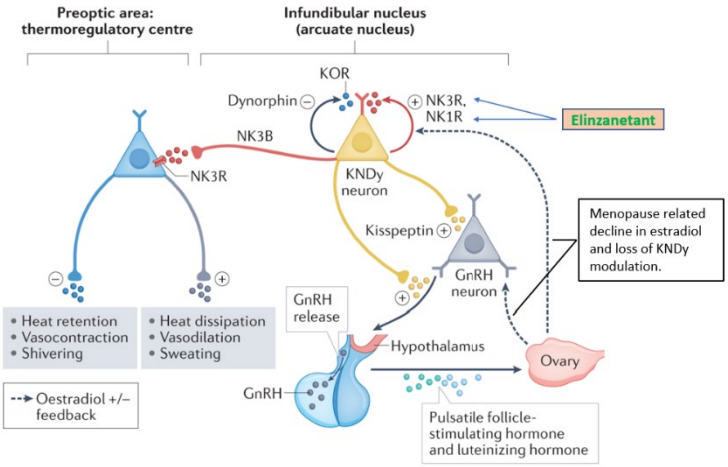


Figure 1: Elinzanetant mechanism of action[13]

2.0 Human ADME and DDI data pertinent to DILI

2.1 Structure: The structural formula is shown in **Figure 2**. The labeled dose and route of administration are 120 mg a day taken orally (60 mg twice daily).

[7] Khan SJ, Kapoor E, Faubion SS, Kling JM. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. *Int J Womens Health*. 2023 Feb 14;15:273-287. doi: 10.2147/IJWH.S365808
[8]Khan SJ *et al*. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. *Int J Womens Health*. 2023 Feb 14;15:273-287. doi: 10.2147/IJWH.S365808
[9] NDA219469 (219469 - 0006 - (6) - 2024-08-30 - ORIG-1 /Non-Clinical/Non-Clinical Information) - Introduction
[10] Simon JA *et al*. Efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist for vasomotor symptoms: a dose-finding clinical trial (SWITCH-1). *Menopause*. 2023 Mar 1;30(3):239-246. doi: 10.1097/GME.0000000000002138
[11] Carson E *et al*. Cooling the flames: Navigating menopausal vasomotor symptoms with nonhormone medications, *American Journal of Health-System Pharmacy*, 2024; zxae254, https://doi.org/10.1093/ajhp/zxae254
[12]Jayasena C *et al*. Neurokinin B Administration Induces Hot Flushes in Women. *Sci Rep*. 2015; 5, 8466 https://doi.org/10.1038/srep08466
[13] Adapted from: Davis SR and Baber RJ. Treating menopause — MHT and beyond. *Nat Rev Endocrinol* 18, 490–502 (2022). https://doi.org/10.1038/s41574-022-00685-4

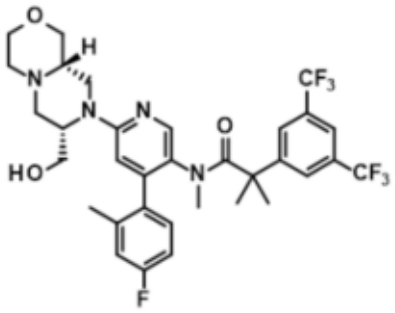


Figure 2: Chemical structure of Elinzanetant [14]

2.2 Absorption: Following oral administration of EZN in fasted state T_{max} was 1 to 1.5 hours. There was a trend toward increase in T_{max} with increase in the dose, suggesting a prolonged absorption phase with increasing dose. The absolute bioavailability of EZN after oral dosing was 52%. Systemic exposure (AUC) increased disproportionately to dose increases. Accumulation ratios ranged from 1.4 to 2.3 following repeat administration. Thus, there is a rapid and moderate absorption of EZN and potential for some accumulation.

2.3 Distribution: EZN is highly plasma protein bound (99.7%). The volume of distribution at steady state was 137 L indicating moderate distribution to tissues.

2.4 Metabolism: EZN is metabolized predominantly by CYP3A4. Following single and repeat dosing, parent EZN accounts for 39% of the total drug radioactivity in human plasma. The three main metabolites have similar pharmacological activity as the parent drug. There was evidence of metabolic autoinhibition with slight but consistent time-dependent increase in exposure across all dose groups. The minimum mean time-dependent increase was 13% on day 7 at 90 mg dosing while the maximum of 61% occurred after 14 days dosing at 30 mg. Hence, metabolic autoinhibition occurred that could lead to time-dependent increase in exposures.

2.5 Excretion: EZN is eliminated from plasma mainly by CYP3A4-mediated oxidative biotransformation. The median terminal $T_{1/2}$ was 45 hours after multiple dosing of 120 mg. Following oral administration of [^{14}C] EZN to six human participants, total recovery from each participant was 89.2% to 92.0% up to 480 hours post dose. Nearly all the radioactivity was recovered in feces (88.0 to 91.2%) with small amounts (0.22 to 0.85%) in urine up to 384 hours post dose. The majority of excretion occurred within 72 hours. EZN was the predominant (~50% of the dose) component in feces, probably from unabsorbed drug. Metabolites found in feces covered about 40% of the dose. Thus, EZN has a long $T_{1/2}$ and is eliminated in feces.

High level ADME summary findings are in **Table 1**.

Table 1: ADME summary table[15]

Item	Finding
Absorption	Rapid, Tmax: 1-1.5 hours
Distribution	High plasma protein binding
Metabolism	CYP3A4, autoinhibition
Elimination	Route(s): Feces and $T_{1/2}$ estimate: 45 hours

[14] NDA219469 (219469 - 0006 - (6) - 2024-08-30 - ORIG-1 /Non-Clinical/Non-Clinical Information) - Introduction
[15] Table made by DILI Team

2.6 Drug-Drug Interactions (DDI):

2.6.1 *EZN as a victim*: EZN is a weak and consistent inhibitor (<2-fold) of CYP3A4 making EZN a victim of its own CYP inhibition. Other moderate and strong CYP3A4 inhibitors may decrease clearance leading to an increase in EZN levels. Therefore, coadministration of EZN with strong CYP3A4 inhibitors is not recommended. EZN inhibited CYP2C8 with IC50: 3.5 μM. CYP3A4 inducers may decrease drug exposure and alter efficacy.

2.6.2 *EZN as a perpetrator*: No clinically relevant induction of CYP1A2 following multiple dosing of EZN, but there was induction of CYP3A4, CYP2B6, and CYP2C19. EZN a weak CYP3A4 inhibitor.

There was no significant clinically relevant interaction with other human CYP enzymes tested including CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 2J2. In vitro, EZN is a weak to moderate inhibitor P-gp, BCRP, MATE1, BSEP, OATP1B1, and OATP1B3 with IC50 of 0.22, 0.08, 0.55, 2.13, 0.69, and 0.25 μM, respectively. Inhibition of UGT1A1 by EZN and its main metabolites also occurred. Drugs pertinent to potential DDI with EZN are in **Table 2.**

Table 2: Common CYP inhibitors relevant to EZN [16],[17] Commonly used medications and substances are highlighted.

CYP	Level of inhibition and drug names
3A4	**Strong:** itraconazole, ketoconazole, posaconazole, clarithromycin, cobicistat, ritonavir, telithromycin, voriconazole, danoprevir and ritonavir, lopinavir and ritonavir, ceritinib, nefazodone, nelfinavir
	Moderate: aprepitant, ciprofloxacin, clotrimazole, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, diltiazem, verapamil, isavuconazole, conivapant, crizotinib, dronedarone, grapefruit juice,

3.0 Non-clinical data

3.1 In vitro data There was increased inhibitory effect of CYP3A4 following incubation with human liver microsomes with NADPH compared to without NADPH, suggesting time dependent inhibition of CYP3A4. There was also irreversible CYP3A4 inhibition by EZN and its main three metabolites in a dilution assay. Two glutathione conjugates (+14 Da and +30 Da species) of phase I metabolites of EZN appeared following incubation of EZN with human liver microsomes in the presence of glutathione and NADPH-generating system. According to the Applicant, the glutathione adducts were not detected at substantial amounts after incubation of EZN with human and animal hepatocytes nor in vivo plasma and excreta from rat, monkeys, and humans.

[16] https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2

[17] Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively

EZN logP ratio which reflects lipophilicity was over three, suggesting an increased risk of DILI. EZN inhibits the BSEP transporter which has also been associated with DILI risk. A summary of in vitro data related DILI risk is in **Table 3.**

3.2 Animal data

NOAEL was 200 mg/kg/day in mice following a 4-week experiment. Following a 13-week toxicity experiment, NOAEL was 100 mg/kg/day in rats and 80 mg/kg/day in monkeys following a 39-week administration. EZN's maximum clinical dose is 120 mg/day, or 1.3 and 1.5 mg/kg/day for an average adult US male (average weight, 91 kg) and female (average weight, 78 kg).[18]

In a four-week toxicity study in mice, there was treatment-related macroscopic findings of discolored liver lobes correlating with microscopic microvesicular vacuolation. On day 29, there was EZN related, minimally higher total bilirubin levels reaching ≥ 150 mg/kg/day.

In a 13-week toxicity study in rats, there was grade 1 mononuclear cell infiltration and focal vascular lymphocytic infiltration with hemorrhage (inflammation) and biliary hyperplasia at 100 mg/kg/day. Minimal to marked increase in total bilirubin occurred without correlation to microscopic findings. There was increase in aminotransferases and bilirubin at ≥ 120 mg/kg/day with liver hypertrophy and abnormal liver coloration. Mild necrosis occurred at 300 mg/kg/day. In a long-term carcinogenicity study in rats, there was EZN associated increased incidence and/or severity of biliary hyperplasia, biliary cysts, and multinucleated hepatocytes at 60 mg/kg/day.

Following a 39-week study in monkeys, there were increases in ALT at weeks 13 and 26 (2.5-fold) and 39 (3.6-fold), elevated ALP, liver enlargement at 80 mg/kg/day. Microscopic findings were limited to sinusoid compression.

Summary of non-clinical findings related to DILI risk is in **Table 3**.

Table 3: Summary of non-clinical data pertaining to DILI risk [19]

Item	Finding
In Vitro Studies	
Major CYPs or UGTs	CYP3A4
Reactive metabolites (i.e., glutathione trapping)	+14 Da and +30 Da species in human liver microsomes
Mitochondria studies/inhibition	Not assessed
Time dependent inhibition	Yes, for CYP3A4
LogP (lipophilicity) values >3 associated with increased DILI risk	5.75
Covalent binding	Irreversible CYP3A4 inhibition by EZN and its three main metabolites

[18] https://www.cdc.gov/nchs/fastats/body-measurements.htm
[19] Table made by DILI Team

Transporter inhibition (BSEP or MRP2 inhibition may increase risk of DILI)	Yes, for BSEP; No for MRP2
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	Increase transaminase and bilirubin in rats; increase ALT and ALP in monkeys
Liver histopathology findings (animal species)	Biliary hyperplasia & inflammation (rats); mild necrosis (rats)

In summary, non-clinical data suggest hepatotoxicity potential for EZN. There was autoinhibition of CYP3A4 and covalent binding with potential neoantigen formation via reactive metabolites. There was also BSEP inhibition. In animals, increased in liver markers and microscopic findings of biliary hyperplasia and inflammation occurred. However, there was no necrosis.

3.3 National Center for Toxicological Research (NCTR) Summary We consulted Minjun Chen, PhD and his group at the Agency's NCTR to evaluate the hepatotoxicity risk of EZN in comparison to fezolinetant. Their full report appears in the **Attachment** to this consult. We provide excerpts on methodology, their conclusions, and summary data (**Table 4**).

Methodology overview (see **Attachment** for full report)*:*

"We applied "rule-of-two" (RO2)[20] and DILIscore[21] models to evaluate the risk for DILI in humans. RO2 is a model developed by the FDA's NCTR to alert for potential risk of drug-induced liver injury (DILI) in humans. When an oral medication is given 100mg/day and above and its logP (the measure of lipophilicity) is ≥ 3, it will be RO2 positive; otherwise, negative. The logP is calculated from the chemical structure of the evaluated drug using AlogP online tool (http://www.vcclab.org/web/alogps/). The RO2 positives are associated with a higher risk of DILI in humans. The performance of RO2 is evaluated based on 164 FDA approved drugs: positive predictive value (PPV): 96%; negative predictive value (NPV): 39%; sensitivity: 38%; specificity: 96%; The AUC of receiver operating characteristic (ROC) curve: 0.668; Matthews correlation coefficient (MCC): 0.342.

DILIscore is another DILI model developed by NCTR to provide a quantitative assessment of risk of clinical DILI by calculating the contribution of daily dose/Cmax, logP, and the formation of reactive metabolites. The formation of reactive metabolites can be determined by the time-dependent inhibition, GSH trapping, or covalent binding. The DILIscore of >6 is defined as high DILI risk and 3-6 as moderate DILI risk and <3 low DILI risk. The performance of DILIscore is evaluated based on 337 FDA approved drugs with AUC of ROC curve of 0.904."

Conclusion (see Attachment for full report)
"Elinzanetant is high lipophilicity (logP =4.47) and is given at a high daily dose (120 mg/day) and can generate reactive metabolites (positives in TDI and GSH adducts). It is RO2 positive and has a moderately high DILIscore of up to 6.75, suggesting the

[20] Chen M, et al. High Lipophilicity and High Daily Dose of Oral Medications Are Associated with Significant Risk for Drug-Induced Liver Injury. *Hepatology*. 2013; 58:388-396.
[21] Chen M, et al. A Model to Predict Severity of Drug-Induced Liver Injury in Humans. *Hepatology*. 2016; 63:931-940.

potential risk for DILI associated with the use of Elinzanetant in humans. If possible, reducing dosages from 120 mg/day to 60 mg/day could decrease the DILIscore to 6.34, which will be close to the low-end of threshold for high risk (6.0).”

Table 4: RO2 and DILIscore analysis for of Fezolinetant and Elinzanetant

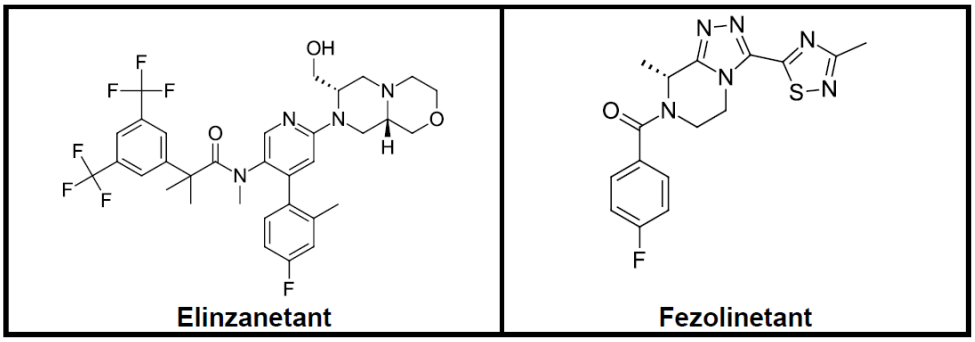
	Fezolinetant	Elinzanetant
Daily dose (mg/day)	45	120
logP	1.15	4.47
Reactive metabolite (RM) formation	TDI negative	TDI positive
RO2 test	Negative	positive
DILIScore	5.41 (if RM =YES) 2.58 (if RM = NO)	6.76

TDI: Time dependent inhibition
^ <3 = low DILI risk, >6 = high DILI risk

3.4 Computational Toxicology Consultation Service (CTCS) Consult Summary

DILI team consulted CTCS to assess potential hepatobiliary toxicity related to EZN (NK-1,3 receptor antagonist) and fezolinetant (NK3 receptor antagonist) using Quantitative Structure-Activity Relationship (QSAR) models. They concluded that there is limited structural similarity between EZN and fezolinetant (**Figure 3**). The team identified a more structurally relevant drug, netupitant (NK1 receptor antagonist), as a comparator to EZN. Netupitant shares substructural features with EZN and does not have known hepatotoxicity in its FDA label.

CTCS concluded that *“(Q)SAR predictions do not support the conclusion that clinical observations of elevated liver enzymes reported for fezolinetant should also be expected for elinzanetant.”*



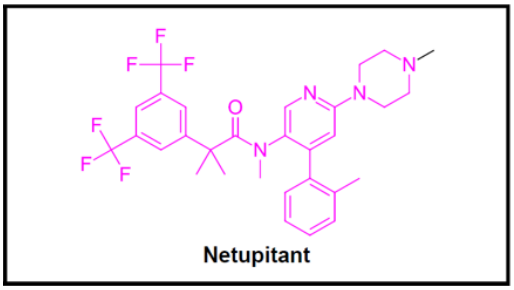


Figure 3. Structural Formulas for Elinzanetant, Fezolinetant, and Netupitant.[22]

4.0 Clinical data:

4.1 In class or near class data: We assessed several market drugs that target NK-1 or NK-3 receptors for DILI liability using labeling, LiverTox, FAERS, and PubMed data.

4.1.1 *Labeling Data*: We summarize package insert data for marketed drugs with similar mechanism of action as EZN in **Table 5**. Only fezolinetant approved in 2023 and aprepitant are substantially labeled for hepatotoxicity with the former having a Box Warning.

Table 5: Approved neurokinin 1 (NK-1), or NK-3 receptor antagonist and near class drugs with DILI information by label

Drug (Brand), Target Disease(s)	**Mechanism of action**	**Approval year**	**Labeling regarding DILI in** • Box Warning (BW) • Warnings/Precautions, Highlights (W/P, HL) • Adverse Reactions, Highlights (AR, HL) • Sections 5 & 6 (S5 & S6)
Fezolinetant (VEOZAH®) Vasomotor symptoms	neurokinin 3 (NK3) receptor antagonist	2023	• **BW**: **Yes** • W/P, HL: Yes • AR, HL: Yes • S5: Yes, transaminase elevation • S6: Yes, transaminase elevation
Fosnetupitant* (AKYNZEO®) Nausea and vomiting	neurokinin 1 (NK1) receptor antagonist	2018	• **BW**: No • W/P, HL: No • AR, HL: No • S5: No • S6: No
Rolapitant VARUBI® Nausea and vomiting	neurokinin 1 (NK1) receptor antagonist	2015	• **BW**: No • W/P, HL: No • AR, HL: No • S5: No • S6: No
Netupitant* (AKYNZEO®) Nausea and vomiting	neurokinin 1 (NK1) receptor antagonist	2014	• **BW**: No • W/P, HL: No • AR, HL: No • S5: No

[22] Source: CDER/OTS/OCP/DARS Computational Toxicology Consultation Service (CTCS) for hepatobiliary toxicity using (Q)SAR models

			• S6: Yes, increased transaminase >3x ULN and bilirubin compared to palonosetron
Fosaprepitant^ (EMEND®) Nausea and vomiting	neurokinin 1 (NK1) receptor antagonist	2008	• **BW**: No • W/P, HL: No • AR, HL: No • S5: No • S6: No
Aprepitant^ (EMEND®) Nausea and vomiting	neurokinin 1 (NK1) receptor antagonist	2003	• **BW**: No • W/P, (b) (4) Yes, Caution in patients with severe hepatic impairment • AR, HL: No • S5: Yes; no clinical or PK data in patients with severe hepatic impairment: Use with caution when administered concomitantly with medications that are primarily metabolized through CYP3A4. • S6: No

*Fosnetupitant is a prodrug of Netupitant and marketed as a fixed combination capsule with palonosetron
^Fosaprepitant is a prodrug of Aprepitant.

4.1.2 *Reports of DILI and hepatotoxicity in FAERS (FDA Adverse Events Reporting System)*. We used Empirica Signal 8.0.1.0.316 to access FAERS DILI and hepatotoxicity report counts since 2010. Empirica also gives an EBGM (Empirical Bayes Geometric Mean) disproportionality score calculated for all drug-to-event combinations. The EBGM is categorically coded by number and color for strength of association between the queried AEs and specific drugs based on how much the number of reports deviates from the EBGM (**Figure 4**). Thus, aprepitant's 38 DILI reports has a strong association with aprepitant based on an EBGM of (b) (4) (color-coated (b) (4), indicating they occurred (b) (4) times more than expected. We restricted to the 2010 and later time frame to allow incidence estimation using Metys™ which estimates the number of patient prescribed medications since 2010 (see Section 4.2.3 below).

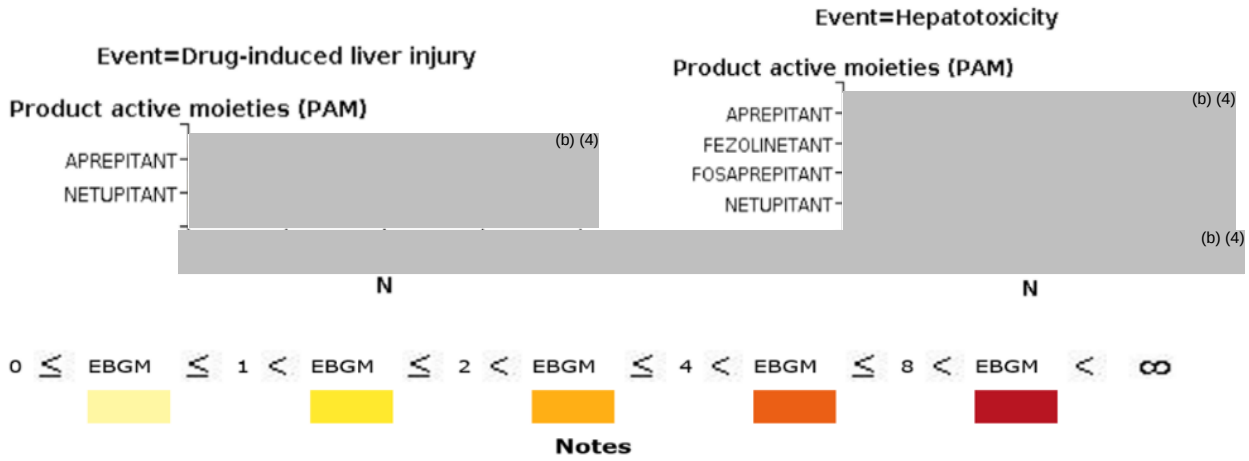


Figure 4: Report counts of DILI and hepatotoxicity for each drug since 2010 (inclusive).[23] Each bar represents the number of DILI or hepatotoxicity reports for each drug and the color of the bars represents the EBGM (Empirical Bayes Geometric Mean) disproportionality score which goes from 0 to ∞. The higher the EBGM score and darker the bar color for a drug-event combination, and the stronger the statistical association between that drug and event. For the

[23] https://esignal.fda.gov/Signal/home.jsp

example, the orange code between four and eight suggests the number of reports is between four and eight times higher than expected compared to all drug-to-event combinations.

4.2.3 *Estimated rates of DILI and LiverTox® categories*: Using the number of DILI and hepatotoxicity AEs provided by Empirica above we estimate the crude DILI incidence rate for each marketed drug by using Metys™ for the patient exposure in United States (**Table 6**). Metys™ uses various prescription databases to estimate the total number of patients in the United States being prescribed a medication. However, Metys™ only captures data from 2010 onward. LiverTox® category based on published reports of DILI found by the National Library of Medicine appears in **Table 6** as well. The crude incidence estimates must be viewed with caution as reporting to FAERS is fraught with reporting biases (both over- and under-reporting) and misclassification biases (i.e., misdiagnosed DILI).

Table 6: DILI or hepatotoxicity report numbers; incidence estimates using Empirica Signal and Metys™; and LiverTox Category neurokinin receptor antagonists.

Drug (Initial approval year)	**Empirica Signal DILI or hepatotoxicity cases since 2010**	**Metys™ based rate of DILI or hepatotoxicity cases per patients prescribed drug since 2010 (%)[24]**	**LiverTox® category [2]**
Fezolinetant (2023)	3	(b) (4)	D: possible rare cause of clinically apparent liver injury
Fosnetupitant* (2018)	0		E: unlikely cause of clinically apparent liver injury
Rolapitant (2015)	0		E: Unlikely cause of clinically apparent liver injury
Netupitant (2014)	2		NA
Fosaprepitant (2008)	1		NA
Aprepitant (2003)	46		E: unlikely causes of clinically apparent liver injury

Metys based rate shows the rate of DILI/hepatotoxicity reports from Empirical Signal per estimated patients prescribed drug in the United States according Metys.
LiverTox categories are based on published reports of DILI.

4.2.4: PubMed search for DILI reports: The DILI Team's own PubMed search using two different search syntaxes yielded no hepatotoxicity cases reported for any of the marketed NK-1 or NK-3 inhibitors.[25]

4.2 Study Protocols:

[24] Metys™ https://metys.symphonyhealth.com/metys/#/home/prescriptionQuery
[25] PubMed https://pubmed.ncbi.nlm.nih.gov/?otool=mdufdrlib "(…) AND ((hepatotoxicity) or (liver injury) or (DILI))," and "(…) AND Human[MH] AND (drug induced liver injury OR jaundice/CI OR bile duct diseases/CI OR liver/DE OR liver diseases/CI) AND ("1900/1/1"[EDat]:"2999/12/31"[EDat])"

Our study level DILI assessment focuses on one phase 2b, study 21686/814-PM-02 (SWITCH-1) and three Phase 3 studies, 21651 (OASIS 1), 21652 (OASIS 2) and 21810 (OASIS 3) (**Table 7**). See DILI review on IND 129492 in DARRTS[26] for details on study design features related to DILI monitoring in these phase 2b and phase 3 studies. Schematics for these studies are also in the **Appendix, Figures A and B**.

Table 7: Overview of Phase 2 and 3 studies for safety assessment of elinzanetant[27]

Study identifier Study no. (Report no.)	Study title	Dose arms (treatment duration)	Number of women treated / completed treatment
Phase 3 – Pivotal studies			
OASIS 1 **21651** ***(PH-42782)***	A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women	Elinzanetant 120 mg, OD (26 weeks) Placebo, OD (12 weeks), followed by elinzanetant 120 mg (14 weeks)	198 [a] / 156 195 [a] / 159
OASIS 2 **21652** ***(PH-42780)***	A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women	Elinzanetant 120 mg, OD (26 weeks) Placebo, OD (12 weeks), followed by elinzanetant 120 mg (14 weeks)	200 [b] / 160 200 [b] / 170
Phase 3 – Long-term study			
OASIS 3 **21810** ***(PH-42784)***	A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 52 weeks in postmenopausal women	Elinzanetant 120 mg, OD (52 weeks) Placebo, OD (52 weeks)	312 / 226 315 / 232
Phase 2 study			
SWITCH-1 **21686 /** **814-PM-02** ***(R-13559)***	A double-blind, randomised, placebo controlled, adaptive design study of the efficacy, safety and pharmacokinetics of NT-814 in female subjects with moderate to severe vasomotor symptoms associated with the menopause	Elinzanetant 40 mg, OD Elinzanetant 80 mg, OD Elinzanetant 120 mg, OD Elinzanetant 160 mg, OD (12 weeks) Placebo, OD (12 weeks)	31 / 29 17 / 14 52 / 51 52 / 43 47 / 43

OD: once daily

4.3 Study level data

4.3.1 *Overview*:

In total, an estimated 1266 subjects with VMS[28] received EZN in the phase 2b and three phase 3 pivotal trials. One other phase 2 (NIRVANA, Study 22423) and one other phase

[26] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806257c2
[27] Source: Table 1-1 of the Applicant's Summary Clinical Safety
[28] Additional studies included in the 120-DSU report are 1) Study 22423 (NIRVANA): A double-blind, randomized, placebo-controlled phase 2 study to investigate efficacy and safety of elinzanetant for the treatment of sleep disturbances associated with menopause over 12 weeks in 110 postmenopausal women; and 2) Study 21656

3 (OASIS 4, Study 21656), are ongoing and not covered in detail for our consult. However, we assessed all subjects with significant liver injury from these latter two studies identified by the Applicant. The target number of subjects to randomize to EZN in NIRVANA and OASIS 4 are 35 and 243, respectively. Thus, approximately 1500 subjects may have been exposed to EZN in phase 2 and 3 protocols.

An additional 632 subjects received at least one dose of EZN in the phase 1 studies and for shorter durations than the phase 2 and 3 studies. For the phase 1 studies, the Applicant provided pooled analysis on 26 phase 1 studies including those completed during the 120-day safety update period (data lock on 9/24/2024). See **Appendix, Table A** for DILI analysis results based on pooled phase 1 studies. There were no phase 1 subjects with liver blood tests elevations that might meet Hy's law and no imbalance in ATs over 3x ULN between treatment and placebo (PBO) groups. There was one healthy volunteer with probable hepatocellular DILI which we discuss in **Section 4.4** below.

For the phase 2b and three phase 3 studies, there were no cases meeting aminotransferase (AT) and total bilirubin (TB) criteria for Hy's law. There were modestly higher proportion of EZN subjects with ALT >3x ULN in EZN 120 mg arm compared to placebo (PBO) subjects during the double blinded placebo-controlled treatment period in Study 21810, OASIS 3 (2.3% vs. 1.6%). For the double blinded placebo-controlled treatment period, Study 21651, OASIS 1, the difference was slight at 1% vs. 0.5%. These differences did not persist at the ALT >5x ULN cut-off though, and there were no differences at any ALT cut-off for Study 21652 OASIS 2 (See **Appendix, Tables B-D**). eDISH and cholestatic (eDISH-AP) DILI screening scatterplots for phase 2b and 3 studies are below.

4.3.2 *eDISH and cholestatic (eDISH-AP) plots for phase 2 and 3 studies:*

Phase 2b Study 21686/814-PM-02 (SWITCH-1): eDISH had one subject (Subject ID: (b) (6) with ATs over 5x ULN without hyperbilirubinemia in the 80 mg treatment arm, but we considered this case as unlikely DILI with an alternative diagnosis of gallstone disease (**Appendix, Figure C**). Cholestatic plot (eDISH-AP) plot had just one subject on EZN (120 mg/d) with AP >2x ULN (3.5x ULN) without hyperbilirubinemia, but this subject had baseline elevation in AP at 3.76 xULN. (Scatterplot not shown).

Phase 3 Studies 21651 (OASIS 1) and 21652 (OASIS 2): Study designs were the same for both studies. Each had the PBO subjects cross-over to EZN 120 mg daily after 12 weeks of taking PBO, while subjects randomized to EZN stayed on EZN for the remaining 14 weeks of treatment. CDS produced separate plots for OASIS 1 and 2 data during the first 12 weeks of PBO controlled therapy, and a single set of plots for pooled OASIS 1 and 2 data spanning 0 to 26 weeks including the PBO controlled and after cross-over periods.

(OASIS 4): A phase 4 double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy, over 52 weeks and optionally for an additional two years in women with, or at high risk for developing hormone-receptor positive breast cancer.

For the 12-week, placebo-controlled periods, eDISH plots did not show obvious shift of ATs or TB between arms (plots not shown). There were no subjects plotting to the potential Hy's law or cholestasis quadrants (i.e., no cases of jaundice). There were no subjects plotting to Temple's Corollary quadrant with ATs over 5x ULN, the accepted threshold for DILI concern if there is no jaundice.[29] (**Appendix, Figures D and E**) Similarly, eDISH-AP plots did not show obvious shift in AP or TB between arms, and no subjects plotted outside the left lower quadrant defined as AP <2x ULN and TB <2x ULN (plots not shown). Thus, there were no cases identified as potential DILI of concern in OASIS 1 or 2 during the 12-week placebo-controlled periods.

For the pooled, 26-week period data, which includes subjects who crossed over to EZN at week 14, there was one subject (Subject ID: (b) (6)) with ALT over 5x ULN occurring 119 days after the subject started EZN (**Figure 5** & **Table 8**). However, the ALT onset (peak of 5.2 xULN and AST to 2.3 xULN) occurred 28 days after the last EZN dose without hyperbilirubinemia and resolved within two weeks. Based on the latency after drug stop of three to four weeks, we considered this case unlikely DILI and did not pursue detailed assessment. Cholestatic DILI screening plot (eDISH-AP) had only one subject (Subject ID: (b) (6)) barely outside the left lower quadrant with AP just over 2x ULN without hyperbilirubinemia (plot not shown). This case was not further assessed.

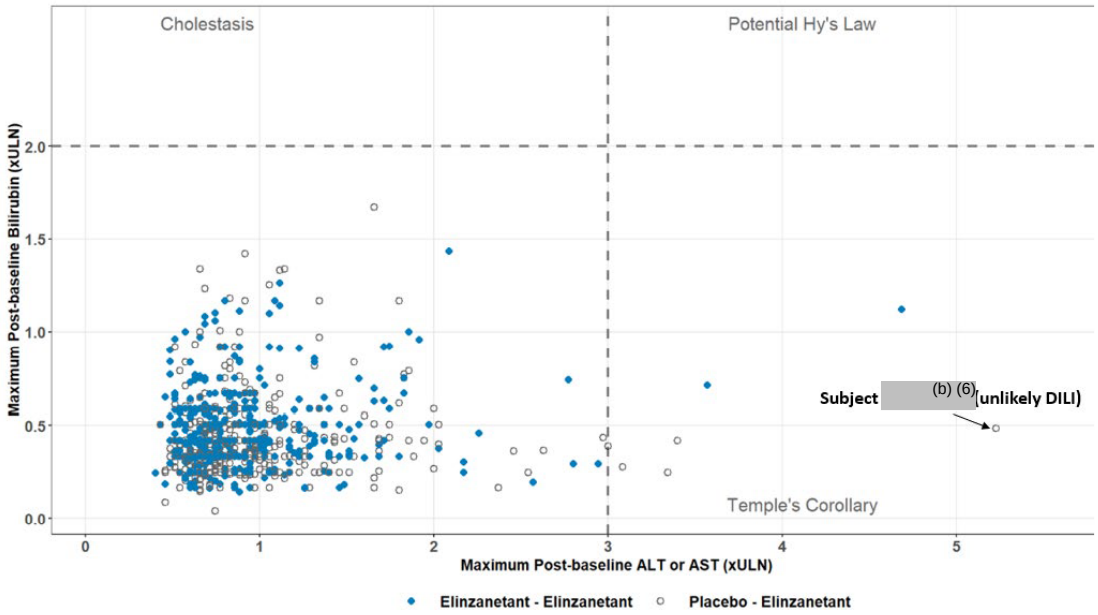


Figure 5: Hepatocellular DILI screening plot (eDISH) for pooled OASIS 1 and 2 data from weeks 0 to 26.[30]

Table 8: Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Studies 21651 and 21652 (pooled).

[29] Aithal GP, et al. Case Definition and Phenotype Standardization in Drug-Induced Liver Injury. *Clin Pharm Therap*. 2011; 89:806-815.
[30] Figure and table made by CDS (AW).

Quadrant	Elinzanetant - Elinzanetant N=400	Placebo - Elinzanetant N=393
Potential Hy's Law (right upper)	0/394 (0)	0/383 (0)
Cholestasis (left upper)	0/394 (0)	0/383 (0)
Temple's corollary (right lower)	2/394 (0.5)	5/383 (1.3)
Total	2/394 (0.5)	5/383 (1.3)

Phase 3 Study 21810 (OASIS 3): The eDISH screening plot had just one subject on EZN outside the left lower quadrant and with ATs over 5x ULN (**Figure 6** & **Table 9**). This case (Subject ID: (b) (6)) was deemed possible DILI and is described in detail in **Section 4.4** below. There were no cases in potential Hy's law quadrant and only one case just in the cholestasis quadrant (**Figure 7** & **Table 10**). This subject did not migrate to the right upper quadrant on the cholestatic screening plot (eDISH-AP), suggesting the subject had hyperbilirubinemia with normal ATs and ALP. We did not review this case further. The only EZN subject with substantial AP elevation on eDISH-AP was the same subject with ATs over 5x ULN mentioned above.

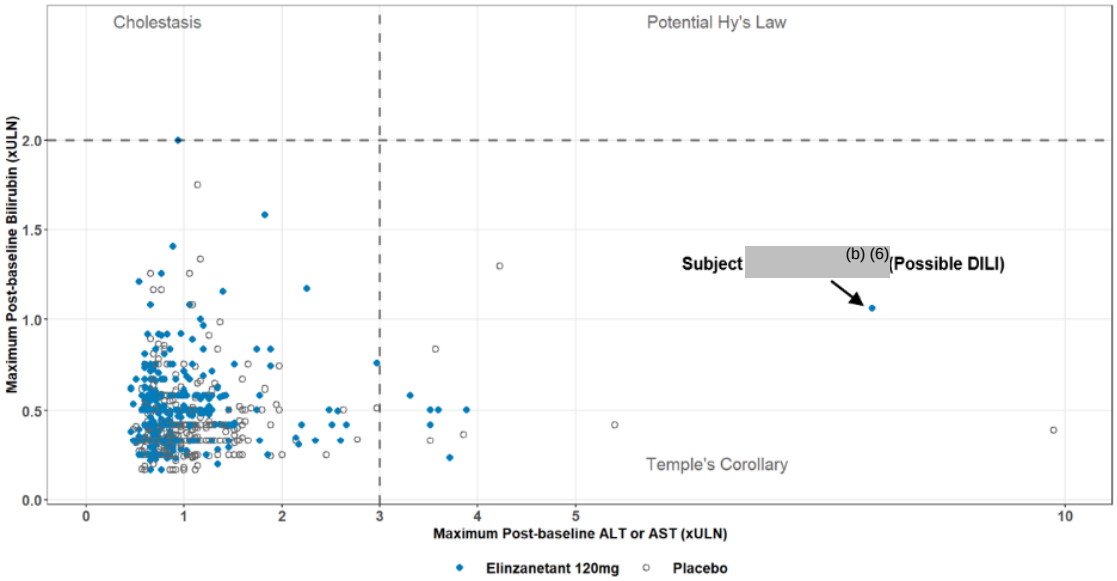


Figure 6: Hepatocellular Drug-Induced Liver Injury Screening Plot (eDISH), Trial 21810[31]

Table 9: Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial 21810.

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

Source: CDS team

[31] Figure and table made by CDS (AW)

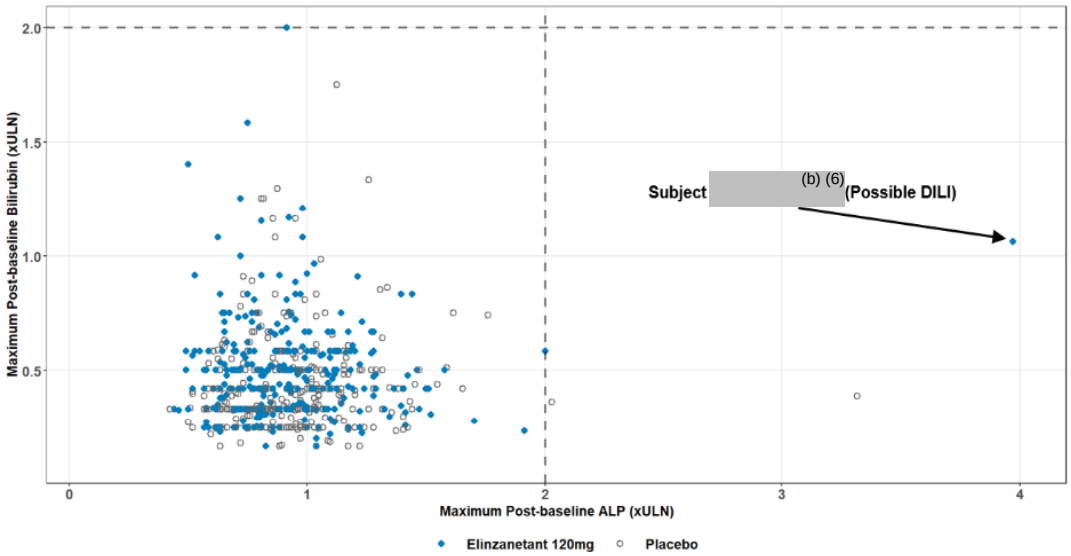


Figure 7: Cholestatic Drug-Induced Liver Injury Screening Plot (eDISH-AP), Trial 21810.[32]

Table 10: Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial 21810.

Quadrant	Elinzanetant 120mg N=313	Placebo N=314
>=2X ULN Bilirubin and >=2X ULN ALP (right upper)	0/307 (0)	0/305 (0)
>=2X ULN Bilirubin and <2X ULN ALP (left upper)	1/307 (0.3)	0/305 (0)
<2X ULN Bilirubin and >=2X ULN ALP (right lower)	2/307 (0.7)	2/305 (0.7)
Total	3/307 (1)	2/305 (0.7)

4.4 Case level analyses

4.4.1 *Summary of cases*: We assessed thirteen cases of liver injury for attribution to EZN using the US Drug Induced Liver Injury Network (DILIN) likelihood categories (**Table 11**).

Table 11: US Drug Induced Liver Injury Network (DILIN) causality assessment scoring.[33]

Score	Label	Descriptor
1	Definite	>95%% likelihood of DILI due to investigational product
2	Highly likely	75% to 95% likelihood of DILI due to investigational product
3	Probable	50% to 74% likelihood of DILI due to investigational product
4	Possible	25% to 49% likelihood of DILI due to investigational product
5	Unlikely	<25% likelihood of DILI due to investigational product
6	Indeterminant	Insufficient data

Our assessments were generally similar to the Applicant's Liver Safety Monitoring Board (LSMB) assessments when available. The six unlikely cases were considered unlikely by both the DILI Team and the LSMB. Alternate diagnoses for the six unlikely

[32] Figure and table made by CDS (AW)
[33] Fontana RJ, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf*. 2009; 32:5-68.

cases were alcohol related liver disease (2), metabolic and alcohol-associated liver disease (1), gallstone disease (1), myopathy (1), and unknown (1).

Based on the DILI Team and LSMB assessments, two were considered probable DILI due to EZN and five as possible. No cases met Hy's law criteria. The probable and possible cases had a wide latency (time from drug start to injury presentation: seven to 362 days), and patterns of injury also ranged widely from cholestatic to hepatocellular with R values[34] of two to 9.8 (**Table 12**). However, the latencies for the two probable cases tended to be shorter (seven and 85 days) and injuries more hepatocellular (R-values 6.5 and 7.7). Only one subject had hyperbilirubinemia, and this case is discussed in detail below.

Table 12: At least possible DILI[35]

#	ID	Causality Score* (DHN)	Causality Score* (LSMB)	Alternate diagnosis	Study	Age (y)	Race	Hy's Law	Latency from drug start (d)	Latency from drug stop (d)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak
1	(b) (6)	3	3	NA	NIRVANA	58	Black AA	No	85	0	259	133	122	0.2	6.5
2		3	NA	NA	Phase 1	40	Latinx	No	7	[2]	261	153	104	0.4	7.7
3		4	4	Viral infection	OASIS 4	55	White	No	31	[3]	599	866	187	3.3	9.8
4		4	5	Unknown	OASIS 3	60	White	No	362	1	281	115	413	1.0	2.1
5		5	4	HDS	OASIS 4	64	White	No	362	[8]	133	59	104	0.3	3.9
6		5	4	APAP, HDS	OASIS 4	55	Unknown	No	56	[302]	409	232	517	0.3	2.4
7		5	4	Gallstone disease	OASIS 3	52	White	No	50	[63]	130	44	199	0.2	2.0
					Average	*54.9*			*136.1*	*[53.9]*	*296*	*229*	*235*	*0.82*	*4.9*
					Std Dev	*7.1*			*144.5*	*103.5*	*152*	*266*	*152*	*1.04*	*2.9*
					Median	*55*			*56*	*[3]*	*261*	*133*	*187*	*0.30*	*3.9*
					Min.	*40*			*7*	*[302]*	*130*	*44*	*104*	*0.22*	*2.0*
					Max.	*64*			*362*	*1*	*599*	*866*	*517*	*3.30*	*9.8*

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did not rise above the ULN

~Bracketed [ ]day values mean the drug continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

LSMB = Liver Safety Monitoring Board

NA = not available or not applicable

APAP = acetaminophen

HDS = herbal/dietary supplement

4.4.2 *Cases of Interest*: We describe four cases in detail below, including the two subjects with probable DILI due to EZN. The other two subjects were considered possible DILI by the DILI Team. One of the possible cases (b) (6) would have met Hy's law had attribution to EZN been higher. The other possible case (b) (6) (b) (6) had a long latency at just over one year.

1. Subject (b) (6) (Study NIRVANA): Probable DILI due to EZN.

Summary: This is a 58-year-old female, Black, with sleep disturbances due to menopause, who developed elevated aminotransferases approximately 85 days after starting study drug (EZN). Initial dose was 120 mg/day. She enrolled in the US.

[34] R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values > 5; mixed: 2-5; cholestatic: R-value < 5

[35] Table made by DILI Team

At baseline, the subject's BMI was 34 kg/m^2. Relevant medical history, besides the target disease, included obesity, hyperlipidemia, liver enzyme elevations (since [redacted]), MASLD, and asthma. Alcohol "abuse" history was "negative." Concurrent medications relevant to DILI risk were nil. The subject's ALT, AST, AP, and TB were 56 U/L, 58 U/L, 91 U/L, and 0.23 mg/dL, respectively.

The subject started study drug (EZN) at 120 mg/d on [redacted] (Day 1). On [redacted] (Day 85), ALT, AST, AP, and TB were 200 U/L, 159 U/L, 131 U/L and 0.23 mg/dL, respectively. No symptoms were mentioned. On this day, EZN was stopped due to end of treatment per protocol. LT climbed further to peak at 259 U/L on [redacted] (Day 91). Thereafter, ATs improved with >50% decline from peak for ALT and AST occurring within nine days (**Figure 8**). Return to baseline occurred within 16 days after peak values for AST. ALT remained mildly elevated at 69 U/L at last follow-up (Day 108).

Evaluation testing included negative acute serologies for HAV, HBV, HCV, HEV, CMV and EBV. HCV RNA testing was not done. Autoimmune markers were in included a negative ANA. IgG level was mildly elevated at 1870 mg/dL; no ULN provided. Liver imaging by ultrasound did not reveal an etiology for rise in liver blood tests.

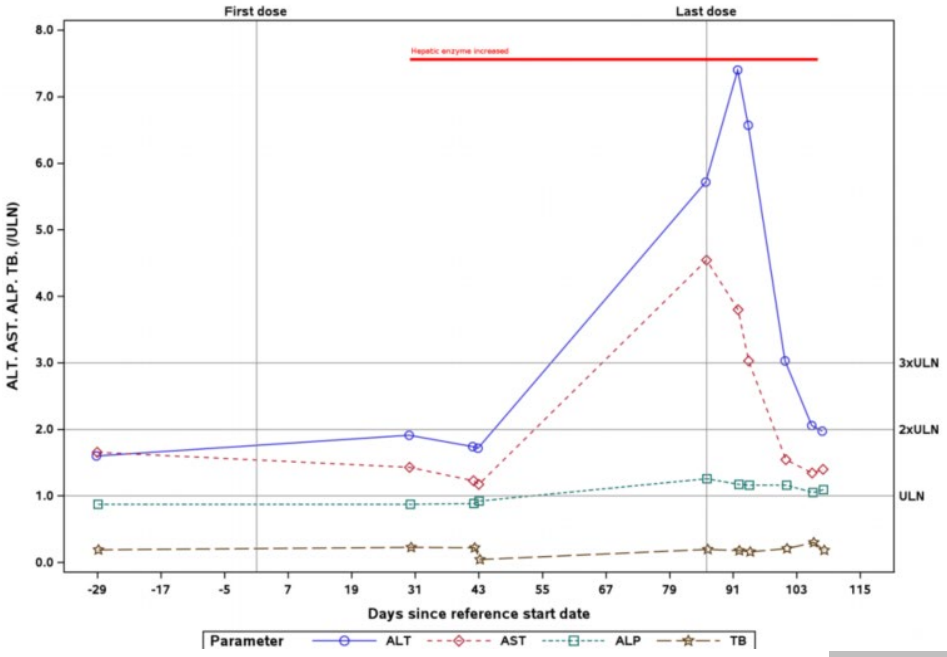


Figure 8: Liver enzymes and total bilirubin levels over time for subject [redacted] [36]

Assessment: We assessed this case as probable DILI due to EZN. Latency and dechallenge washout were consistent with DILI. Evaluation testing was adequate; HCV RNA was not checked so acute hepatitis C remains a possibility. Enzyme rise and fall

[36] NDA219469 (219469 - 0020 - (20) - 2025-02-21 - ORIG-1 /Clinical/Response To Information Request) - Response to FDA Information Request - Appendix 4.1 - 07Feb2025 (#23)

could fit with acute HCV and clearance which occurs more frequently in women. However, no risk factors for hepatitis C infection were provided.

2. Subject [redacted] (b) (6) (Phase 1 Study): Probable DILI due to EZN.

Summary: This is a 40-year-old female, white, healthy volunteer, who developed elevated aminotransferases approximately seven days after starting EZN. Initial dose was 40 mg/day. She enrolled in the US.

At baseline, the subject's BMI was 26 kg/m^2. Relevant medical history was non-contributory to this liver injury event. Alcohol history was "negative." Concurrent medications relevant to DILI risk were nil. The subject's baseline ALT, AST, AP, and TB were 22 U/L, 21 U/L, 68 U/L, and 0.3 mg/dL, respectively.

The subject started study drug (EZN) at 40 mg/d on [redacted] (b) (6) (Day 1). On [redacted] (b) (6) (Day 7), ALT, AST, AP, and TB were 170 U/L, 94 U/L, 83 U/L and 0.30 mg/dL, respectively. The subject had no symptoms. The study drug continued without change until study completion on [redacted] (b) (6) (Day 9) when last dose was given. The next day, [redacted] (b) (6) (Day 10), ALT, AST, AP, and TB were 261 U/L, 153 U/L, 93 U/L and 0.40mg/dL, respectively. Still no symptoms were mentioned. Thereafter, liver enzymes improved with >50% decline from peak for ALT and AST occurring within two days (**Figure 9**). Return to baseline occurred within two to seven days after peak values. Evaluation testing included negative acute serologies for HAV, HBV, HCV and HEV. HCV RNA testing was not done. Autoimmune markers were not done. IgG level was not checked. Liver imaging by ultrasound showed no obvious etiology for liver injury.

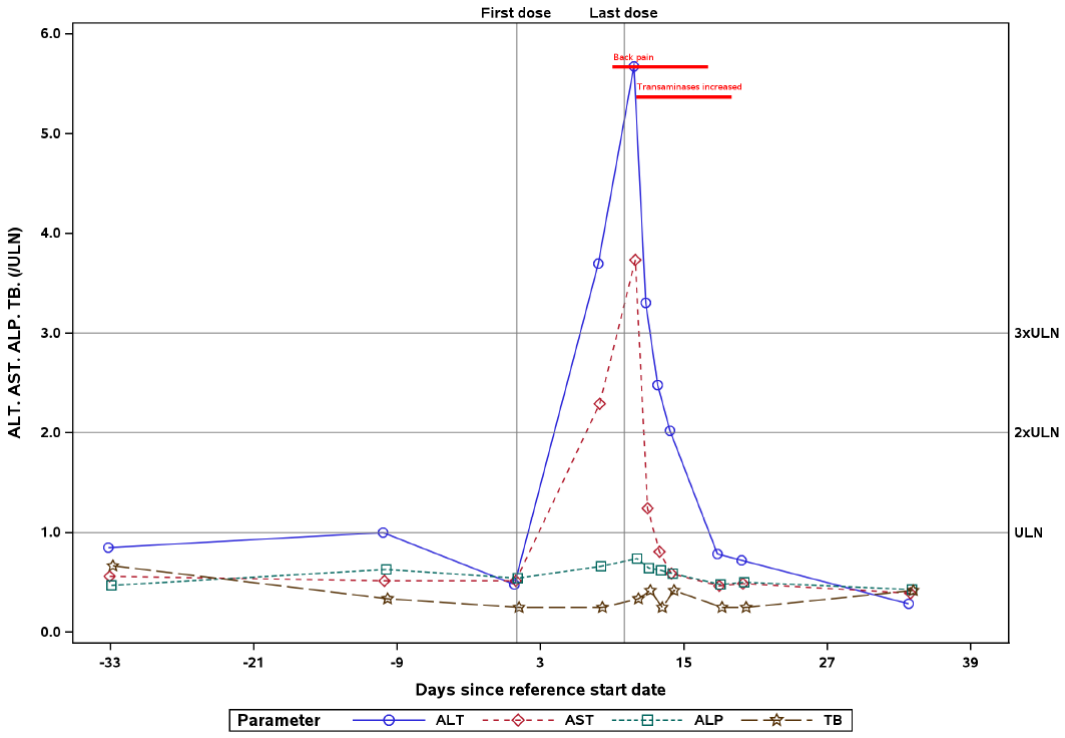


Figure 9: Liver enzymes and total bilirubin levels over time for subject [redacted][37]

Assessment: We assessed this case as probable to highly likely DILI due to EZN. Latency and dechallenge improvement are consistent with DILI. Evaluation testing adequate though no HCV RNA testing was done. However, healthy volunteer status, short EZN exposure, and short latency to injury make non-DILI diagnoses less likely.

3. Subject [redacted] (Study OASIS 3): Possible DILI due to EZN

Summary: This is a 60-year-old female, white, with post-menopausal vasomotor symptoms, who developed elevated liver enzymes approximately 362 days after starting study drug (EZN). Initial dose was 120 mg/day. She enrolled in the US.

At baseline, the subject's BMI was 21 kg/m^2. Relevant medical history, besides the target disease, included hypertension and asthma. "Alcohol abuse" history was "negative." Concurrent medications relevant to DILI risk included methylprednisolone (dosages not provided) [redacted] (Day 356-66) and [redacted] (Day 430) The subject's ALT, AST, AP, and TB were 47 U/L, 36 U/L, 132 U/L, and 0.90 mg/dL, respectively.

The subject started study drug (EZN) at 120 mg/d on [redacted] (Day 1). She had no liver blood test elevations while taking EZN and had her last dose on [redacted] (Day 361). The next day, [redacted] (Day 362), ALT, AST, AP, and TB were 73 U/L, 59 U/L, 117 U/L and 0.99 mg/dL, respectively. No symptoms were mentioned. EZN had already stopped for study completion. On [redacted] (Day 399), ALT, AST, AP, and TB were 281 U/L, 115 U/L, 413 U/L and 0.79 mg/dL, respectively. Still no symptoms were mentioned. Thereafter, liver analytes improved with >50% decline from peak for ALT, AST, and AP occurring within 13 to 20 days (**Figure 10**). AST and ALT return to baseline occurred within 13 days after peak values but AP remained minimally elevated a 144 U/L. Evaluation testing included negative serologies for HAV, HCV, HEV, CMV and EBV. HCV RNA and HBsAg testing was negative. Autoimmune markers were all negative. IgG level was normal. Liver imaging by ultrasound was normal.

[37] NDA219469 (219469 - 0017 - (17) - 2025-01-08 - ORIG-1 /Clinical/Response To Information Request) - Response to Information Request Appendix 5.1 Tables and Figures (#22)

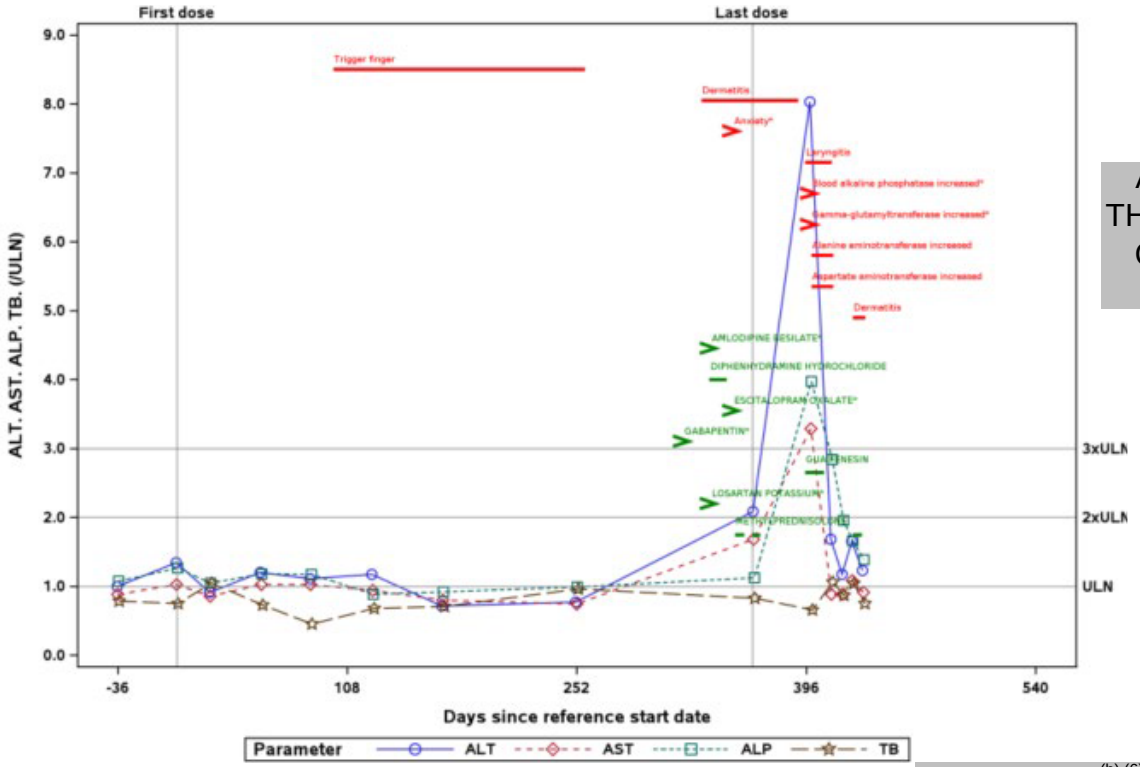


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Figure 10: Liver enzymes and total bilirubin levels over time for Subject (b) (6).[38]

Assessment: The dechallenge washout implicates ELZ, but the long latency weakens the case to just possible DILI. Nevertheless, other common causes were ruled out for the most part. The evaluation was missing an anti-HBc IgM, but HBsAg was negative. Passage of a gallstone would fit here, but US was negative and she had no symptoms. The injury was modest without hyperbilirubinemia and cholestatic-mixed in pattern. She was on methylprednisolone presumably for a dermatitis AE or asthma. We suspect the dose was not in the range associated with DILI (i.e., 1-2 grams IV daily). She was also still on it at onset when ALT was up to 73 U/L; typically, the DILI occurs after the course of high dose methylprednisolone has ended. The Liver Safety Monitoring Board (LSMB) considered this case as unlikely, but we suspect they did not acknowledge the onset of liver injury with the mild rise in liver enzymes on Day 362.

4. Subject (b) (6) (Study OASIS 4): Possible to Unlikely DILI due to EZN.

Summary: This is a 55-year-old female, white, with post-menopausal vasomotor symptoms, who developed elevated aminotransferases and jaundice approximately 31 days after starting EZN. Initial dose was 120 mg daily. She enrolled in Poland. At baseline, the subject's BMI was 31 kg/m2. Relevant medical history, besides the target disease, included a history of breast cancer (Stage II) (b) (6), and hepatic steatosis, (b) (6). "Alcohol abuse" history was "negative." Concurrent medications

[38] Adapted from NDA219469 (219469 - 0017 - (17) - 2025-01-08 - ORIG-1 /Clinical/Response To Information Request) - Response to Information Request Appendix 5.1 Tables and Figures (#14)

relevant to DILI risk included letrozole started (b) (6) (Day -138). The subject's ALT, AST, AP, and TB were 34 U/L, 26 U/L, 73 U/L, and 0.2 mg/dL, respectively.

The subject started EZN at 120 mg daily on (b) (6) (Day 1). On (b) (6) (b) (6) (Day 32), ALT, AST, AP, and TB were 599 U/L, 866 U/L, 187 U/L and 1.5 mg/dL, respectively. The subject also had upper abdominal pain; she also reported having fevers and yellow skin. The study drug continued without change, until (b) (6) (b) (6) (Day 35) when it was stopped. Thereafter, ALT and AST fell, but in a saw-toothed up and down manner (**Figure 11**). TB peaked at 3.3 mg/dL (DB 2.9 mg/dL) on (b) (6) (b) (6) (Day 43). From (b) (6) (Days 54-61) she had an upper respiratory infection, but there was no mention of medication or antibiotics taken. ALP gradually rose to peak at 629 U/L with a GGT of 1119 U/L by (b) (6), (Day 71). Through this decline in ATs and rise in ALP, "pyrexia" was reported twice (Figure x). TB returned to normal within 10 days from peak, but liver enzymes would not return to normal for 84 to 105 days after peak levels. Evaluation testing included negative serologies for HAV, HBsAg, EBV, CMV, and HCV antibody. HCV RNA testing was not done. Autoimmune markers were all negative. IgG level was normal. Liver imaging by CT, and EUS gave conflicting biliary results but were done at different times. CT on (b) (6) (Day 73) showed a common bile duct (CBD) dilated to 10-11 mm with an ill-defined "hyperdense area" near the ampulla. EUS on (b) (6) (Day 95) showed a CBD of only 5 mm with "heterogenous lesion," 6-7 mm in size in the area of ampulla.

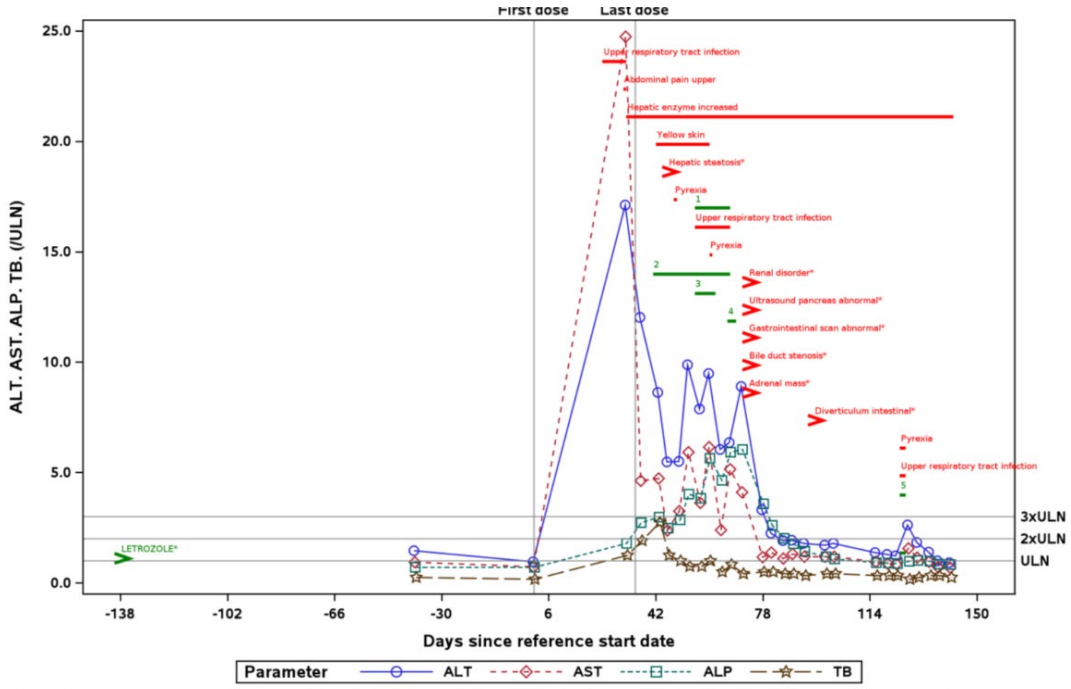

Figure 11: Liver enzymes and total bilirubin levels over time for Subject (b) (6).[39]

[39] NDA219469 (219469 - 0020 - (20) - 2025-02-21 - ORIG-1 /Clinical/Response To Information Request) - Response to FDA Information Request - Appendix 4.1 - 07Feb2025 (#15)

Assessment: We assessed this case as possible to unlikely, DILI due to EZN. Latency is consistent. Dechallenge, though saw-toothed could also be consistent with DILI; however, the recurrent upper respiratory infections and fever don't fit well with DILI and raise the possibility of an atypical infection or undisclosed use of antibiotics. Intermittent passage of biliary sludge also competes and would fit with the abdominal pain and intermittent fever. The CT scan suggested modest CBD dilation (8-10 mm) and EUS done a few weeks later showed a five mm diameter but persistent "heterogenous lesion" near the ampulla of Vater. Such passage of stones/sludge would also be consistent with this clinical presentation and later rise in ALP.

5.0 Assessment & Recommendations

5.1 Assessment

Elinzanetant (EZN) is a first in class, NK-1 and N-3 receptor inhibitor, given orally at 120 mg daily. The indication for this NDA is vasomotor symptoms (VMS) of menopause. Activation of the kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the arcuate nucleus is modulated by estrogen pre-menopause. With the decline in estrogen during menopause, KNDy neurons are thought to be more active leading to VMS. Thus, EZN is thought to help replace some of estrogen's modulating effects by inhibiting KNDy neurons via NK-1 and NK-3 receptor blockade.

The Division of Urology and Gynecology (DUOG) initially consulted the DHN DILI Team on Sep 21, 2022, regarding non-clinical data suggesting hepatotoxicity risk and elevated liver enzymes seen in phase 1 and 2 trials (IND 129492). At that time, we found the protocol changes enhancing liver safety to be largely adequate and made non-hold recommendations (see **Attachment**). The Applicant submitted its NDA (21946) on Jul 26, 2024. DUOG reconsulted the DILI Team for opinion of overall DILI risk and labeling recommendations in the context of another oral NK-3 inhibitor, fezolinetant (FZT), approved under NDA 216578 for the same indication in May 2023. The DILI Team's consult for that NDA is also attached. FZT was labeled for hepatotoxicity under Warnings and Precautions which has since been elevated to a Box Warning based on post-market DILI cases. Different Applicants submitted the EZN and FZT NDAs.

The clinical and non-clinical data for EZN DILI risk are remarkably discordant, with non-clinical data supporting hepatotoxicity risk, but clinical data suggesting a mild risk of severe DILI. We discuss the non-clinical data first, followed by the clinical data, and end with approval and labeling recommendations in the context of FZT.

1. Non-Clinical Data: EZN has several characteristics associated with hepatotoxicity risk including firm evidence for reactive metabolite formation with time dependent inhibition of its own CYP; microsomal trapping studies; and irreversible (covalent) binding of proteins. It also has high lipophilicity, and BSEP transporter inhibition, both of which are associated with DILI risk. Indeed, the NCTR DILIScore which is based on lipophilicity, reactive metabolite formation, and daily dose is in the range associated high risk of DILI.

Animal studies also support some liver injury with elevations in liver enzymes and bilirubin, as well as histologic changes including inflammation. However, in vitro and animal studies suggesting DILI do not necessarily translate to human risk. The NCTR DILIScore for FZT is substantively lower (moderate risk) than EZN (high risk), yet FZT seems to have a higher clinical signal for hepatotoxicity.

2. Clinical data: Study level data did not suggest a substantial DILI risk. There were minimal to no imbalances in liver enzyme elevations across the pivotal phase 2b and phase 3 trials. eDISH plots had few subjects plotting outside the left lower quadrant and none in the potential Hy's law quadrant; moreover, there were no probable DILI cases in the pivotal trials, and no subjects across the development program met Hy's law. However, there was one healthy volunteer in a phase 1 study and one subject in a phase 2 study for menopause related sleep disturbance who had probable hepatocellular DILI. Peak AT levels were below 270 U/L and total bilirubin levels were normal in both cases. The injury resolved without sequalae upon end of EZN treatment. The total number exposed to EZN in the phase 2b and three phase 3 trials was 1266 with another 632 healthy volunteers receiving at least one dose. The ongoing phase 3 study, OASIS 4, has treated an additional 240-250 patients.[40] So, the liver injury signal is weak, but the number exposed is still low relative to the number of women who may be treated post-market. Thus, liver injuries of clinical significance could still arise in post-market, similar to what was seen for FZT. Furthermore, the risk tolerance for fatal or life-threating liver injury for both EZN and FZT is low due to the targeted disease, which has substantial morbidity but low risk of mortality. Also, more substantial liver injury may have been mitigated by the scheduled liver blood test monitoring and end-of-treatment. The two probable cases of DILI had liver injury as EZN was stopped per protocol end-of-treatment, not because of liver enzyme elevations.

Considering the non-clinical data, it is difficult to reconcile the higher liver injury signal being seen with FZT compared to EZN. Based on in vitro and animal studies, EZN should have more clinical DILI than FZT. However, QSAR (molecular structural) analysis offers a possible explanation. Despite the similar target of NK-3 receptors, EZN and fezolinetant are not so similar, structurally. In fact, EZN shares more similarity with another NK-3 inhibitor, netupitant marketed for nausea and vomiting since 2014. Netupitant is less heavily labeled for hepatotoxicity than fezolinetant, and the rate of FAERS reports of liver injury based on estimated patients prescribed is low.

Overall, the risk of DILI in the clinical trials should not hold up EZN approval. Labeling should describe the potential of hepatotoxicity and baseline liver blood tests should be done. Repeat tests on a scheduled basis should be considered in light of some association with FZT in terms of mechanism of action, and the non-life-threatening nature of the target disease. In other words, the tolerance for severe liver injury will be low in this potentially large post-market population.

5.2 Recommendations

[40] NDA219469 (219469 - 0026 - (26) - 2025-04-23 - ORIG-1 /Patent & Exclusivity/Patent Information) - Tabular Listing of Clinical Studies (#30)

1) Residual uncertainty about DILI risk associated with EZN should not hold up approval.
2) Do not start therapy if serum transaminase concentration is equal to or exceeds two to three times the ULN.
3) Hepatotoxicity should be discussed in Warnings and Precautions. Consider mentioning liver injury seen with agents in this class.
4) Perform liver biochemical tests prior to initiation of EZN to evaluate for hepatic function and injury.
5) Perform unscheduled liver biochemical tests if new onset symptoms occur (e.g., pruritus, jaundice, nausea, fatigue, or abdominal pain) suggestive of acute liver injury occur during EZN treatment.
6) Consider repeat hepatic liver blood tests at 3 months, and possibly at 6 months, and 9 months after initiation of therapy.
7) EZN should not be given to those with moderate to severely advanced cirrhosis (i.e., Childs B or C)
8) Consider more frequent liver test monitoring if EZN is given to patients with Childs A cirrhosis.
9) Consider designating spontaneously reported post-market cases of acute liver injury as Adverse Events of Special Interest (AESIs) to ensure their timely reporting and follow-up to the agency.

Ling Lan -S
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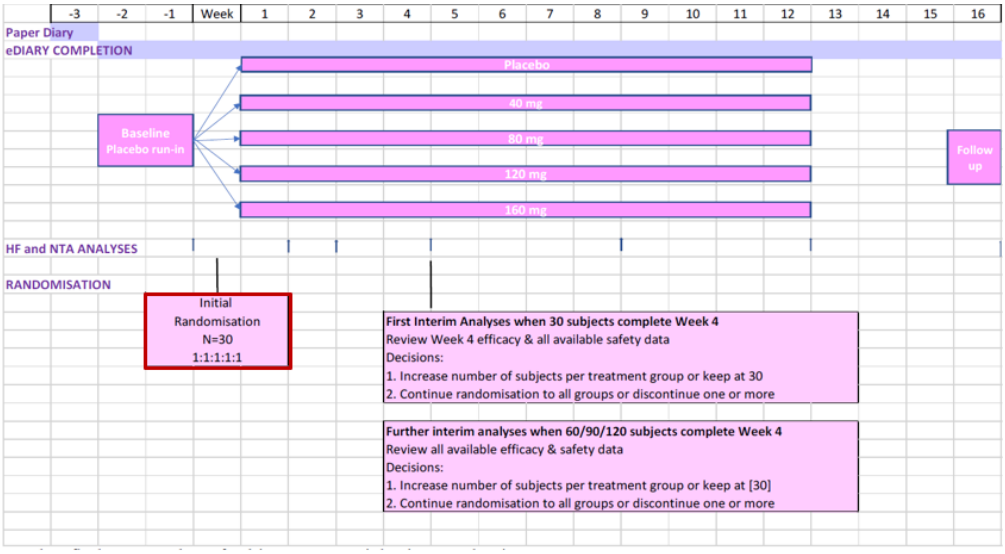
Date: 2025.05.13 11:25:27 -04'00'

Ling Lan, MD, PhD
Clinical Analyst, DILI Team, DHN
CDER/OND

Paul H. Hayashi -S
Digitally signed by Paul H. Hayashi -S
Date: 2025.05.13 12:36:40 -04'00'

Paul H. Hayashi, MD, MPH
Associate Director, DHN
CDER/OND

Appendix:



- Adaptive design resulted in discontinuation of 40 mg and 80 mg group.

Figure A: Schema for phase 2b study 21686/814-PM-02 (SWITCH-1).[41]

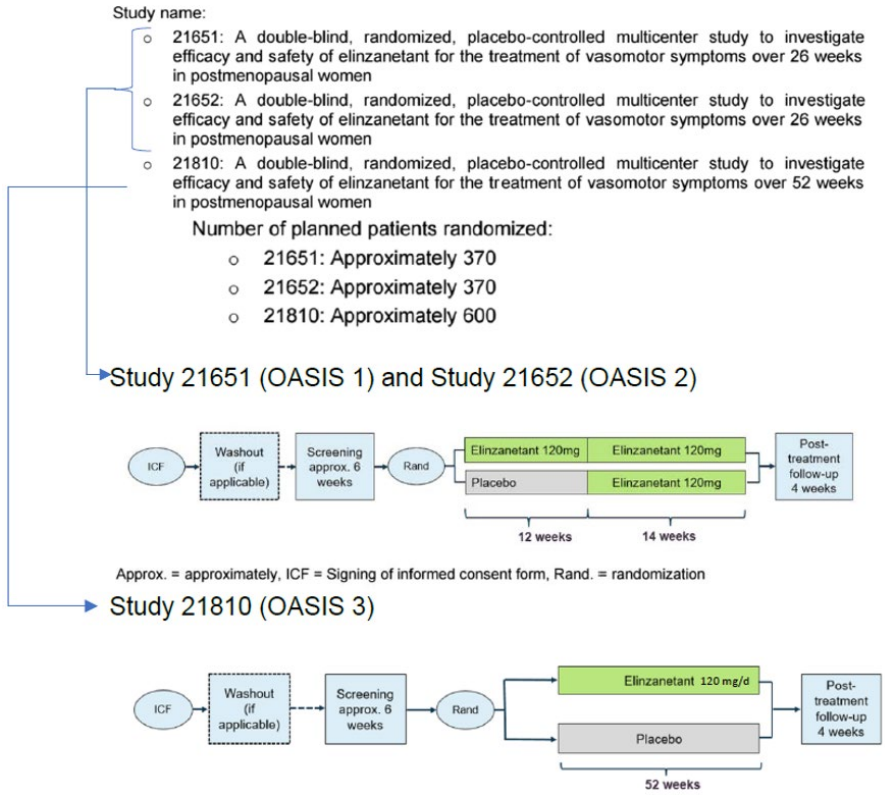


Figure B: Schemas for three Phase 3 Studies[42]

[41] CDS DILI Planning Meeting, Dec 9, 2024. Aaron Waddell, PhD. Slide 11.
[42] DILI review in DARRTS at https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806257c2

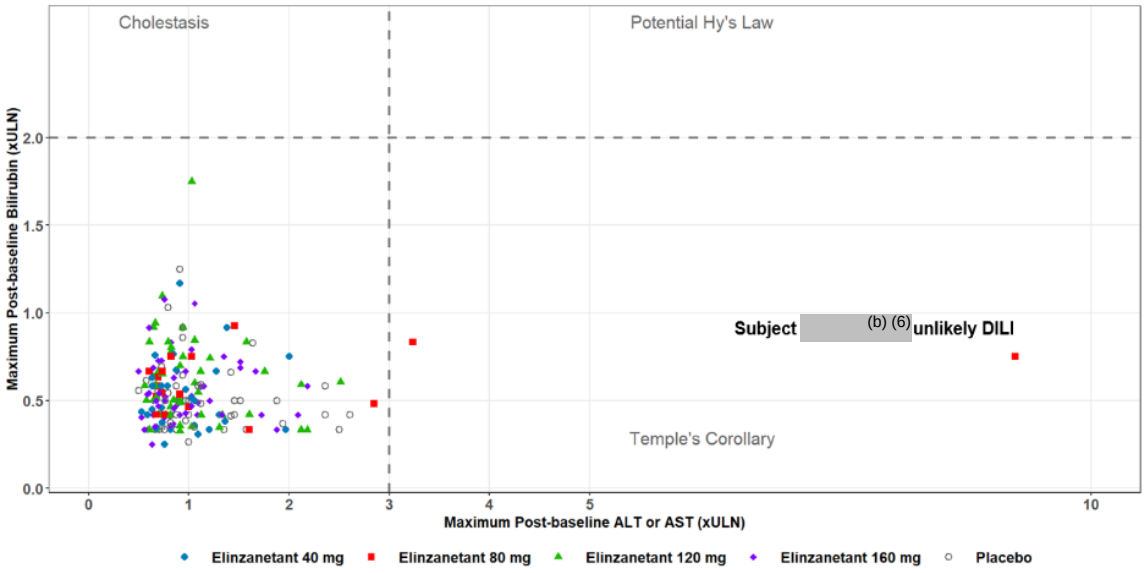


Figure C: eDISH plot for phase 2b study 21686/814-PM-02; SWITCH-1[43]

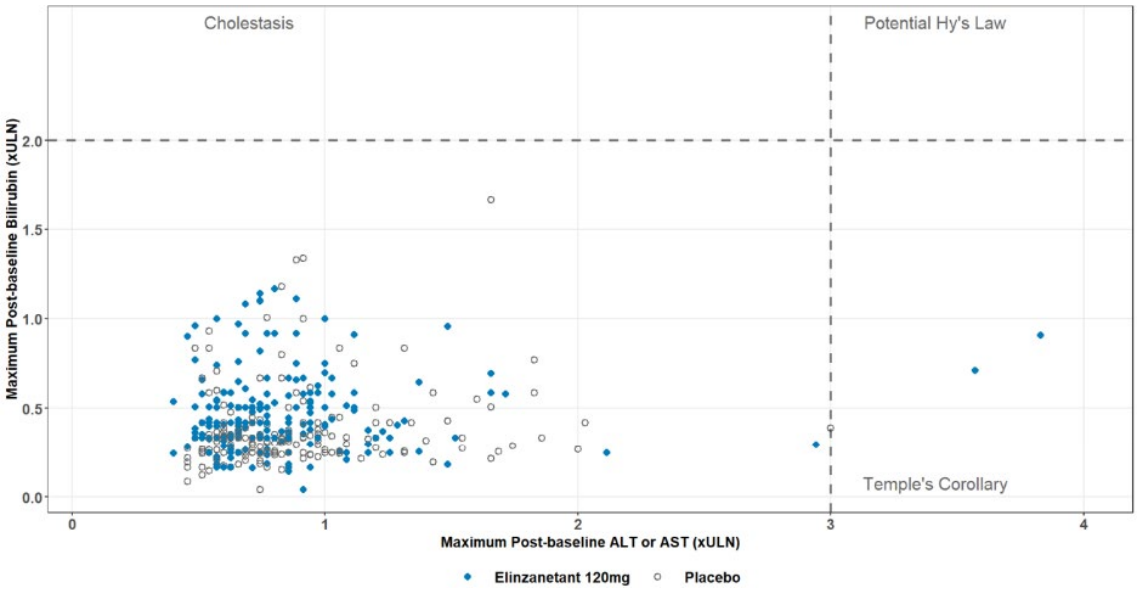


Figure D: eDISH plot for phase 3, Study 21651, weeks 0-12 (OASIS 1).[44]

[43] Made by CDS (AW)
[44] Made by CDS (AW)

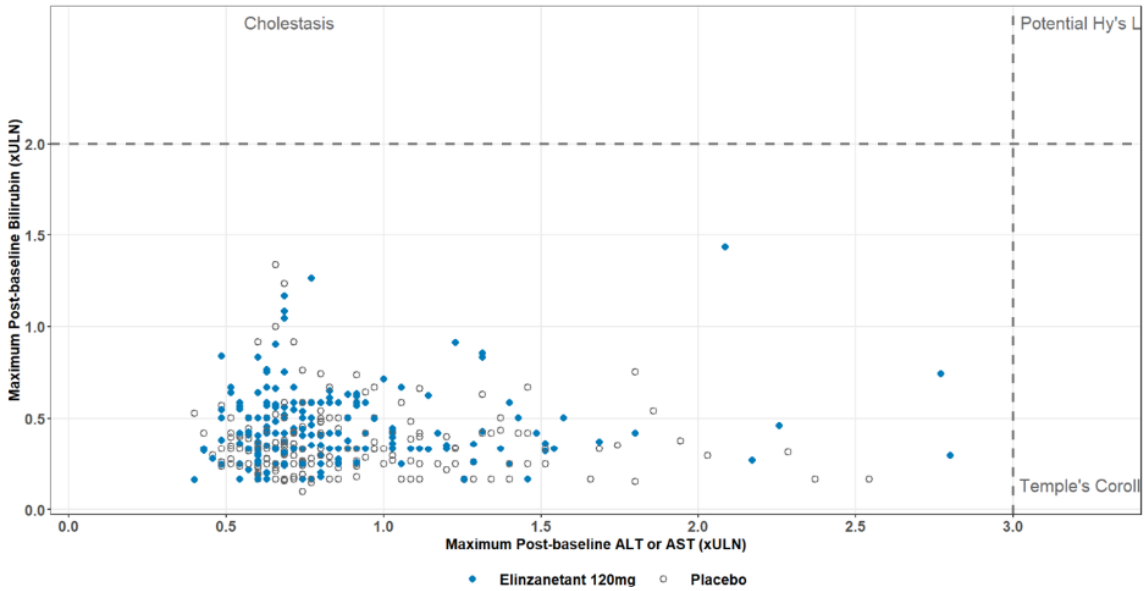


Figure E: eDISH plot for phase 3, Study 21652, weeks 0-12 (OASIS 2).[45]

[45] Made by CDS (AW)

Table A: Overview of DILI related liver biochemistry results across Phase 1 studies

	Subjects with DILI related liver biochemistry results		
	Elinzanetant n=632	Placebo n=247 (100%)	Total n=879
DILI related biochemistry results			
ALT or AST ≥ 3 x ULN	2 (0.3%)	0	3 (0.3%)
ALP ≥ 2 X ULN	0	0	0
Total Bilirubin ≥ 2 x ULN	2 (0.3%)	1 (0.4%)	3 (0.3%)
ALT or AST ≥ 3xULN and TB ≥ 2xULN	0	0	0

Source: Modified Table 44 in response-to-fda-information-request-appendix-41-07feb2025.pdf dated 2/21/2025

Table B: Frequencies of liver blood tests elevations between EZN and placebo groups for OASIS 3.[46]

Laboratory Abnormality	Elinzanetant 120mg N=313 n (%)	Placebo N=314 n (%)	Risk Difference (%) (95% CI)
ALT			
>=1X ULN	87/307 (28.3)	113/305 (37.0)	-8.7 (-16.1, -1.3) *
>=3X ULN	7/307 (2.3)	5/305 (1.6)	0.6 (-1.8, 3.2)
>=5X ULN	1/307 (0.3)	2/305 (0.7)	-0.3 (-2.1, 1.2)
>=10X ULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
>=20X ULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
AST			
>=1X ULN	68/307 (22.1)	80/305 (26.2)	-4.1 (-10.9, 2.7)
>=3X ULN	3/307 (1.0)	4/305 (1.3)	-0.3 (-2.5, 1.7)
>=5X ULN	0/307 (0)	1/305 (0.3)	-0.3 (-1.8, 0.9)
>=10X ULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
>=20X ULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
ALP			
>=2X ULN	2/307 (0.7)	2/305 (0.7)	-0.0 (-1.8, 1.8)
>=3X ULN	1/307 (0.3)	1/305 (0.3)	-0.0 (-1.5, 1.5)
Total Bilirubin			
>=2X ULN	1/307 (0.3)	0/305 (0)	0.3 (-0.9, 1.8)
>=5X ULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
>=8X ULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
Direct Bilirubin			
>=2X ULN	0/307 (0)	1/305 (0.3)	-0.3 (-1.8, 0.9)
>=5X ULN	0/307 (0)	0/305 (0)	0.0 (-1.2, 1.2)
GGT			
>=2X ULN	19/307 (6.2)	24/305 (7.9)	-1.7 (-5.9, 2.5)
INR			
>=1.5X ULN	2/308 (0.6)	7/305 (2.3)	-1.6 (-4.1, 0.3)
>=3X ULN	0/308 (0)	3/305 (1.0)	-1.0 (-2.9, 0.3)
>=5X ULN	0/308 (0)	0/305 (0)	0.0 (-1.2, 1.2)

Source: adlb.xpt; Software: R
The frequency represented here are based on peak levels. Appropriate cutoff for liver biochemistries should be adjusted based on the study population (e.g., pediatric population, those with underlying liver disease etc.). For patients with chronic liver disease, cutoff should be established using multiples of baseline (e.g. 2X, 3X, 5X).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, prothrombin international normalized ratio; N, number of patients in group; n, number of patients meeting criteria; ULN, upper level of normal

[46] Made by CDS (AW)

Table C: Frequencies of liver blood test elevations between EZN and placebo groups, OASIS 1[47]

Laboratory Abnormality	Elinzanetant 120mg N=199 n (%)	Placebo N=194 n (%)	Risk Difference (%) (95% CI)
ALT			
>=1X ULN	28/197 (14.2)	39/188 (20.7)	-6.5 (-14.2, 1.1)
>=3X ULN	2/197 (1.0)	1/188 (0.5)	0.5 (-2.0, 3.2)
>=5X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
>=10X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
>=20X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
AST			
>=1X ULN	21/197 (10.7)	25/188 (13.3)	-2.6 (-9.3, 3.9)
>=3X ULN	2/197 (1.0)	0/188 (0)	1.0 (-1.0, 3.6)
>=5X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
>=10X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
>=20X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
ALP			
>=2X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
>=3X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
Total Bilirubin			
>=2X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
>=5X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
>=8X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
Direct Bilirubin			
>=2X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
>=5X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)
GGT			
>=2X ULN	7/197 (3.6)	10/188 (5.3)	-1.8 (-6.4, 2.5)
INR			
>=1.5X ULN	0/197 (0)	2/188 (1.1)	-1.1 (-3.8, 0.9)
>=3X ULN	0/197 (0)	1/188 (0.5)	-0.5 (-3.0, 1.4)
>=5X ULN	0/197 (0)	0/188 (0)	0.0 (-2.0, 1.9)

Source: adlb.xpt; Software: R
The frequency represented here are based on peak levels. Appropriate cutoff for liver biochemistries should be adjusted based on the study population (e.g., pediatric population, those with underlying liver disease etc.). For patients with chronic liver disease, cutoff should be established using multiples of baseline (e.g. 2X, 3X, 5X).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, prothrombin international normalized ratio; N, number of patients in group; n, number of patients meeting criteria; ULN, upper level of normal

[47] Made CDS (AW)

Table D: Frequencies of liver blood test elevations between EZN and placebo groups, OASIS 2[48]

Laboratory Abnormality	Elinzanetant 120mg N=201 n (%)	Placebo N=199 n (%)	Risk Difference (%) (95% CI)
ALT			
>=1X ULN	37/197 (18.8)	46/195 (23.6)	-4.8 (-12.9, 3.3)
>=3X ULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=5X ULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=10X ULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=20X ULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
AST			
>=1X ULN	21/199 (10.6)	25/195 (12.8)	-2.3 (-8.8, 4.2)
>=3X ULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=5X ULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=10X ULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=20X ULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
ALP			
>=2X ULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=3X ULN	0/199 (0)	0/195 (0)	0.0 (-1.9, 1.9)
Total Bilirubin			
>=2X ULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=5X ULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=8X ULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
Direct Bilirubin			
>=2X ULN	1/197 (0.5)	0/195 (0)	0.5 (-1.4, 2.8)
>=5X ULN	0/197 (0)	0/195 (0)	0.0 (-1.9, 1.9)
GGT			
>=2X ULN	5/199 (2.5)	6/195 (3.1)	-0.6 (-4.4, 3.1)
INR			
>=1.5X ULN	1/198 (0.5)	0/195 (0)	0.5 (-1.4, 2.8)
>=3X ULN	0/198 (0)	0/195 (0)	0.0 (-1.9, 1.9)
>=5X ULN	0/198 (0)	0/195 (0)	0.0 (-1.9, 1.9)

Source: adlb.xpt; Software: R
The frequency represented here are based on peak levels. Appropriate cutoff for liver biochemistries should be adjusted based on the study population (e.g., pediatric population, those with underlying liver disease etc.). For patients with chronic liver disease, cutoff should be established using multiples of baseline (e.g. 2X, 3X, 5X).
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; INR, prothrombin international normalized ratio; N, number of patients in group; n, number of patients meeting criteria; ULN, upper level of normal

[48] Made by CDS (AW)

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/s/

PAUL H HAYASHI
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Clinical Inspection Summary

Date	04/22/2025
From	Regina Zopf, MD, Senior Medical Officer Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sergio Oehninger, Clinical Reviewer Shelley Slaughter, Clinical Team Leader Samantha Bell, Regulatory Project Manager Division of Urology, Obstetrics and Gynecology (DUOG)
NDA #	219469
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Drug	Elinzanetant
NME (Yes/No)	Yes
Therapeutic Classification	Selective neurokinin 1,3 (NK-1,3) receptor antagonist
Proposed Indication	Moderate to severe vasomotor symptoms (VMS) associated with menopause.
Consultation Request Date	09/23/2024
Summary Goal Date	05/31/2025
Action Goal Date	07/26/2025
PDUFA Date	07/26/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Bayer HealthCare Pharmaceuticals Inc. (Bayer), submitted clinical data from three Studies OASIS 1, 2, and 3 to the Agency in support of a New Drug Application (NDA 219469) for elinzanetant capsules (120 mg), a selective neurokinin 1,3 (NK-1,3) receptor antagonist, for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

Six clinical investigators (CI) Drs. Farsad, Mika, Dinnerstein, Tomaszewski, Makowska-Mainka, and Babajide, and the Sponsor, Bayer, were inspected.

At the site of Dr. Babajide, the inspection identified 6 unreported AEs (alopecia, COVID-19 infection, leg cramp, shingles, face injury and common cold). Alopecia and leg cramp were determined by Dr. Babajide as related to the investigative product. OSI reviewed the proposed package insert (PI) submitted by the sponsor (b) (4)

(b) (4) OSI recommends the review division include this case of alopecia in the safety analysis.

The inspections of the other CIs and the sponsor did not reveal significant concerns regarding the conduct and the oversight of the clinical trials or Good Clinical Practice (GCP) or regulatory compliance. Based on the results of these inspections, the data generated by the inspected CIs and submitted by the Applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

Bayer seeks approval for a new drug application (NDA) for elinzanetant for the treatment of moderate to severe vasomotor symptoms (VMS). In support of the NDA, the Applicant submitted clinical data from three phase 3 studies. OASIS 1 and OASIS 2 were pivotal efficacy studies, and OASIS 3 was primarily a long-term safety study providing additional supportive efficacy data. The following is a summary of the study protocol and key study information relevant to the clinical inspections.

21651/OASIS 1 and 21652/OASIS 2 (Identical studies different study sites):

OASIS 1 and 2 were identical phase 3, double-blind, randomized, placebo-controlled, international, multicenter, trials completed over 26 weeks to evaluate the safety, tolerability, and efficacy of elinzanetant capsules in the treatment of VMS associated with menopause.

Trial Numbers and Titles

21651/OASIS 1: A double-blind, randomized, placebo-controlled, multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women

21652/OASIS 2: A double-blind, randomized, placebo-controlled, multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women

Trial Status:
Study Initiation and Completion Dates: **OASIS 1,** August 27, 2021 to November 27, 2023/ **OASIS 2,** October 29, 2021 to October 10, 2023

Study Sites: **OASIS 1**, 89 (US, Europe, and Israel)/ **OASIS 2,** 95 (North America and Europe)

Subject Enrollment and Completion Status:

	OASIS 1	OASIS 2
Randomized	396	400
Treated	393	400
Discontinuations	87	76
Completed study	309	324

Trial Design

Subjects were screened and, if they met criteria were enrolled and were administered elinzanetant capsules of 120 mg tablet daily for 12 weeks. Participants were on elinzanetant for the first 12 weeks continued treatment for a total or 26 weeks while participants in the placebo arm crossed over after 12 weeks for an additional 12 weeks of treatment with elinzanetant.

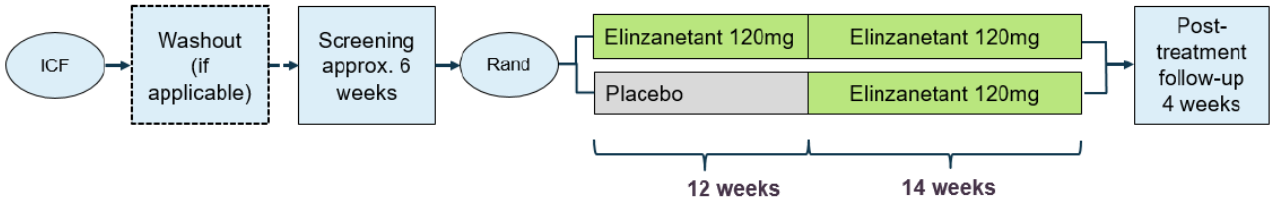
The trials were comprised of three periods: screening period, treatment period, and post-treatment follow-up:

Screening Period (approximately 6 weeks): The screening included a wash-out period if needed (women on hormonal therapies) as well as the collection of at least 2 weeks of HFDD data collection. Eligibility criteria were assessed (including laboratory and gynecological assessments), informed consent was obtained, and randomization was completed.

Treatment Period (26 weeks): During the Treatment Period, subjects received elinzanetant 120 mg capsules or placebo for the first 12 weeks and then all crossed-over to elinzanetant 120 mg for the final 14 weeks of the study.

Safety Follow-up: The follow-up visit took place 14 days after end of treatment (EOT).

Trial Schema:



Approx. = approximately, ICF = Signing of informed consent form, Rand. = randomization

Source: CSR, section 3.1

Objectives and Endpoints

The primary objective of these trials was to assess the assess the efficacy of elinzanetant for the treatment of VMS associated with menopause by evaluation of the following endpoints:

- Mean change in frequency of moderate to severe hot flash (HF) from baseline to Week 4 (assessed by Hot Flash Daily Diary (HFDD))

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

A key secondary objective was to evaluate the endometrial safety of elinzanetant using the endpoint endometrial thickness on transvaginal ultrasound and/or endometrial biopsy when indicated (determined by endometrial thickness greater than 0.4 mm).

Trial Conduct

Subjects underwent a washout period prior to enrollment if they were taking CYP3A4 inhibitors or inducers or hormonal therapies. There were 7 scheduled in person visits and 1 telephone visit. Subjects were given a handheld device for completion of trial questionnaires including the primary outcome measure of HFDD (completed twice daily). In person visits occurred at baseline, weeks 4, 8, 12, 16, 26 and 30 (post treatment follow up). The telephone visit occurred at week 20. A symptom based physical exam, vital signs, AEs and safety laboratories were assessed at every in person visit. HFDD and additional questionnaire data flowed directly from handheld devices to a central data collection system. Transvaginal ultrasound/biopsy (when indicated) were performed at baseline and end of treatment visits. There was a four-week safety follow-up visit at week 30.

21810/OASIS 3:
Oasis 3 was a phase 3, prospective, double-blind, placebo-controlled, international multicenter, 52-week study to evaluate the safety, tolerability, and efficacy of elinzanetant 120 mg capsules in the treatment of vasomotor symptoms associated with menopause.

Trial Number and Title
21810/OASIS 3: A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 52 weeks in postmenopausal women

Trial Status:

Study Initiation and Completion Dates: August 27, 2021, to February 24, 2024

Study Sites: 75 (North America and Europe)

Subject Enrollment and Completion Status:
- 628 subjects were randomized.
- 627 were treated with the study drug.

- 175 discontinued the study drug.
- 453 completed the trial.

Study Design

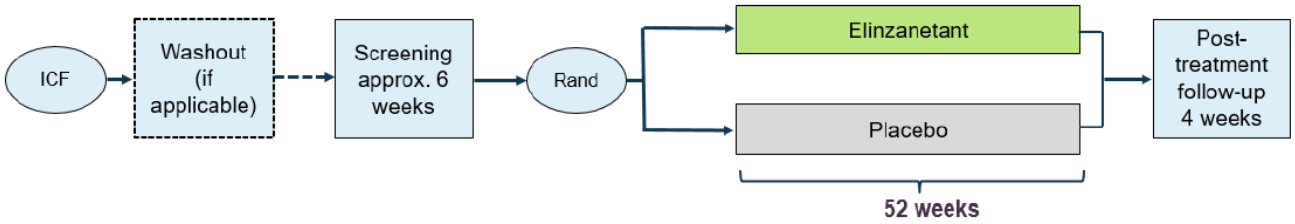
The study was comprised of three periods: screening period, treatment period, and post-treatment follow-up:

Screening Period (approximately 6 weeks): The screening included a wash-out period if needed (women taking hormonal therapies or CYP 3A4 inhibitors or inducers) as well as the collection of at least 2 weeks of HFDD data collection. Eligibility criteria were assessed (including laboratory and gynecological assessments), informed consent was obtained, and randomization was completed.

Treatment Period (52 weeks): During the Treatment Period, subjects received elinzanetant 120 mg capsules or placebo.

Safety Follow-up: The follow-up visit took place 4 weeks after end of treatment (EOT).

Study Schema:



Approx. = Approximately, ICF = Signing of informed consent form, Rand. = randomization

Source: CSR, Section 3.1

Objectives and Endpoints

The primary objective of this study was to assess the efficacy of elinzanetant capsules in the treatment of vasomotor symptoms associated with menopause. The endpoint defined to assess this objective was the mean change in frequency of moderate to severe hot flashed from baseline to Week 12 (assessed by HFDD).

Study Conduct

Subjects underwent a washout period prior to enrollment if they were taking CYP3A4 inhibitors or inducers. There were 9 scheduled in person visits and 2 telephone visits. Subject were given a handheld device for completion of trial questionnaires including the primary outcome measure of HFDD (completed twice daily). In person visits occurred at baseline, weeks 4, 8, 12, 18, 24, 36, 52 and 56 (post treatment follow up). The telephone visits occurred at week 30 and 42. A symptom based physical exam, vital signs, AEs and safety laboratories

were assessed at every in person visit. HFDD and additional questionnaire data flowed directly from handheld devices to a central data collection system. Transvaginal ultrasound/biopsy (when indicated) were performed at baseline and end of treatment visits. There was a four-week safety follow-up visit at week 56.

RESULTS

1. **Dr. Ramin Farsad (Site 14037)**
   477 N El Camino Real Ste A100,
   Encinitas, CA, 92024-1329, US

Inspection Dates: January 6 – 10, 2025

This investigator was inspected as a BIMO review-based inspection for OASIS 1. This was the first FDA inspection for this investigator.

Dr. Farsad enrolled the first subject in OASIS 1 in April 2022 and completed the final study visit on October 24, 2023. The site screened 40 subjects and enrolled 20 subjects. There were no deaths. 1 subject discontinued and 19 subjects completed the trial. All recruitment methods appeared appropriate, accurately described the trial medication, and non-coercive in nature.

Informed consent forms were reviewed for all 40 screened subjects and found to be complete and accurate. Additional forms and data reviewed included the following: eligibility worksheets, case report forms (CRF), and screening and eligibility logs.

The primary efficacy endpoint data was reviewed for 15 out of 19 enrolled subjects at baseline, week 4 and week 12. The raw source matched the sponsor provided data listings from this site. Data listings for serious adverse events (AEs) and AEs were also verified for these subjects. AEs were reported accurately and there did not appear to be any underreporting. There were no unreported protocol deviations.

To evaluate safety, source data was compared with the submitted data line listings for the medical history, transvaginal ultrasounds, endometrial biopsies, ECGs, cervical cytology, inclusion/exclusion criteria, ICFs/reconsents, mammograms, pertinent blood tests/samples, physical exams, vitals, concomitant medications for all 19 subjects who completed the study and found no discrepancies in the procedures listed.

Other study-related documents were reviewed and included: trial protocols and amendments, delegation logs, case report forms, financial disclosure forms, monitoring procedures, monitoring logs, monitoring letters/follow-ups, trainings, investigational product accountability, investigator agreements, IRB submissions and approvals, IRB reporting, IRB correspondence, sponsor correspondence and sponsor reporting. There were no significant concerns.

Based on the results of the inspection, data generated at Dr. Farsad's site appear acceptable in support of the proposed indication in the NDA.

2. Dr. Ondrej Mika (Site 38010)
Matice Skolske 17, Euc Klinika Room 806,
Ceske Budejovice, Czech Republic

Inspection Dates: January 6 – 10, 2025

This investigator was inspected as BIMO review-based inspection for OASIS 1 and 2. This was the first FDA inspection for Dr. Mika.

The site screened 24 subjects and enrolled 20 subjects. There were no deaths. 2 subjects discontinued due to AEs, and 18 subjects completed the trial. The first participant enrolled in February 2022 with the last subject enrollment in November 2023.

Informed consent forms were reviewed for enrolled 12 subjects and found to be completed prior to initiation of any study procedures. Additional forms and data reviewed included the following: eligibility, case report forms (CRF), medical history, visit records, ultrasounds, study visits, medications, and protocol deviations.

The primary efficacy endpoint data was reviewed for 7 randomly selected subjects. The source eDiary data on site was compared to the submitted data listings from this site and there were no discrepancies identified. Data listings for SAEs and AEs were also verified for these subjects. AEs were reported accurately and there did not appear to be any underreporting of AEs. There were no incidents of underreported abnormal transvaginal ultrasounds.

Study-related documents were also reviewed and included: approved protocols; signed 1572s; financial disclosure statements; training information, enrollment log, IEC submissions and correspondence; and sponsor monitoring activities.

Protocol Deviations:

There were two participants enrolled who did not meet eligibility criteria based on systolic blood pressure ≤ 130 mmHg and diastolic ≤ 80 mmHg. Subject (b) (6) had values that were slightly elevated to 135 mmHg systolic, and Subject (b) (6) had a value of 85 mmHg diastolic, both on one occasion. All other blood pressures were in eligibility range. These deviations were addressed with the investigator who reported that normal values in Czech Republic were considered ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic. He acknowledged the necessity of following the protocol more closely in the future trials.

Reviewer Comment: Subject safety does not appear to have been negatively impacted by the protocol deviations identified at this site.

Based on the results of the inspection, data generated at Dr. Mika's site appear acceptable in

support of the proposed indication in the NDA.

3. Dr. Allen Dinnerstein (Site number 14001 (OASIS 2)/14002 (OASIS 3))
2828 S Seacrest Blvd Ste 209, Boynton Beach, FL, 33435-7944, US

Inspection Dates: October 29 - November 4, 2024

This investigator was inspected as a BIMO review-based inspection for OASIS 2 and OASIS 3. This was the first FDA inspection for this investigator.

Dr. Dinnerstein conducted OASIS 2 at Site 14001, from initial subject enrollment in October 2021 through the last visit in January 2024. The site screened 52 subjects and enrolled 18 subjects. 3 subjects discontinued (withdrew consent). 15 subjects completed the trial. There were no deaths or SAEs. Dr. Dinnerstein conducted the OASIS 3 trial at site 14002 from the first subject enrollment September 2021 through the last patient follow up visit in February 2024. The site screened 55 subjects and enrolled 18 subjects. 3 subjects discontinued (withdrew consent). 15 subjects completed the trial. There was one SAE but no deaths. For both trials, subjects were recruited from a (b) (4) research database, as well as IRB approved social media, and third-party recruiter references.

For OASIS 2 and 3, informed consent forms were reviewed for all enrolled subjects and found to be accurate and completed prior to enrollment. Additional forms and data reviewed included the following: medical history, inclusion/exclusion checklist, visit specific tasks and progress notes, adverse event forms, concomitant medication log, investigational product accountability, patient reported outcome assessments, imaging and biopsy results, and laboratory results.

The primary efficacy endpoint data flowed directly from the subject's handheld device to a central database according to the protocol. All ultrasound and endometrial biopsy reports were reviewed. There were no unreported protocol deviations or endometrial cancer cases identified.

Study-related documents were also reviewed and included: informed consents; approved protocols; signed 1572's; financial disclosure statements; IRB submissions and correspondence; adverse event reports; protocol deviations; subject source review; IP accountability; concomitant medications and monitoring activities.

There were no concerning issues related to study records. The site obtained IRB approval of all protocols in advance of study initiation/enrollment. The OII inspector reviewed the site visit log, and the site completed the study according to the appropriate schedule. Monitoring records showed that monitoring occurred as scheduled and required.

Based on the inspection findings, the data generated at Dr. Dinnerstein's site appear acceptable in support of the proposed indication in the NDA.

4. **Dr. Janusz Tomaszewski (Site number 18001)**
   Ginekologiczna Sp., U1, Parkowa 6,
   Bialystok, Poland

Inspection Dates: December 2 – December 6, 2024

This investigator was inspected as a BIMO review-based inspection for OASIS 2 and OASIS 3. This was the 3rd FDA inspection for this investigator with the prior FDA inspection taking place February 2022. No major issues were identified in the prior inspection.

Dr. Tomaszewski conducted OASIS 2 and 3 at Site 18001. For OASIS 2, he conducted the trial from initial subject enrollment in February 2022 through the last visit in August 2023. The site screened 100 subjects and enrolled 54 subjects. 10 subjects discontinued (4 due to AEs, 6 withdrew consent). 44 subjects completed the trial. There were no deaths or SAEs. For OASIS 3, Dr. Tomaszewski conducted the trial from the first subject enrollment February 2022 through the last patient follow up visit in January 2024. The site screened 78 subjects and enrolled 46 subjects. 11 subjects discontinued (5 due to AEs, 6 withdrew consent). 35 subjects completed the trial. There were no SAEs or deaths.

For OASIS 2 and 3, informed consent forms were reviewed for all enrolled subjects and found to be accurate and completed prior to enrollment. Additional forms and data reviewed included the following: subject's medical history, eligibility review, subject randomization, concomitant medication reporting, adverse event reporting, IP dosing, questionnaires, and study completion status. The source documentation at the site was compared against data line listings and no significant discrepancies were observed.

The inspector reviewed the primary efficacy HFDD daily diary raw data for both trials and found no discrepancies compared to sponsor submitted data listings. The inspector also reviewed the HFDD data audit trail and help desk reports and there were no concerns identified. All safety data and ultrasound and endometrial biopsy reports were reviewed. There were no unreported AE/SAEs, protocol deviations or endometrial cancer cases identified.

Study-related documents were also reviewed and included: approved protocols; signed 1572's; financial disclosure statements; IRB submissions and correspondence; protocol deviations; subject source review; IP accountability; and monitoring activities.

There were no concerning issues related to study records. The site obtained IRB approval of all protocols in advance of study initiation/enrollment. The OII inspector reviewed the site visit log, and the site completed the study according to the appropriate schedule. Monitoring records showed that monitoring occurred as scheduled and required.

Based on the inspection findings, the data generated at Dr. Tomaszewski's site appear acceptable in support of the proposed indication in the NDA.

5. Dr. Dagmara Makowska-Mainka (Site number 18005)
Aleja Wojciecha Korfantego 138,
Katowice, Poland

Inspection Dates: December 9 – December 12, 2024

This investigator was inspected as a BIMO review-based inspection for OASIS 2 and OASIS 3. This was the first FDA inspection for this investigator.

Dr. Makowska-Mainka conducted OASIS 2 and 3 at Site 18005. For OASIS 2, she conducted the trial from initial subject enrollment in March 2022 through the last visit in August 2023. The site screened 36 subjects and enrolled 16 subjects. 3 subjects discontinued. 13 subjects completed the trial. There were no deaths or SAEs. For OASIS 3, Dr. Makowska-Mainka conducted the trial from the first subject enrollment March 2022 through the last patient follow up visit in January 2024. The site screened 27 subjects and enrolled 17 subjects. 5 subjects discontinued. 12 subjects completed the trial. There were no SAEs or deaths.

For OASIS 2 and 3, informed consent forms were reviewed for all enrolled subjects and found to be accurate and completed prior to enrollment. Additional forms and data reviewed included the following: inclusion/exclusion criteria, adverse event reporting, randomization, concomitant medications, protocol deviations, medical history, questionnaires, demographics, IP dosing, vitals, laboratory, and PK sampling.

The inspector reviewed the primary efficacy HFDD daily diary raw data for both trials and found no discrepancies compared to sponsor submitted data listings. The investigator also reviewed the HFDD data audit trail and there were no concerns identified. All safety data and ultrasound and endometrial biopsy reports were reviewed. There were no unreported AE/SAEs, protocol deviations or endometrial cancer cases identified.

The inspection found inadequate record keeping as described below.

For OASIS 2, the site failed to maintain ultrasound images for 5 subjects. Dr. Makowska-Mainka acknowledged the oversight and explained the root cause of printer error and noted that the sub-Investigator (Dr. Agnieska Mierzwa-Daniluk) recorded all required data parameters directly from the ultrasound machine screen during the ultrasound visit and did provide these parameters in source data. Additionally, in her December 23, 2024 response, Dr. Makowska-Mainka acknowledged the observation and described the CAPA, which appears acceptable.

Reviewer Comment: The Sub (b) (6) record of the measurements is adequate to capture the data from the source images. Therefore, the results acquired are reliable, there were no adverse impact as a result of the inadequate records, and the safety profile of the investigational product should remain unchanged.

Study-related documents were also reviewed and included: informed consents; approved

protocols; signed 1572's; financial disclosure statements; IRB submissions and correspondence; and monitoring activities.

The site obtained IRB approval of all protocols in advance of study initiation/enrollment. The inspector reviewed the site visit log, and the site completed the study according to the appropriate schedule. Monitoring records showed that monitoring occurred as scheduled and required.

Based on the inspection findings, the data generated at Dr. Makowska-Mainka's site appear acceptable in support of the proposed indication in the NDA.

6. Dr. Abimbola O. Babajide (Site number 12007)
1 Faraday Way Kaman Court,
Blackpool, United Kingdom

Inspection Dates: January 6 - November 10, 2025

This investigator was inspected as a BIMO review-based inspection for OASIS 3. This was the first FDA inspection for this investigator.

Dr. Babajide conducted the OASIS 3 trial from the first subject enrollment February 2022 through the last patient follow up visit in January 2024. The site screened 134 subjects and enrolled 27 subjects. 6 subjects discontinued. 21 subjects completed the trial. There were no SAEs or deaths.

Informed consent forms were reviewed for all enrolled subjects and found to be accurate and completed prior to enrollment. Additional forms and data reviewed included the following: protocols, financial disclosure statements, site training, concomitant medications (CM), Ethics Committee (EC) submissions and correspondence, AE/SAE reporting, clinical source data, ultrasound imaging, study test article accountability, and sponsor monitoring activities for the inspected protocol.

The investigator reviewed the primary efficacy HFDD daily diary raw data for all enrolled subjects and found no discrepancies compared to sponsor submitted data listings. The investigator also reviewed the HFDD data audit trail and there were no concerns identified.

The inspector reviewed the safety data including AE/SAEs and concomitant medications for 15 out of enrolled 27 subjects and endometrial biopsy reports for 12 enrolled subjects. There were no unreported protocol deviations or endometrial cancer cases identified.
The inspection identified 6 unreported AEs:

Subject ID	Treatment Group	AE	Dates
(b) (6)	Elinzanetant	Alopecia	(b) (6)
	Placebo	COVID-19	
	Elinzanetant	Left leg cramp	

(b) (6)	Placebo	Shingles	(b) (6)
	Placebo	Face injury	
	Elinzanetant	Common Cold	

Reviewer Comment: The underreported AEs were discussed at inspection closeout with Dr. Babajide who has agreed to perform complete and timely AE reports in future trial conduct. Alopecia and left leg cramp were determined by Dr. Babajide as related to the IP (b) (4) (b) (4) *The Review Division may want to consider including these in their safety evaluation and labeling. All other unreported AEs are not likely related to be related to the IP in the opinion of this reviewer.*

Study-related documents were also reviewed and included: informed consents; approved protocols; signed 1572's; financial disclosure statements; IRB submissions and correspondence; screening and enrollment logs, adverse event reports; protocol deviation log; subject source review; and IP accountability.

There were no concerning issues related to study records. The site obtained IRB approval of all protocols in advance of study initiation/enrollment. The ORA inspector reviewed the site visit log, and the site completed the study according to the appropriate schedule. Monitoring records showed that monitoring occurred as scheduled and required.

Based on the inspection findings, the data generated at Dr. Babajide's site appear acceptable in support of the proposed indication in the NDA.

7. Bayer Healthcare Pharmaceuticals Inc. (FEI 2243252)
100 Bayer Blvd,
Whippany, NJ, 07981-1544, US

Inspection Dates: December 9 – 17, 2024

Bayer Healthcare Pharmaceuticals Inc. (Bayer) was inspected to evaluate their conduct and oversight of OASIS 1, 2, and 3 as the study sponsor. This sponsor has been inspected multiple times previously.

Sponsor's documents and procedures related to the conduct and monitoring of the OASIS trials were reviewed, including the sponsor's organizational charts, standard operating procedures (SOPs), key individuals and their responsibilities for the study, selection of investigators, monitors, and contract research organizations (CROs) for the study, training records, electronic data capture system used for the study, Form FDA 1572s, financial disclosures, site monitoring activities and reports, study randomization and data management, safety monitoring and reports, oversight of the participating CROs and related correspondences, protocol deviations, quality assurance plans, and investigational product accountability.

The inspector also reviewed details regarding the closure of site (b) (4) The site was removed from OASIS 1 due to GCP non-compliance identified during site monitoring. Deficiencies included (b) (4) (b) (4) At the time of removal, there were 7 screen failures and 2 early discontinuation subjects. Both subjects were included in the full analysis set and the safety analysis set. The Sponsor's oversight of clinical investigators appeared adequate.

Bayer contracted with (b) (4) to provide the Electronic Patient Reported Outcome (ePRO) for data collection. All ePRO software changes and User Acceptance Testing (UAT) were reviewed along with all ePRO errors for inspected sites. There were no deficiencies observed. The data management team reconciled ePRO data with diary data and study drug usage in the Interactive Response Technology (IRT).

(b) (4) was responsible for the management of project, sites, monitoring, regulatory submissions, grant administration, Trial Master File (TMF), database development, and managing the Independent Monitoring Committee (IDMC). (b) (4) (b) (4) was responsible for the randomization of patients and management of drug supply logistics, dispensing and unblinding; (b) (4) who was responsible for the electronic data capture. The Sponsor's oversight of (b) (4) appeared adequate.

The inspection found no compliance deficiencies in the sponsor's conduct and oversight of the OASIS trials. The numbers of subjects randomized in the study and participating investigator sites were consistent with those reported in the NDA. Data management, including data capture and analyses, was found to be adequate, with no issues noted.

{See appended electronic signature page}

Regina Zopf, M.D., M.P.H.,
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division/Division Director/
Review Division/Project Manager/
Review Division/Cross Discipline Team Lead/
Review Division/Clinical Reviewer/
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

REGINA R ZOPF
04/22/2025 10:55:50 AM

MICHELE B FEDOWITZ
04/22/2025 11:03:28 AM

JENN W SELLERS
04/22/2025 11:08:05 AM

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 20, 2025

To: Christina Chang, MD, MPH, Director
Division of Urology, Obstetrics and Gynecology

Through: Dominic Chiapperino, PhD, Director
Controlled Substance Staff

Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Neil B. Varshneya, PhD, MBA, Senior Pharmacologist
Controlled Substance Staff

Subject: **NDA 219469** for Lynkuet (elinzanetant) oral capsules, 60 mg
Indication: Moderate to severe vasomotor symptoms due to menopause
Dosage and Route: 120 mg (2 x 60 mg capsules), PO, QD
Sponsor: Bayer HealthCare Pharmaceuticals, Inc.
PDUFA Goal Date: July 26, 2025

Materials Reviewed: NDA 219469 received on July 26, 2024, and all amendments received to date.

Table of Contents

I. Executive Summary

1. Background

This memorandum is a response to a consult request by the Division of Urology, Obstetrics and Gynecology (DUOG) to evaluate abuse-related preclinical and clinical data submitted by Bayer HealthCare Pharmaceuticals, Inc. in NDA 219469 for Lynkuet (elinzanetant). This product is an opaque red soft capsule containing 60 mg of elinzanetant, administered orally. The drug product is indicated for moderate to severe vasomotor symptoms due to menopause. The recommended dose is 2 x 60 mg orally once daily. Elinzanetant is a new molecular entity that is a neurokinin-1 (NK-1) and neurokinin-3 (NK-3) receptor antagonist. It is not currently scheduled under the Controlled Substances Act (CSA). Elinzanetant achieves its therapeutic effect by selectively binding to and inhibiting NK-1 and NK-3 receptors, which are involved in the regulation of body temperature and vasomotor symptoms. The Sponsor hypothesizes that by blocking these receptors, elinzanetant can reduce the frequency and severity of hot flashes and night sweats associated with menopause. Preclinical studies have demonstrated high selectivity for NK-1 and NK-3 receptors, with minimal binding to other receptor types, supporting its targeted mechanism of action and low potential for off-target effects.

2. Conclusions

- Elinzanetant appears to be selective for NK-1 and NK-3 receptors and does not bind with significant affinity to receptor subtypes or targets associated with abuse potential.

- In nonclinical assessments, elinzanetant was not self-administered by non-human primates, suggesting a lack of reinforcing effects and negligible potential for abuse.

- In nonclinical assessments of physical dependence in non-human primates, elinzanetant did not produce a withdrawal syndrome upon discontinuation after 30 days of administration.

- Elinzanetant did not function as a discriminative stimulus in trained non-human primates, further supporting its low abuse potential.

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

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

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

- Elinzanetant does not appear to have a meaningful abuse potential and does not require scheduling under the Controlled Substances Act (CSA).

- Elinzanetant does not require section 9 (Drug Abuse and Dependence) in its label.

II. Discussion

1. Chemistry
1.1 Substance Information

Drug Substance. The chemical structure of elinzanetant is shown in **Figure 1**. Elinzanetant has a molecular formula of C33H35F7N4O3 and a molecular weight of 668.6 g/mol. The IUPAC name for elinzanetant is N-[6-[(7S,9aS)-7-(hydroxymethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-4-(4-fluoro-2-methylphenyl)pyridin-3-yl]-2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamide. The chemical properties and structural identifiers of elinzanetant including the IUPAC Name, PubChem ID, CASRN, UNII, Molecular Formula, Molecular Weight, Canonical SMILES, Isomeric SMILES, InChI, and InChIKey are shown in **Table 1**.

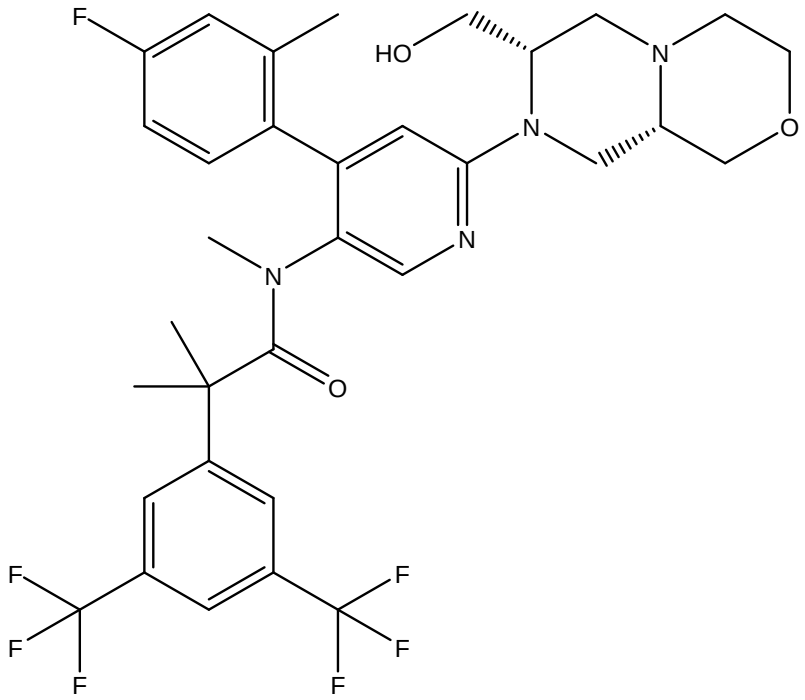


Figure 1. Chemical Structure of Elinzanetant.

Table1. Chemical Properties and Structural Identifiers of Elinzanetant	
Property or Identifier	**Value**
Common Name	elinzanetant
IUPAC Name	N-[6-[(7S,9aS)-7-(hydroxymethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-4-(4-fluoro-2-methylphenyl)pyridin-3-yl]-2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamide
PubChem ID	16063568
CASRN	929046-33-3
UNII	NZW2BOW35N
Molecular Formula	C33H35F7N4O3
Molecular Weight	668.6 g/mol
Isomeric SMILES	CC1=C(C=CC(=C1)F)C2=CC(=NC=C2N(C)C(=O)C(C)(C)C3=CC(=CC(=C3)C(F)(F)F)C(F)(F)F)N4C[C@H]5COCCN5C[C@H]4CO
InChI	InChI=1S/C33H35F7N4O3/c1-19-9-23(34)5-6-26(19)27-13-29(44-16-25-18-47-8-7-43(25)15-24(44)17-45)41-14-28(27)42(4)30(46)31(2,3)20-10-21(32(35,36)37)12-22(11-20)33(38,39)40/h5-6,9-14,24-25,45H,7-8,15-18H2,1-4H3/t24-,25-/m0/s1
InChIKey	DWRIJNIPBUFCQS-DQEYMECFSA-N
IUPAC = International Union of Pure and Applied Chemistry CASRN = Chemical Abstract Service Registry Number UNII = Unique Ingredient Identifier SMILES = Simplified Molecular-Input Line-Entry System InChI = International Chemical Identifier InChIKey = InChIKey is a hashed version of the full InChI (using the SHA-256 algorithm)	

Elinzanetant shares structural similarities with netupitant, and both are neurokinin receptor antagonists. Netupitant is a component of Akynzeo, an FDA-approved antiemetic medication used to prevent chemotherapy-induced nausea and vomiting. The structural similarity between elinzanetant and netupitant has implications for elinzanetant's potential abuse liability. Given that netupitant is not classified as a controlled substance and has not shown significant abuse potential in clinical use, it suggests that elinzanetant may also have a low risk of abuse. However, it's important to note that structural similarity alone does not guarantee identical pharmacological properties or abuse potential.

Drug Product. The drug product is described as an opaque red soft capsule with an oblong shape, measuring approximately 24.4 mm in length and 10.7 mm in diameter. Each capsule weighs 1840.13 mg and is marked with "EZN60". The capsules are packaged in blister containers.

The composition of each capsule includes 60 mg of the active ingredient elinzanetant, along with various excipients. The fill mass contains (b) (4),

including all-rac-α-Tocopherol, caprylocaproyl macrogolglycerides, glycerol monocaprylocaprate, glycerol mono-oleate, and polysorbate 80. (b) (4) (b) (4) gelatin, (b) (4) ferric oxide red and yellow, titanium dioxide (b) (4) (b) (4) (b) (4)

The capsules are printed with a white ink containing various components, including (b) (4) (b) (4) (b) (4)

From an abuse potential perspective, none of the excipients are controlled substances or are otherwise known to have abuse-related effects.

2. Nonclinical Pharmacology

2.1 Receptor Binding Affinity and Functional Activity

Elinzanetant was evaluated for its in vitro receptor binding affinity and functional activity. Elinzanetant demonstrated high selectivity for human NK-3 and NK-1 receptors in a (b) (4) screen, showing >100-fold and >300-fold selectivity, respectively, compared to 88 other non-tachykinin targets. In a panel of 44 molecular target assays, elinzanetant showed no significant activity (EC50 and/or IC50 < 1 µM) and only weak activity (EC50 and/or IC50C50 > 10 µM) in other assays. Further, radioligand binding assays revealed weak interactions with estrogen and progesterone receptors, with IC50 values of 22.5 µM and 0.64 µM, respectively. No significant effects were observed on estrogen or progesterone receptor coactivators. Additionally, elinzanetant showed no significant activity against monoamine oxidase MAO-A, dopamine D1, and opiate δ1 receptors at concentrations up to 10 µM. These results collectively demonstrate elinzanetant's selective activity at NK-1 and NK-3 receptors and suggest a low potential for off-target effects. None of elinzanetant’s receptor targets are known to be associated with abuse potential.

2.2 Findings from Safety Pharmacology and Toxicology Studies

GSK1144814C: Acute Neurobehavioural Effects Following Oral Administration in the Conscious CD™ Rat (Report ID: R-13668; Study ID: 20080011PGRB; Report Date: June 4, 2008)

Elinzanetant was evaluated for potential effects on central nervous system (CNS) activity in a modified Irwin test. The experiment involved 8 male Sprague-Dawley rats per group, with single oral administration of elinzanetant at doses of 0, 5, 25, or 100 mg/kg. The drug was prepared in 1.0% aqueous methylcellulose and administered via oral gavage at 10 mL/kg. General behavior, motor activity, vigilance, and core body temperature were assessed. Results showed no changes related to elinzanetant in body temperature, peripheral, or CNS activities up to 48 hours post-dose at any dose level. Additionally, information from a separate 4-week toxicity study revealed that daily oral administration of 100 mg/kg/day to male Sprague-Dawley rats resulted in Cmax or AUC values on Day 25 that were 15-fold (unbound) or 44-fold (unbound) greater than therapeutic human plasma levels. This study demonstrated no significant changes in the

measured parameters.

2.3 Animal Behavioral Studies

Assessment of the Subjective Effects of Elinzanetant in Male Cynomolgus Monkeys in a Drug Discrimination Model (Report ID: B003002; Study ID: T105225-5; Report Date: April 17, 2024)

Elinzanetant was evaluated for potential subjective-like effects in a drug discrimination paradigm. The experiment was conducted in two distinct phases, each utilizing a separate group of male non-human primates (NHPs). The first phase, a dose-finding experiment, employed six trained animals in a single-lever operant conditioning task with an FR30 schedule. This group was tested with ascending doses of elinzanetant (0, 5, 10, 20, and 40 mg/kg) and vehicle, with each dose administered orally via gavage at 4 mL/kg on separate days, allowing for training and washout periods between doses. The second phase, the drug discrimination phase, used a different set of six trained animals in a two-choice, two-lever operant discrimination task, also with an FR30 schedule. This phase compared elinzanetant (40 mg/kg) to vehicle over a 30-day period (Days 29-58), with treatments alternated daily according to a pseudo-random schedule. In both phases, oral administration of treatments occurred approximately 60 minutes before testing. The study aimed to determine if elinzanetant could function as a discriminative stimulus. However, no additional testing was conducted as elinzanetant failed to function as a discriminative stimulus.

Abuse Liability of Elinzanetant Administered Intravenously: Assessment of the Reinforcing Potential in Cynomolgus Monkeys Maintained to Self-Administer Cocaine (Report ID: B003288; Study ID: T105226-6; Report Date: April 17, 2024)

Elinzanetant was evaluated for potential reinforcing efficacy in a drug self-administration paradigm using adult NHPs previously trained to self-administer cocaine. Six male NHPs were initially conditioned to self-administer 0.18 mg/kg/injection of cocaine using a standard operant single-lever training procedure. The experiment then tested various doses of cocaine (0.032 to 0.32 mg/kg/injection) as a positive control, and elinzanetant (0 to 0.195 mg/kg/injection) as the test article. Treatments were administered intravenously through surgically-implanted venous catheters during 1-hour access periods for 3 consecutive daily sessions. The study assessed toxicity and abuse liability based on mortality, clinical observations, body weight, and behavioral measures. Plasma concentrations of elinzanetant were also determined following the 0.05 mg/kg/injection dose. Results showed that elinzanetant did not initiate or maintain self-administration in the NHPs. Elinzanetant intakes were significantly lower than those of cocaine, saline, or vehicle, and response patterns were variable and inconsistent across subjects regardless of the dose. The study demonstrated that elinzanetant has minimal abuse liability as measured in this behavioral assay.

2.4 Tolerance and Physical Dependence Studies in Animals

Physical Dependence Liability of Elinzanetant in Male Cynomolgus Monkeys and an Assessment of Discontinuation Syndrome After Repeated Dose Treatments for 30 Days (Report ID: B003013; Study ID: T105227-7; Report Date: April 17, 2024)

Elinzanetant was evaluated for its potential to produce a physical dependence and signs of a discontinuation (withdrawal syndrome) in NHPs after 30 days of twice-daily administration. The experiment involved five groups of male NHPs, with elinzanetant administered orally (Groups 2-3) or intravenously (Group 4), a vehicle control group (Group 1), and a methamphetamine positive control group (Group 5). Dosing occurred twice daily for 29 days, followed by a single dose on Day 30 leading into the discontinuation phase. The study evaluated various parameters including mortality, clinical signs, functional observational battery (FOB) evaluations, body weights, hemodynamic parameters, body temperature, activity counts, ECG, and toxicokinetics. Results showed that elinzanetant did not elicit any significant behavioral, cardiovascular, or physiological markers consistent with known withdrawal syndromes from common drugs of abuse. A single parameter of rectal body temperature differences was observed in FOB data but was attributed to handling and restraint rather than true core body temperature changes. The study demonstrated that elinzanetant did not produce significant signs of physical dependence or withdrawal syndrome upon discontinuation.

3. Pharmacokinetics

An open-label single-sequence crossover study to investigate the Pharmacokinetics of repeat doses of NT-814 and the effect of food on single doses of NT-814 in healthy female volunteers (Reference Number: RD-SOP-1154; Report Number: R-13551; Report Date: November 6, 2019).

Elinzanetant was assessed for its pharmacokinetic (PK) properties at various doses (40, 80, 120, and 160 mg) in a Phase 1 open-label, single-sequence, crossover design study in healthy female volunteers (n = 49). The study was divided into two parts: Part 1 involved a single dose administration under fed conditions, while Part 2 consisted of repeated daily dosing for 7 days under fasted conditions. Subjects were screened within 21 days before the first dose and assigned to one of the four dose levels. In Part 1, subjects received a single dose of elinzanetant 30 minutes after a high-fat breakfast. In Part 2, subjects took daily doses of elinzanetant for 7 days, with the first dose under fasted conditions and subsequent doses 3 hours after breakfast. Blood samples were collected for PK and metabolite profiling, and urine was collected for 24 hours after the final dose in Part 2. Safety was monitored throughout the study through various assessments, including adverse events, vital signs, ECGs, and clinical laboratory tests. A follow-up visit was conducted one week after the final dose.

Elinzanetant demonstrated consistent PK parameters across all dose levels. On Study Day 1 (fed conditions), mean plasma concentrations peaked at 3-4 hours post-dose, with Cmax ranging from 225.1 to 1063 ng/mL. On Study Days 11 (fasted) and 17 (3 hours post-breakfast), Cmax values were higher and reached more quickly (within 1.5 hours), ranging from 556.2 to 3290 ng/mL. The absorption phase was longer and flatter on Study Day 1 compared to Days 11 and 17. Greater than dose-proportional increases were observed for Cmax and AUC parameters with increasing dose levels. Dose accumulation assessment showed a slight decrease in Cmax but an increase in AUCtau on Day 17 compared to Day 11. Variability in Cmax and AUCtau was generally less than 50% across dose levels. Food effect analysis revealed that administration after a high-fat breakfast (Day 1) resulted in lower Cmax (approximately one-third) and AUC24 (30-

40% reduction) compared to fasted conditions (Day 11). This study demonstrated that elinzanetant 's PK is influenced by dose level and food intake, with higher exposures observed under fasted conditions.

4. Clinical Studies

Table 2 shows an overview of the studies included in the integrated safety analysis for abuse-potential-related adverse events. The table outlines three main studies: SWITCH-1, OASIS 1, and OASIS 2, with an additional long-term study, OASIS 3. SWITCH-1 (Study ID 21686) was a Phase 2b trial lasting 12 weeks. It tested four different doses of Elinzanetant (40 mg, 80 mg, 120 mg, and 160 mg) against a placebo. Only the 120 mg dose and placebo arms from this study were included in the integrated analysis. OASIS 1 (Study ID 21651) and OASIS 2 (Study ID 21652) were both Phase 3 trials with a planned treatment duration of 12+14 weeks. Both studies included an Elinzanetant 120 mg arm and a placebo arm that switched to Elinzanetant 120 mg. All arms from these studies were included in the integrated analysis. OASIS 3 (Study ID 21810) was a longer-term Phase 3 study lasting 52 weeks. It compared Elinzanetant 120 mg to placebo, with both arms included in the integrated analysis. Across all studies, the 120 mg dose of Elinzanetant was consistently included, because it was the focus of the drug development program. The studies progressively increased in duration from 12 weeks in the Phase 2b trial to 52 weeks in the long-term Phase 3 study, allowing for assessment of both short-term efficacy and long-term safety and efficacy.

Table 2. Summary of Clinical Studies

Study name	Study ID	Phase	Planned treatment duration	Treatment arms	Inclusion in this integrated analysis
SWITCH-1	21686	2b	12 weeks	Elinzanetant 40 mg	No
				Elinzanetant 80 mg	No
				Elinzanetant 120 mg	Yes
				Elinzanetant 160 mg	No
				Placebo	Yes
OASIS 1	21651	3	12+14 weeks	Elinzanetant 120 mg	Yes
				Placebo - Elinzanetant 120 mg	Yes
OASIS 2	21652	3	12+14 weeks	Elinzanetant 120 mg	Yes
				Placebo - Elinzanetant 120 mg	Yes
OASIS 3	21810	3	52 weeks	Elinzanetant 120 mg	Yes
				Placebo	Yes

4.1 Human Abuse Potential Studies

A human drug abuse potential study was not required nor conducted for elinzanetant.

4.2 Abuse-Related Adverse Event Profile Through all Phases of Development

Drug Abuse Potential

The drug abuse potential of elinzanetant, a centrally acting dual NK-1/3 antagonist, was assessed in accordance with FDA guidelines. Non-clinical studies, conducted alongside Phase 3 trials, showed no indication of abuse potential. Clinical data from the OASIS 1, 2, 3, and SWITCH-1 studies revealed a higher proportion of abuse potential-related events in the elinzanetant 120 mg group (7.2%) compared to placebo (2.3%) during the first 12 weeks, primarily due to increased reports of dizziness and somnolence. Similar patterns were observed in longer-term analyses. Post-treatment adverse events related to abuse potential were rare and balanced between groups. Based on both non-clinical and clinical assessments, elinzanetant is not expected to have a clinically relevant abuse potential.

The data from **Table 3** presents a comparison of on-treatment adverse events (AEs) related to abuse potential between the elinzanetant (EZN) 120 mg group and the placebo group during the first 12 weeks of treatment. A notably higher percentage of women in the EZN group (7.2%) experienced at least one such event compared to the placebo group (2.3%). The most common AEs were in the nervous system disorders category, with somnolence (3.4% vs 0.5%) and dizziness (3.0% vs 1.1%) being more prevalent in the EZN group. Psychiatric disorders were also more frequent in the EZN group, including irritability (0.5% vs 0.3%) and mood alterations (0.3% vs 0%). Overall, while the incidence of abuse potential-related AEs was relatively low in both groups, there was a clear trend towards more frequent occurrences of dizziness and somnolence in the EZN 120 mg group compared to placebo.

Table 3. On-treatment AEs up to Week 12 related to abuse potential by primary System Organ Class and PT (SAF, pooled safety population)

Primary System Organ Class	**EZN 120 mg**	**Placebo**
Preferred Term (PT)	**(Week 1–12)**	**(Week 1–12)**
MedDRA Version 26.1	**N=765 (100%)**	**N=754 (100%)**
Number of women with at least one such event	55 (7.2%)	17 (2.3%)
General disorders and administration site conditions		
Feeling abnormal	0	1 (0.1%)
Nervous system disorders		
Dizziness	23 (3.0%)	8 (1.1%)
Somnolence	26 (3.4%)	4 (0.5%)
Psychiatric disorders		
Apathy	1 (0.1%)	0
Confusional state	1 (0.1%)	0
Dysphoria	1 (0.1%)	0
Irritability	4 (0.5%)	2 (0.3%)
Mood altered	2 (0.3%)	0
Mood swings	1 (0.1%)	2 (0.3%)

MedDRA = medical dictionary for regulatory activities, PT = preferred term, SAF = safety

analysis set. On-treatment AEs are defined as adverse events with onset between the first and the last study drug intake.

Table 4 presents data on on-treatment adverse events (AEs) related to abuse potential for elinzanetant (EZN) 120 mg and placebo groups over 26 and 52 weeks. The EZN group consistently showed a higher incidence of AEs compared to placebo. At 26 weeks, 5.8% of EZN patients experienced at least one such event (IR: 16.88 per 100 person-years) versus 2.9% in the placebo group (IR: 9.64). This trend continued at 52 weeks with 5.9% in the EZN group (IR: 12.90) compared to 3.2% in the placebo group (IR: 7.57). Nervous system disorders, particularly dizziness and somnolence, were the most common AEs in both groups, with higher rates in the EZN group. Psychiatric disorders such as irritability and mood alterations were also more frequent in the EZN group. Interestingly, some rare events like alcohol use disorder and confusional state were only reported in the EZN group, while dependence was only observed in the placebo group. Overall, the data suggests a higher risk of dizziness and somnolence with EZN treatment, though the absolute rates remained relatively low.

Table 4. On-treatment AEs up to Weeks 26 and 52 related to abuse potential by primary System Organ Class and PT (SAF, pooled safety population)

Primary System Organ Class **Preferred Term (PT)** **MedDRA Version 26.1**	**Week 1–26**		**Week 1–52**	
	EZN 120 mg	Placebo	EZN 120 mg	Placebo
	N=1113 (100%)	N=754 (100%)	N=1113 (100%)	N=754 (100%)
	n (%) / IR (100 py)a)	n (%) / IR (100 py)a)	n (%) / IR (100 py)a)	n (%) / IR (100 py)a)
Number of women with at least one such event	64 (5.8%) / 16.88	22 (2.9%) / 9.64	66 (5.9%) / 12.90	24 (3.2%) / 7.57
General disorders and administration site conditions				
Feeling abnormal	0	1 (0.1%) / 0.29	0	1 (0.1%) / 0.22
Nervous system disorders				
Dizziness	28 (2.5%) / 6.75	8 (1.1%) / 3.69	31 (2.8%) / 5.61	9 (1.2%) / 2.93
Somnolence	27 (2.4%) / 7.30	6 (0.8%) / 2.46	27 (2.4%) / 5.35	7 (0.9%) / 2.03
Psychiatric disorders				
Alcohol use disorder	1 (<0.1%) / 0.19	0	1 (<0.1%) / 0.14	0
Apathy	1 (<0.1%) / 0.30	0	1 (<0.1%) / 0.22	0
Confusional state	1 (<0.1%) / 0.30	0	1 (<0.1%) / 0.22	0
Dependence	0	1 (0.1%) / 0.29	0	1 (0.1%) / 0.22

Dysphoria	1 (<0.1%) / 0.19	0	1 (<0.1%) / 0.14	0
Emotional disorder	0	0	1 (<0.1%) / 0.22	0
Irritability	6 (0.5%) / 1.38	3 (0.4%) / 1.21	6 (0.5%) / 1.01	3 (0.4%) / 0.89
Mood altered	3 (0.3%) / 0.69	0	3 (0.3%) / 0.50	0
Mood swings	1 (<0.1%) / 0.30	3 (0.4%) / 1.55	1 (<0.1%) / 0.22	3 (0.4%) / 1.13

MedDRA = medical dictionary for regulatory activities, PT = preferred term, SAF = safety analysis set. On-treatment AEs are defined as adverse events with onset between the first and the last study drug intake. a) IR (100 py) = incidence rate per 100 person-years. IRs are study size adjusted incidence rates according to (Crowe et al 2016). Switchers from OASIS 1 and 2 are included in all groups but the event is assigned only to the treatment they received when the event started.

Table 5 presents data on post-treatment adverse events (AEs) related to abuse potential for the elinzanetant (EZN) 120 mg group and the placebo group over a 52-week period. The overall incidence of such events was low in both groups, with a slightly higher percentage in the placebo group (0.5%) compared to the EZN group (0.3%). In the EZN group, all reported events were related to nervous system disorders, specifically dizziness, affecting 3 women (0.3%). The EZN group also had one case of apathy (<0.1%) in the psychiatric disorders category. In contrast, the placebo group experienced no cases of dizziness but had one case each of somnolence (0.2%) and irritability (0.2%). Overall, the data suggests that post-treatment AEs related to abuse potential were infrequent in both groups.

Table 5. Post-treatment AEs related to abuse potential by primary System Organ Class and PT (SAF, pooled safety population)

Primary System Organ Class	**EZN 120 mg**	**Placebo**
Preferred Term (PT)	**(Week 1-52) a)**	**(Week 1-52) a)**
MedDRA Version 26.1	**N=1113 (100%)**	**N=406 (100%)**
Number of women with at least one such event	3 (0.3%)	2 (0.5%)
Nervous system disorders		
Dizziness	3 (0.3%)	0
Somnolence	0	1 (0.2%)
Psychiatric disorders		
Apathy	1 (<0.1%)	0
Irritability	0	1 (0.2%)

AEs = adverse events, MedDRA = medical dictionary for regulatory activities, PT = preferred term, SAF = safety analysis set. For abuse potential, post-treatment AEs are all AEs with an onset after the last study drug intake date. a) Placebo (Week 1-52) includes women who received placebo only. Switchers are included in EZN 120 mg (Week 1-52) group only

Withdrawal

Based on the available non-clinical and clinical data there is currently no indication of withdrawal or rebound effects after discontinuation of elinzanetant. In the clinical studies conducted so far, participants were followed for up to 4 weeks after discontinuation of the study drug.

Overdose

There have been no reported cases of accidental or intentional overdose of elinzanetant. Clinical studies have tested single doses up to 600 mg in healthy volunteers, with adverse events at higher doses being similar to those observed at the therapeutic dose of 120 mg, albeit slightly more frequent and moderately more intense. Multiple daily doses up to 240 mg over 5 days were also tested in a driving ability study and were well-tolerated. No dose-limiting toxicities were observed in these studies.

Conclusion

Potential abuse-related AEs in human trials included somnolence and dizziness which were mild, self-resolving, and not associated with euphoria, intoxication, stimulation, or other signals suggesting they would be pleasant or attractive to recreational drug users. Consistent with the nonclinical data, the clinical adverse events data do not suggest that elinzanetant has meaningful abuse potential or is likely to produce physical dependence and withdrawal.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 219469
Submission Number	1
Submission Date	7/26/2024
Date Consult Received	8/7/2024
Drug Name	Elinzanetant (BAY 3427080)
Indication	Treatment of moderate to severe vasomotor symptoms associated with menopause
Therapeutic Dose	120 mg once daily
Clinical Division	DUOG
Protocol Review	Previous IRT review 04/19/2024 (link)

Note: Any text in the review with a light background should be considered to be copied from the Applicant's document.

This review responds to your consult dated 8/7/2024 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 10/28/2020, 04/19/2022, 08/16/2022 under IND 129492 in DARRTS;
- Proposed label (NDA219469 / SN0001; link);
- QT evaluation report (NDA219469 / SN0001; link);
- Clinical study report for study 21670 (NDA219469 / SN0001; link);
- Tables and Figures of further safety analyses for study 21670 (NDA219469 / SN0001; link)
- QT evaluation checklist (NDA219469 / SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA219469 / SN0001; link).

1 SUMMARY

Elinzanetant did not prolong the QTcF interval in this QTc assessment of PK/ECG data from study 21670 (see Table 1 for overall results). However, due to the limitations of the clinical study and the non-clinical assays, this QTc assessment does not sufficiently characterize QTc effects of elinzanetant at the anticipated high clinical exposure scenario which is in patients co-administered with strong CYP3A4 inhibitors.

Study 21670 had 2 parts. Part 1 was a double-blind, randomized, placebo-controlled, single ascending dose study (with sequential dose groups: 240 mg, 360 mg, 480 mg, and 600 mg) evaluating the effect of elinzanetant on the QTc interval in healthy subjects. Part 2 of the study was an open-label, randomized, 2-period, 2-sequence cross-over design.

Study 21670 lacks adequate assay sensitivity to characterize QTc effects at the anticipated high clinical scenario for the following reasons:

- The moxifloxacin treatment in part 2 cannot serve as a positive control for QTc assessment in part 1 because it was not evaluated concurrently with the investigational product. We did not agree with this design when we reviewed the protocol, and our comments were sent to the applicant in an Advice Letter on 09/15/2022.
- The highest tested dose in part 1 does not provide sufficient coverage of high clinical exposure (at least 2-fold) to waive the requirement for positive control. Although the highest dose covers high clinical exposure by 1.6-fold, non-clinical assays do not support integrated clinical and non-clinical QTc assessment as: (1) hERG assay had significant deviations from recommended best practices and hERG margin was not sufficiently high (only about 120-fold); and (2) highest exposure in animal cardiovascular QTc assessment did not provide sufficient coverage of high clinical exposure in humans.

Part 1 was used for the current QTc assessment. Data were analyzed using exposure-response as the primary analysis, which did not suggest that elinzanetant is associated with significant QTc prolonging effect (refer to section 4.5). The findings of the primary analysis are further supported by absence of concerning cardiovascular adverse events in healthy subjects and postmenopausal women with vasomotor symptoms (Section 3.2.4), and lack of outlying QTc prolongations events (Section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☒ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• High clinical exposure is anticipated to be 3.3-fold increase in the clinical exposure is expected in patients with coadministration of strong CYP3A4 inhibitor (section 3.1)
• The highest dose in QT assessment covers ~1.6 fold over high clinical exposure scenario.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTcF</td><td>Elinzanetant 120 mg QD</td><td>1426 µg/mL</td><td>-0.5</td><td>(-2.6 to 1.7)</td></tr>
<tr><td>QTcF</td><td>Elinzanetant 120 mg QD + strong CYP3A4 inhibitors</td><td>4696 µg/mL</td><td>-0.9</td><td>(-3.3 to 1.5)</td></tr>
<tr><td>QTcF</td><td>Elinzanetant (600 mg)</td><td>7,393.3 µg/mL</td><td>-1.2</td><td>(-4.2 to 1.7)</td></tr>
</table></td></tr>
<tr><td>Nonclinical findings</td><td>Integrated nonclinical QTc assessment was not conducted due to the limitations of the non-clinical assays (See section 3.1.2)</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY APPLICANT

There are no questions from applicant.

1.2 COMMENTS TO THE REVIEW DIVISION

Elinzanetant did not prolong the QTc interval based on assessment of ECG/PK data from study 21670. However, the QTc assessment does not sufficiently characterize QTc effects at the anticipated high clinical exposure scenario in patients co-administered with strong CYP3A4 inhibitors. This QTc assessment can serve as a substitute for a thorough QT study provided that therapeutic dose does not exceed 600 mg or/and provided that elinzanetant is not used in patients with strong CYP3A4 inhibitor.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 001 (link). Our changes are highlighted (addition, ~~deletion~~). However, we have some. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology *No clinically relevant prolongation of the QTc interval was observed after single oral administration of elinzanetant at doses up to 5 times the maximum recommended dose. However, QTc prolongation effect of elinzanetant when co-administered with strong CYP3A4 inhibitors has not been sufficiently characterized.*
Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

Elinzanetant (LYNKUET™, NT-814, BAY3427080, GSK1144814; MW: 668.7 g/mol) is a non-hormonal, neurokinin (NK-1 and NK-3) receptors antagonist indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. The recommended dose is 120 mg capsules orally once daily at bedtime with or without food.

We reviewed the QT assessment proposal previously (DARRTS 10/28/2020, 04/19/2022, 08/16/2022). The Applicant requested substitution of thorough QT study and planned to conduct a high dose safety study in parallel with phase 3 study. We recommended the Applicant to submit study protocol for review (10/28/2020).

The Applicant subsequently submitted the study protocol for 21670. It was a [redacted] However, we disagreed with the design as it could have been [redacted] We suggested alternative designs (04/19/2022).

The Applicant subsequently proposed a revised design that was different from our suggestions. They proposed a double-blind, randomized, placebo-controlled, single ascending dose study (4-sequential dose groups 240, 360, 480, and 600 mg; n=12; 9+3/dose group with sentinel sub-group; soft gel capsules) (Part 1) and an open-label, randomized, cross-over design with 2 cross-over periods (P1: Moxifloxacin or placebo and P2: Placebo or Moxifloxacin) (Part 2). We disagreed with the study design because the positive control (in Part 2) was not evaluated concurrently with the investigational product (in Part 1) (08/16/2022).

In this submission, the Applicant submitted QT evaluation report based on multiple studies. The Applicant provided outlier analysis for 7 phase 1 studies and safety analysis for phase 1, 2 and 3 studies. Concentration-QTc analysis was provided for study 21670 Part 1 (Cmax 7390 µg/L for 600 mg). Note that we did not agree to use Part 2 for assay sensitivity (see 08/16/2022).

3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety.

The steady state therapeutic exposure with a dose of 120 mg/day is based on final popPK Model supported by pharmacokinetics (PK) data from Phase 3 studies (OASIS 1-3). In phase 3 studies study treatments were taken before going to bed, with or without food.

Three principal metabolites were detected in human plasma: M30/34 (monooxidation, > 10% of drug related exposure), M27 (monooxidation, <10% of drug related exposure), and M18/21 (double oxidation <10% of drug related exposure). The principal metabolites circulating in human plasma are also present in rat, mouse, rabbit, and monkey plasma.

Median Tmax for parent is 1 hour. Main elimination route is through feces (~90%). Terminal half-life after multiple doses is 45 hours. Mean accumulation ratios are ranging from 1.4 to 2.0 after 5-7 days treatment.

In subjects with moderate renal impairment (eGFR: 30 to < 60 mL/min/1.73 m2), geometric mean Cmax is increased by 2.29-fold, with severe impairment (eGFR <30 mL/min/1.72 m2) Cmax increased by 1.91-fold after single dose of 120 mg compared to normal renal function (Study 21669). [redacted] No dose adjustment is required for mild or moderate renal impairment.

Following multiple-dose administration of 120 mg elinzanetant in women with mild chronic hepatic impairment (Child-Pugh Class A), mean (90%CI) Cmax,md (multiple-dose) of elinzanetant increased by 1.16-fold (0.81;1.67) relative to women with normal hepatic function. In women with moderate (Child-Pugh Class B) chronic hepatic impairment (cirrhosis), mean Cmax,md increased by 2.32-fold (1.61;3.34) (study 21668). Elinzanetant has not been studied in subjects with severe hepatic impairment. The proposed label does not recommend use in moderate or severe hepatic impairment. No dose adjustment is required for mild hepatic impairment.

Co-administration of elinzanetant with strong CYP3A4 and P-gp inhibitor itraconazole resulted in a mean (90%CI) 3.31-fold (2.74;3.99) higher Cmax. This is considered as high clinical exposure scenario. Label has no contraindications but concomitant use with strong (b) (4) CYP3A4 inhibitors is not recommended. According to the Applicant, safety of concomitant use of moderate and strong CYP3A4 inhibitors with elinzanetant has not been investigated in Phase 3 studies and this scenario is not likely to occur often.

Geometric mean Cmax under fed conditions were reduced by approximately 70% with high fat, high calorie meal compared with the fasted state.

Table 2: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	120 mg QD, oral capsules	1423 µg/L ($C_{max,ss}$)
Applicant's High clinical exposure scenario	3.3-fold increase with strong CYP3A4 inhibition	4696 µg/L
Highest dose in QT assessment	600 mg single dose oral capsules in study 21670	7390 µg/L
C_{max} Ratio	1.6-fold over high clinical exposure (co-administration with strong CY3A4 inhibitor 5.2-fold over clinical exposure	

3.1.2 Nonclinical Safety Pharmacology Assessments

The Applicant evaluated the effects of elinzanetant on hERG current in the study report (R-13675, link). The hERG current was assessed at room temperature using a step-step voltage protocol (from a holding potential of -80 mV to a step pulse at + 20 mV for 5 s, followed by a repolarizing pulse to -50 mV for 5 s) at a frequency of 15 s. Samples collected from the stock solution were used for drug concentration verification. The results of analysis showed that the measured concentrations were within 100±10% of the nominal concentrations. The reduction in hERG current at the highest tested concentration of 1.91 µmol/L (1275 µg/L, limit of solubility) was 18.2%. This concentration provides 27-fold (MW: 668.7 g/mol; PB: 99%) the unbounded high clinical exposure (see Table 2). Assuming a hill coefficient of 1 this corresponds to an IC50 of 5730 µg/L and a safety margin of 122-fold.

Reviewer's Comments: *The hERG assay deviated (room temperature; slow pacing frequency; sample solutions were collected from the stock for drug concentration verification) from the best practice recommendations by S7B Q&As 2.1. Additionally, to*

support an integrated risk assessment, the Applicant will need to demonstrate that the hERG safety margin is higher than safety margins computed under the same experimental protocol for a series of reference drugs known to cause TdP. Therefore, the current hERG assay may not be included to support an integrated risk assessment.

The in vivo QT study (R-13670, link) assessed the effects of elinzanetant on ECG parameters following single oral doses of vehicle or 6, 20, and 60 mg/kg elinzanetant to conscious telemetrized male (n=4) cynomolgus monkeys. Plasma concentrations were not reported in this study. In a 7-day toxicology study (R-13627; link), Cmax was 0.619 µg/mL in female (n = 1) and 2.62 µg/mL in male (n = 1) after a single dose of 60 mg/kg. The results from study PH-42081 showed the protein binding was 98.3% (i.e, 97% in male and 99.6% in female) in monkeys (see Table 1 in study PH-42081, link). The exposure of the highest dose in the study is ~0.95x the high clinical exposure (4696 µg/L). No arrhythmia or abnormality in HR, QTc, PR, or QRS were observed at the highest dose.

Reviewer's comments: *No QTc prolongation was observed at exposure ~0.95 x the high clinical exposure in the in vivo monkey study.*

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for Elinzanetant was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *The Applicant used the time-matched baseline and provided the summary statistics (mean (SD), median, minimum, and maximum) and descriptive parametric statistics of QTcF, ΔQTcF, RR, ΔRR, PR, ΔPR, QRS, and ΔQRS for each dose. However, since this is a parallel study in Part 1 and the sample size for each dose group is small, reviewer used the pre-dose baseline and conducted non-parametric analysis. The upper bound of the 90% CI of median ΔΔQTcF are larger than 10 msec for 360 mg at hour 36 and 480 mg at hour 48. Please see Section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the highest dose in QTc assessment providing 1.6-fold coverage over high clinical exposure, lack of hERG activity and lack of QTc prolongation effect in animal studies.

Reviewer's comment: *Moxifloxacin in Part 2 cannot be used to establish assay sensitivity since moxifloxacin-placebo data in Part 2 was not concurrently administered with study drug in Part 1. Reviewer did not analyze data from Part 2.*

3.2.1.1.1 QT Bias Assessment

Not applicable

3.2.2 Categorical Analysis

There were no significant outliers per the Applicant's analysis for QTc (i.e., >450 msec or >30 msec over baseline).

Reviewer's comment: *The Applicant's results for QTc are the same as the reviewer's results. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The Applicant used the model recommended in the white paper. The results of the Applicant's analysis show an absence of significant QTc prolongation.

Reviewer's comment: *The reviewer's model, and Applicant's model both predicted upper bound of 90% CI of ΔΔQTc is below 10 msec at Cmax (See section 4.5).*

3.2.4 Safety Analysis

The Applicant conducted categorical analysis on pooled phase 1 studies that had ECG measurements within the first 12 hours after administration of elinzanetant alone (21665, 21668, 21669, 21670, 21673, 21674, and 21774, total n = 215). The maximum tested doses in these studies were 600 mg capsule single dose (study 21670), 120 mg capsule QD (study 21774), and 200 mg TID oral suspension (study 21674). No subjects had QTcF > 500 msec or change from baseline QTcF > 60 msec.

There were three phase 3 studies OASIS 1, OASIS 2, and OASIS 3. All three studies were randomized, parallel-group, placebo-controlled trials. Postmenopausal women with moderate to severe VMS associated with menopause were treated with elinzanetant 120 mg QD or with placebo for 12 weeks (OASIS 1, 2) or 52 weeks (OASIS 3), followed by elinzanetant 120 mg QD for 14 weeks (OASIS 1, 2). ECGs were only collected at screening of these three studies. There were no deaths.

In OASIS 1, 198 women started treatment with elinzanetant 120 mg and 195 women started with placebo. After 12 weeks, 168 women from the placebo arm switched treatment to elinzanetant 120 mg. 315 women completed the 26-week treatment period. Serious TEAEs and AEs leading to treatment discontinuation were reported in 13 and 26 women when treated with elinzanetant 120 mg, respectively. One SAE of syncope led to treatment discontinuation.

- ***Syncope:*** *Subject* (b) (6) *is a 52-year-old white female randomized to the elinzanetant 120 mg group. 5 days after starting elinzanetant, the subject was reported with syncope, which led to treatment discontinuation and was an SAE (reason: other medically important serious event), considered severe in severity by the investigator. The investigator noted normal ECG in a comment. The subject had ongoing medical history of hypertension.*

In OASIS 2, 200 women started with elinzanetant 120 mg, and 200 women started with placebo. After 12 weeks, 180 women from the placebo arm switched treatment to elinzanetant 120 mg. 330 women completed the 26-week treatment period. Serious TEAEs and AEs leading to treatment discontinuation were reported in 5 and 18 women when treated with elinzanetant 120 mg, respectively. One SAE of seizure led to treatment discontinuation.

- ***Seizure:*** *Subject* (b) (6) *was a 58-year-old white female randomized to the elinzanetant 120 mg group. She experienced two episodes of generalized tonic-clonic seizure (SAE) 46 days after switching from placebo to elinzanetant treatment. The event was considered moderate in severity by the investigator and*

was serious (requires or prolongs hospitalization). The subject had a medical history (>30 years) of generalized tonic-clonic seizures.

In OASIS 3, 627 started study treatment: 312 with elinzanetant 120 mg, and 315 with placebo. 52-week treatment period was completed by 226 women (72.2%) in the elinzanetant 120 mg arm and 232 women (73.7%) in the placebo arm. Serious TEAEs were reported in 13 (4.2%) women in the elinzanetant 120 mg arm and 6 (1.9%) women in the placebo arm. One SAE of acute myocardial infarction and one SAE of syncope were reported in the elinzanetant 120 mg group.

- ***Syncope:*** *Subject* (b) (6) *was a 56-year-old white female randomized to the elinzanetant 120 mg group. 55 days after starting elinzanetant, the subject was reported with syncope, which the investigator considered serious because it "requires or prolongs hospitalization". The investigator considered this event to be moderate in intensity. The study drug was interrupted for 3 days and resumed after the event was resolved. The investigator also provided the following comment: "cause is indeterminate".*

In addition, the Applicant also conducted search in phase 1 and phase 2 studies of deaths, SAEs, episodes of ventricular tachycardia or fibrillation, episodes of syncope, and AEs leading to discontinuation. We reviewed the below relevant AEs leading to discontinuation.

- ***Ventricular tachycardia****: Subject* (b) (6) *was a 32-year-old white healthy male in study 21673. He received 120 mg elinzanetant (oral suspension) as two split doses of 60 mg, separated by 3 hours in Period 2. Approximately 11 hours after the first dose, the subject experienced a single episode of mild, non-sustained monomorphic ventricular tachycardia that lasted for 0.48 seconds. There were no clinically significant changes to 12-lead ECGs at screening or during his dosing periods. Slight increases in post-dose QRS durations of 112 and 116 msec were recorded in Period 2. The event of ventricular tachycardia led to study discontinuation.*
- ***Vasovagal syncope (with loss of consciousness), ventricular tachycardia and atrial fibrillation*** *occurred in subject* (b) (6) *(41 year old Asian male) approximately 1 hour after being first dosed with 45 mg elinzanetant during blood collection. The syncope was associated with a 12 second pause on the ECG Holter monitor. Blood pressure was low (measurements were 74/58 mmHg [pulse rate 102 bpm] at the time of the pause and 78/52 mmHg [pulse rate 97 bpm] 4 minutes after the pause). The subject also reported palpitations. The atrial fibrillation and ventricular extrasystoles was first observed on the 2 hours post-dose ECG. Subsequently the subject was commenced on continuous ECG telemetry for additional monitoring. The subject spontaneously reverted to sinus rhythm, and palpitations and ventricular extrasystoles stopped. QTcF was below 450 msec in the ECG dataset. The subject was withdrawn from the study and referred to a cardiologist for further assessments, all of which were normal. (Study 21674, 90 mg split-dose, multiple doses, oral suspension, see narrative in CSR of study 21674, page 31)*

- ***Palpitation:*** *The participant reported palpitations about 11 hours after having received the first dose of 240 mg elinzanetant. An additional safety assessment including an unscheduled ECG on that day were performed resulting in normal ECG parameters (Study 22653)*

Reviewer's comment: *In the 3 phase 3 studies, no ventricular arrhythmias or sudden cardiac deaths were reported. One seizure SAE was reported in a subject with medical history of seizure. Two subjects experienced SAEs of syncope. The reviewer cannot locate ECG data for these subjects.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to treatment. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.2.2 QT Bias Assessment

Not Applicable

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer evaluated the ΔQTcF effect using descriptive nonparametric statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum median ΔΔQTcF values by treatment are shown in Table 3.

The upper bound of the 90% CI of median ΔΔQTcF are larger than 10 msec for 360 mg at hour 36 and 480 mg at hour 48. However, since the sample size for each dose group is small, the confidence interval might be wide and not reliable.

Figure 1: Median and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

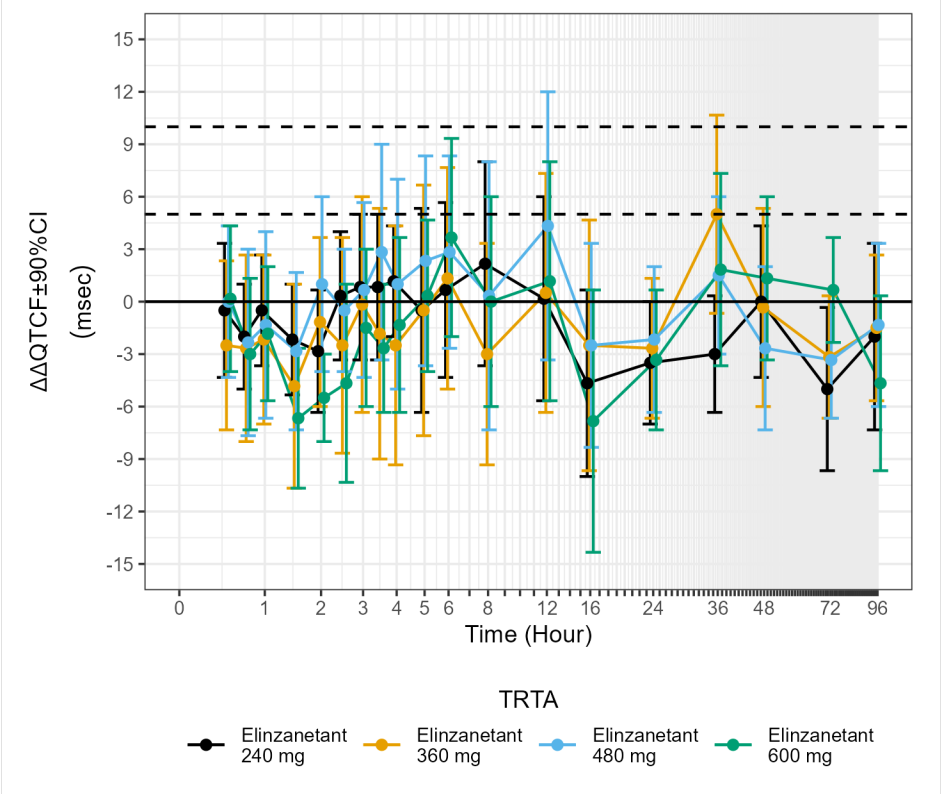


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hour)	ΔΔQTCF (msec)	90.0% CI (msec)
Elinzanetant 240 mg	9 / 12	8.0	2.2	(-3.7 to 8.0)
Elinzanetant 480 mg	9 / 12	12.0	4.3	(-3.3 to 12.0)
Elinzanetant 360 mg	9 / 12	36.0	5.0	(-0.7 to 10.7)
Elinzanetant 600 mg	9 / 12	6.0	3.7	(-2.0 to 9.3)

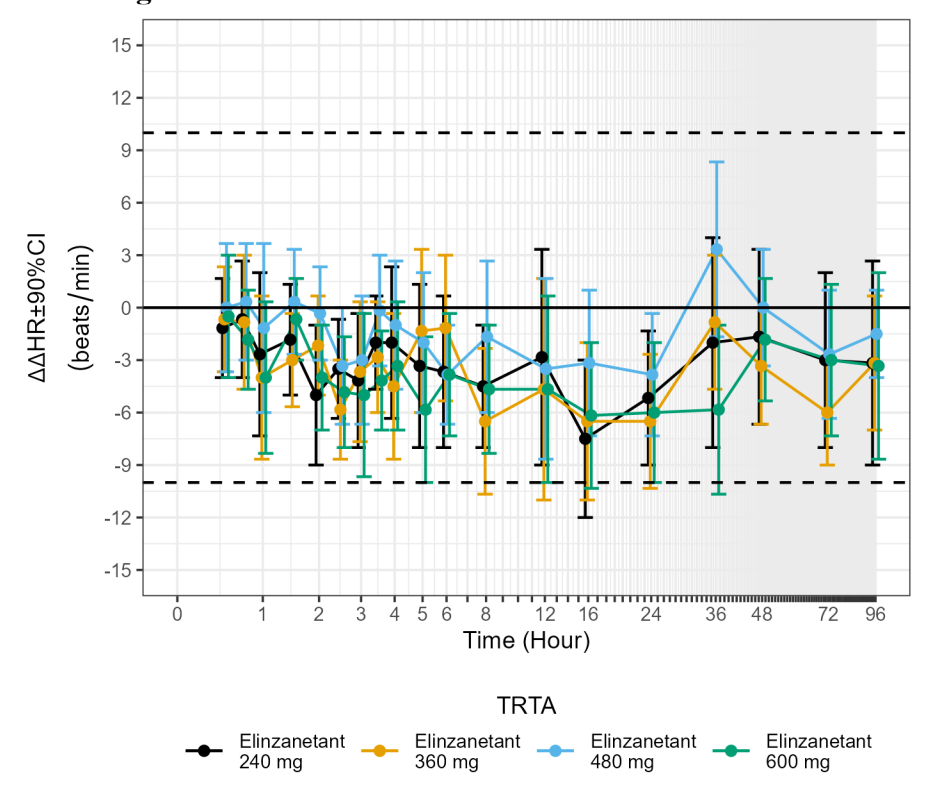
4.3.1.1 Assay Sensitivity

Moxifloxacin in Part 2 cannot be used to establish assay sensitivity since moxifloxacin-placebo data in Part 2 was not concurrently administered with study drug in Part 1. Reviewer did not analyze data from Part 2.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

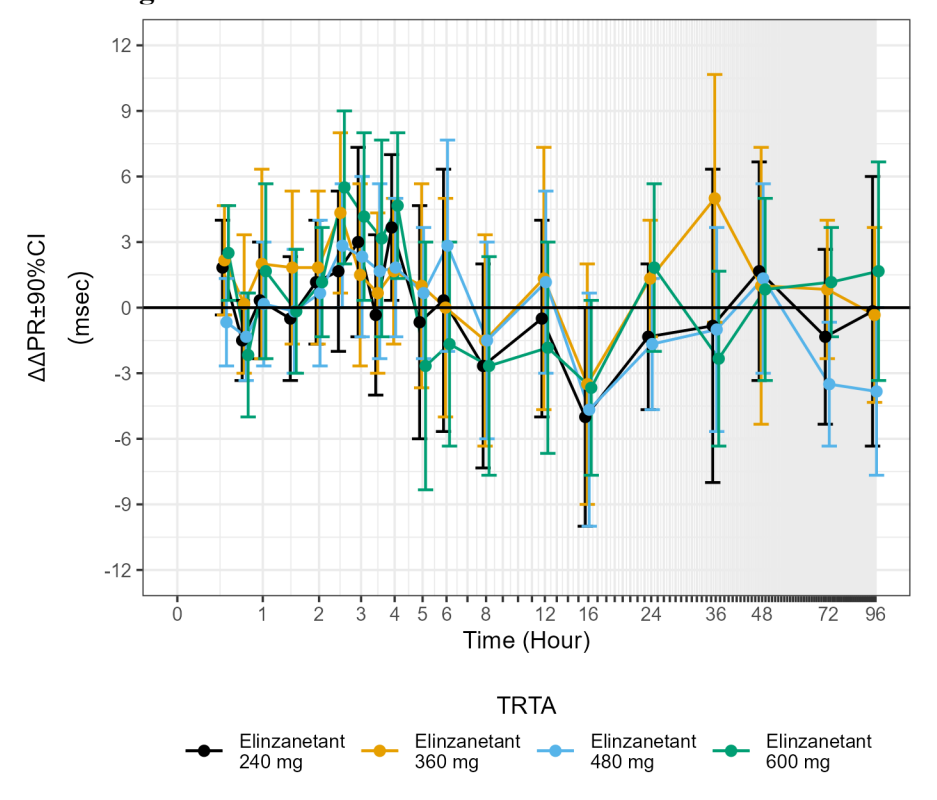
Figure 2: Median and 90% CI of ΔΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

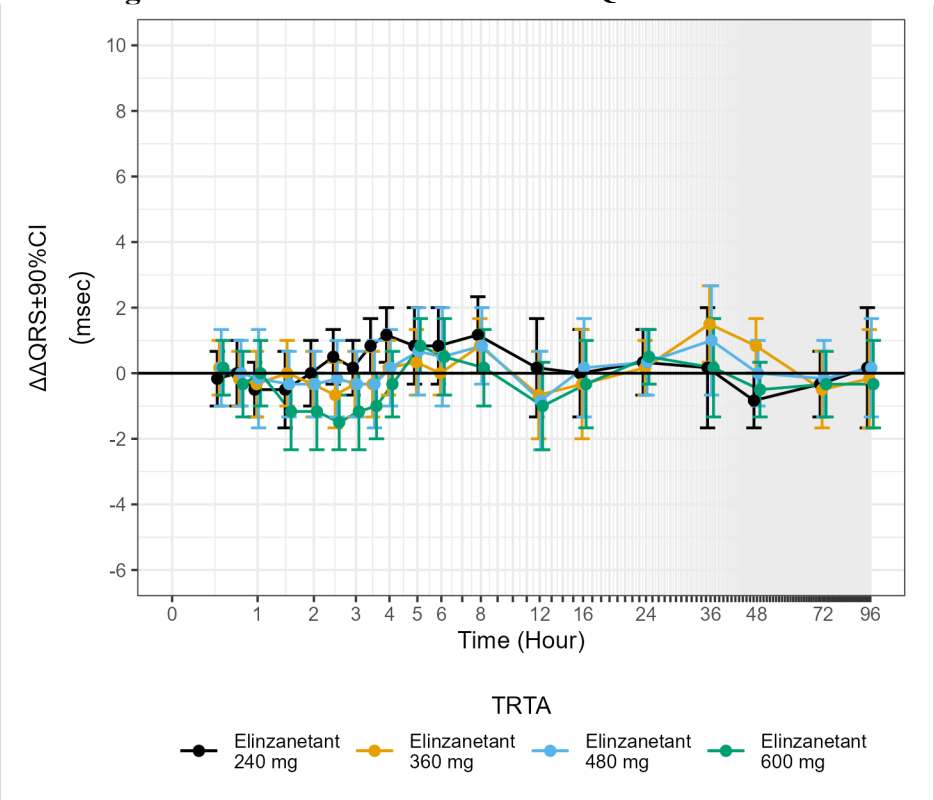
Figure 3: Median and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Median and 90% CI of ΔΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

There were no subjects who experienced QTcF >450 msec or ΔQTcF >30 msec.

4.4.2 HR

There were no subjects who experienced HR >100 beats/min.

4.4.3 PR

There were no subjects who experienced PR >220 msec.

4.4.4 QRS

There were no subjects who experienced QRS >120 msec.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK (n=36). However, the sampling

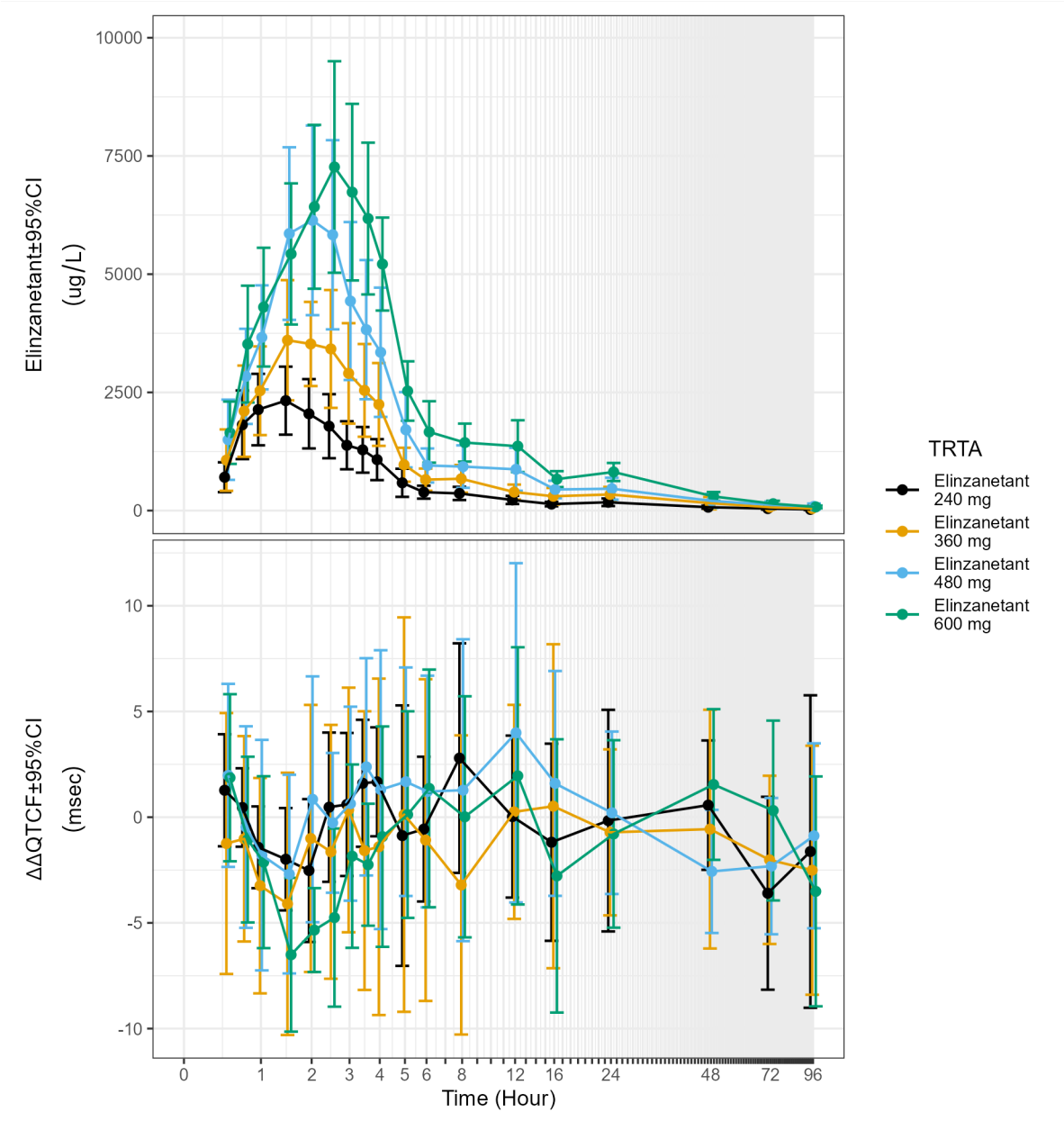
timepoints are different in QT and PK. There was no hour 36 in PK. Thus, hour 36 is not included in exposure-response analysis but included in by-time analysis.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

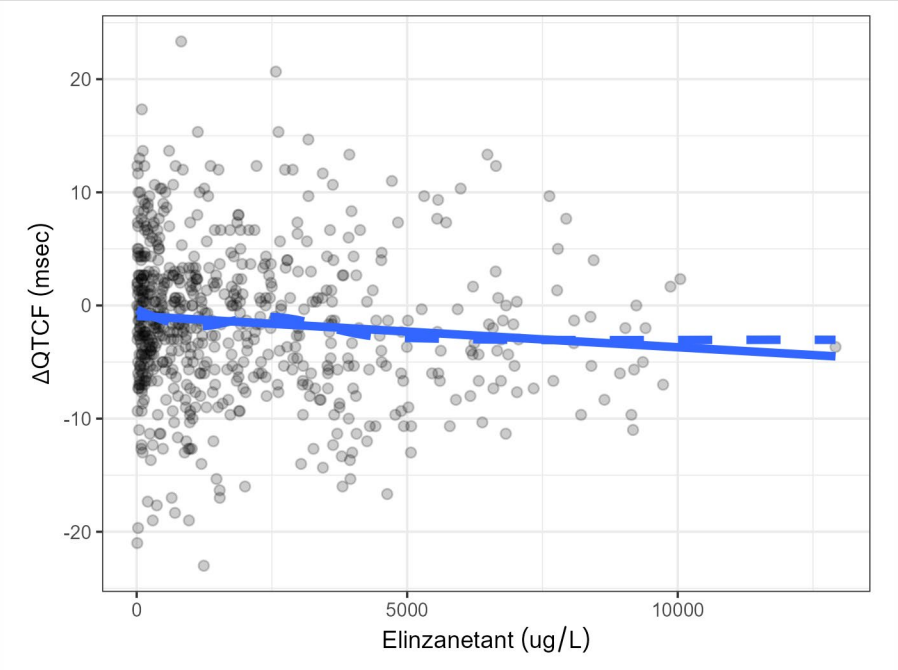
Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 4.

Figure 7: Goodness-of-fit Plot for QTcF

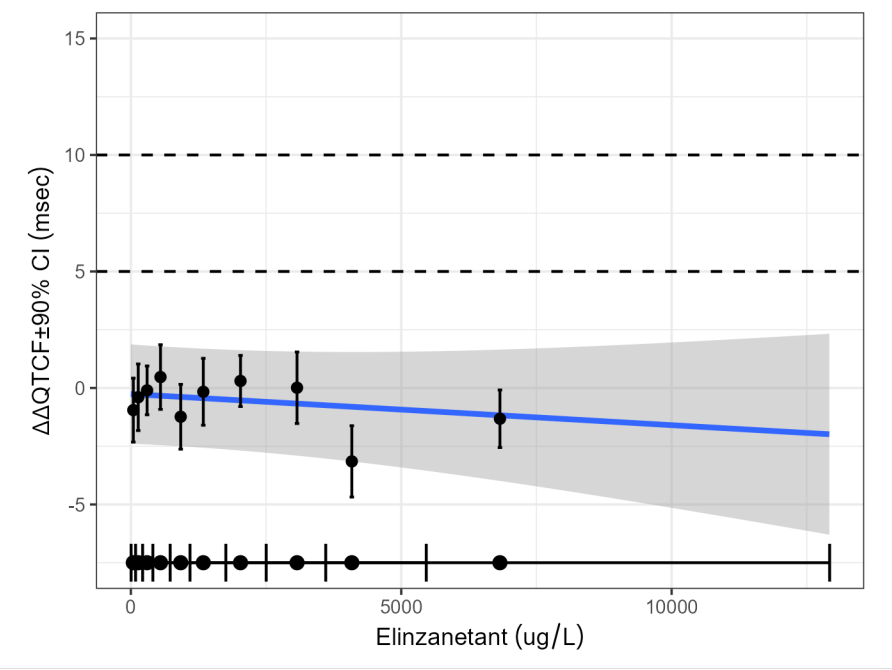


Table 4: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Elinzanetant (ug/L)	ΔΔQTCF (msec)	90.0% CI (msec)
Elinzanetant 120 mg QD		1,426	-0.5	(-2.6 to 1.7)
Elinzanetant 600 mg	1	7,393.3	-1.2	(-4.2 to 1.7)

4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

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