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RESEARCH**

APPLICATION NUMBER:

210493Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # **210493**
PMR/PMC Set (####-#) **3292-1**
Product Name: **Akynzeo (fosnetupitant and palonosetron) inj.**
Applicant Name: **Helsinn Healthcare SA**
ODE/Division: **III/ DGIEP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with fosnetupitant (pro-netupitant) alone.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission:	03 /2020
Final Protocol Submission:	06 /2020
Study/Trial Completion:	06 /2021
Final Report Submission:	09 /2021

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

An (b) (4) toxicity study with fosnetupitant (pro-netupitant) alone of at least 8 weeks duration in neonatal rats (b) (4)

(b) (4)

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- PREA PMR: Meets PREA postmarketing pediatric study requirements *[Skip to Q.5]*
- FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial *[Go to Q.3]*
- PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. *[Go to Q.3]*

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f. Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study

TYPE OF STUDY

Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

Based on results of the combination toxicity studies of fosnetupitant + palonosetron in adult rats and dogs, and the toxicity profile of palonosetron alone in neonatal rats, juvenile animal studies with the drug combination are not considered necessary to support the pediatric study.

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # **210493**
PMR/PMC Set (####-#) **3292-2**
Product Name: **Akynzeo (fosnetupitant and palonosetron) inj.**
Applicant Name: **Helsinn Healthcare SA**
ODE/Division: **III/ DGIEP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

An open-label, pharmacokinetic and safety study of intravenous fosnetupitant/palonosetron combination in pediatric cancer patients ages 0-17 years for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

2. PMR/PMC Schedule Milestones^{2, 3}

Final Protocol Submission: 01/2022
Study/Trial Completion: 07/2024
Final Report Submission: 12/2024

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² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

The goal of the trial is to obtain safety and efficacy data in order to inform labeling for pediatric use.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [\[Skip to Q.5\]](#)
- PREA PMR: Meets PREA postmarketing pediatric study requirements [\[Skip to Q.5\]](#)
- FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [\[Go to Q.3\]](#)
- PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [\[Go to Q.3\]](#)

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [\[Select all that apply\]](#)

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to approval*.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f. Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study

TYPE OF STUDY

Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe)

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

(b) (4) open-label, pharmacokinetic and safety study of intravenous (IV) pro-
netupitant / palonosetron combination in pediatric cancer patients for the prevention of nausea and
vomiting associated with emetogenic chemotherapy.

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

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Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # **NDA 210493**
PMR/PMC Set (####-#) **3292-3**
Product Name: **Akynzeo (fosnetupitant and palonosetron) inj.**
Applicant Name: **Helsinn Healthcare SA**
ODE/Division: **ODE 3/ DGIEP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

In vitro study to evaluate the inhibition potential of fosnetupitant towards MATE2-K.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission: 10/2018
Final Protocol Submission: 01/2019
Study/Trial Completion: 01/2020
Final Report Submission: 07/2020

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Fosnetupitant is a new molecular entity and its inhibition potential towards MATE2-K transporter has not been evaluated. Thus, in vivo drug drug interaction cannot be ruled out following IV administration of Akynzeo.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- PREA PMR:** Meets PREA postmarketing pediatric study *requirements* *[Skip to Q.5]*
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial *[Go to Q.3]*
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. *[Go to Q.3]*

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior* to approval.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only [for PMCs skip to Q.5]. Complete this entire section**

a. The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f. Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY

Other (describe) **In vitro drug interaction studies**

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # **NDA 210493**
PMR/PMC Set (####-#) **3292-4**
Product Name: **Akynzeo (fosnetupitant and palonosetron) inj.**
Applicant Name: **Helsinn Healthcare SA**
ODE/Division: **ODE 3/ DGIEP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

<i>In vitro</i> study to evaluate the potential of fosnetupitant to be a substrate for P-gp/MDR1, BCRP, BSEP, MATE1, MATE2-K, OAT1, OAT3, OCT1, and OCT2.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission:	<u>10/2018</u>
Final Protocol Submission:	<u>01/2019</u>
Study/Trial Completion:	<u>01/2020</u>
Final Report Submission:	<u>07/2020</u>

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

Fosnetupitant is a new molecular entity and its drug drug interaction potential via these transporter has not been evaluated. Thus, *in vivo* drug drug interaction cannot be ruled out following IV administration of Akynzeo.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- PREA PMR:** Meets PREA postmarketing pediatric study *requirements [Skip to Q.5]*
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial *[Go to Q.3]*
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. *[Go to Q.3]*

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to approval.*]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f. Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study

TYPE OF STUDY

Other (describe) **In vitro drug interaction studies**

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
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- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
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- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e., with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. **This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.**

Insert electronic signature (usually the Deputy Director for Safety)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H CHUNG
04/19/2018

ANIL K RAJPAL
04/19/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	January 18, 2018
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 210493
Product Name and Strength:	Akynzeo (fosnetupitant and palonosetron) for injection 235mg/0.25mg
Submission date:	December 14, 2017
Applicant/Sponsor Name:	Helsinn Healthcare, SA
OSE RCM #:	2017-864-2
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised carton labeling and container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to a recommendation that we made during a previous label and labeling review, OSE RCM #: 2017-864-1^a.

2 CONCLUSION

Although we find the revised carton labeling for Akynzeo acceptable, the revised container label is unacceptable from a medication error perspective. As presented, strength presentation on the container label lacks the prominence as required by 21 CFR 201.15(a)(6).

^aAbraham.S. Label and Labeling Review for Akynzeo (NDA 210493). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Dec 7. 32 p. OSE RCM No.:2017-864-1

3 RECOMMENDATION FOR HELSINN HEALTHCARE, SA

We recommend the following be implemented prior to approval of this NDA:

A. CONTAINER LABEL:

1. Please ensure that the strength presentation is prominent as required by 21 CFR 201.15(a)(6). Please note that the proprietary name, established name, dosage form and strength presentation are the most prominent information on the principal display panel (PDP).^b

Appendix A: Label and Labeling Submitted on December 14, 2017

Container label:



^bDraft Guidance for Industry: Safety Consideration for container labels and carton labeling design to minimize medication errors. 2013.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

Carton labeling:



(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERLY ABRAHAM
01/18/2018

SARAH K VEE
01/18/2018



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 18, 2017

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Error Products

Through: Dominic Chiapperino, Ph.D., Acting Director
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Evaluation of Abuse-Related Studies
Akynzeo for Injection (Fosnetupitant and Palonosetron HCl
Fixed-Dose Combination (b) (4) (235 mg fosnetupitant +
(b) (4) palonosetron as a lyophilized powder in single-dose
vial for reconstitution)
NDA 210,493 (IND 115,191)
Indication: Prevention of acute and delayed nausea and
vomiting associated with initial and repeat courses of cancer
chemotherapy. (b) (4)
Sponsor: Helsinn Healthcare, SA

Materials reviewed: Abuse-related preclinical data in NDA submission (eCTD
0000, 4/20/17)

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1. Background

This memorandum evaluates two new self-administration studies in support of NDA 210,493 for the drug product Akynzeo for Injection, which is under review in the Division of Gastroenterology and Inborn Errors Products (DGIEP). Akynzeo is a combination product containing 235 mg of fosnetupitant (a NK1 antagonist) and 0.25 milligrams of palonosetron (a 5HT3 antagonist). Akynzeo for Injection is proposed for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Palonosetron is thought to prevent nausea and vomiting during the acute phase and fosnetupitant is thought to prevent nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

This product is formulated as a lyophilized powder contained in a vial that is reconstituted in 50 ml of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. Dosing recommendations propose that the reconstituted solution of Akynzeo be infused intravenously over a 30-minute period immediately prior to the initiation of chemotherapy. Dexamethasone (12 mg) should also be administered 30 minutes prior to chemotherapy, with additional dosing of 8 mg dexamethasone once daily on Days 2 to 4.

A similar drug product, Akynzeo capsules (NDA 205,718), was approved by FDA on October 10, 2014. Akynzeo capsules are formulated as a fixed combination of netupitant (a NK-1 antagonist), and palonosetron, and is similarly indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. (Notably, the fosnetupitant in Akynzeo for Injection is a prodrug for netupitant). CSS reviewed this NDA and concluded from the preclinical and clinical abuse-related data that the drug combination did not have abuse potential and should not be recommended for scheduling under the Controlled Substances Act. The NDA for Akynzeo for Injection is a 505(b)1 submission.

At a pre-IND meeting in 2012, CSS informed the Sponsor that, “It is not necessary to conduct abuse potential studies with fosnetupitant, as long as you submit data establishing that the fosnetupitant rapidly converts to the CNS-active metabolite, netupitant; that netupitant is responsible for the drug’s activity; and that the pro-drug makes no contribution to the activity of the drug product.” The Sponsor subsequently submitted pharmacokinetic information showing that fosnetupitant converts completely to netupitant in rats, dogs, and monkeys. They also provided information showing that fosnetupitant is not CNS-active because it cannot cross the blood-brain barrier (although its metabolite, netupitant, does penetrate the CNS).

In an IND meeting in 2014, CSS informed the Sponsor that additional self-administration studies with fosnetupitant alone or with the combination of fosnetupitant + palonosetron would not be necessary. However, the Sponsor conducted these studies anyway and submitted them in the current NDA.

2. Conclusions

In two self-administration studies in baboons that were conducted with netupitant (the active metabolite of fosnetupitant) and with netupitant + palonosetron, neither drug treatment produced self-administration that was statistically significantly different than that produced by placebo. This suggests that these drug treatments do not produce rewarding effects.

The clinical review by Dr. Charles Line of DGIEP confirms that there were no abuse-related AEs observed during clinical studies with intravenous fosnetupitant + palonosetron.

3. Recommendations

(b) (4)
the lack of abuse-related signals from netupitant alone and from netupitant + palonosetron.

The drug product Akynzeo for Injection should not be recommended for control under the CSA, because the results from the preclinical abuse potential studies show that the drug combination lacks abuse potential. This is similar to the lack of abuse potential of Akynzeo capsules (netupitant + palonosetron), which was also not recommended for CSA scheduling when it was approved in 2014.

4. Discussion

Self-Administration Study (Studies #NETU-13-73 and NETU-13-74)

The Sponsor conducted a self-administration drug study in which netupitant was tested for its ability to induce self-administration as a measure of the rewarding property of the drug.

Study Design

Male olive baboons (n = 3) were trained to self-administer cocaine (0.32 mg/kg/infusion, i.v.) during 24 hour continuous access sessions. After stable cocaine self-administration was produced using a fixed ratio (FR) 100 or FR 160 with a 3 hour timeout between injections, which allowed up to 8 injections per day. Animals self-administered cocaine 6 to 8 times per day during training.

Animals were allowed access to netupitant (0.6, 1.0, 1.3, 1.8 mg/kg, i.v.), netupitant + palonosetron (0.6 + 0.01 mg/kg, i.v.) or vehicle (either saline or Captisol vehicle). The test doses and testing times were selected based on the results of the pharmacokinetics/

pharmacodynamics study. This is the first study in which netupitant alone has been tested in self-administration.

Cocaine, vehicle and each fixed-dose netupitant, or the combination of netupitant + palonosetron were available sequentially for self-administration 24 hours a day, 7 days a week, for a total of 15 contiguous days. The last 5 days of each period of access to netupitant alone, netupitant + palonosetron or saline/vehicle was used to characterize the reinforcing effects of the treatment.

Results

Cocaine was self-administered 7 to 8 times in 24 hours, which was significantly higher than that shown for saline or the Captisol-based vehicle (0 to 3.0 times in 24 hours). These data validate the study.

The number of self-administrations of netupitant alone or netupitant + palonosetron (0.4 to 1.8 times in 24 hours) was similar to or less than that produced by saline/vehicle alone (0 to 3.0 times) at all doses of the drug treatments that were tested.

Conclusion

Netupitant alone or netupitant + palonosetron was not self-administered, suggesting these treatments do not appear to have rewarding properties. This outcome is similar to the outcome seen in the previous self-administration studies conducted with netupitant + palonosetron submitted for Akynzeo capsules under NDA 205,718.

Abuse-Related Adverse Events

The clinical review by Dr. Charles Line of DGIEP (DARRTS, 12/15/17) confirms that there were no abuse-related AEs observed during clinical studies with intravenous fosnetupitant + palonosetron.

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/s/

KATHERINE R BONSON
12/18/2017

DOMINIC CHIAPPERINO
12/18/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH),
Office of Drug Evaluation IV (ODE IV)

Through: Mona Khurana, M.D., Pediatric Team Leader,
John J. Alexander, M.D., M.P.H., Deputy Director,
DPMH, ODE IV

To: Division of Gastroenterology and Inborn Errors Products
(DGIEP)

Drug: Akynzeo IV (fosnetupitant/palonosetron)

Application Number: NDA 210493

Sponsor: Helsinn Healthcare SA

Proposed Indication: For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy in adults

Proposed Dosage Form: 235 mg fosnetupitant/0.25 mg palonosetron, as a sterile, lyophilized powder in a single-use vial for reconstitution.

Route of Administration: For intravenous (IV) administration

Proposed Dosing Regimen: Single IV dose administered as 30-minute infusion starting approximately 30 minutes prior to the start of chemotherapy

Consult Request:

DGIEP consulted DPMH on March 4, 2017 to provide assistance with labeling recommendations for pediatric use, preparation for the Pediatric Review Committee (PeRC) meeting and development of pediatric postmarketing requirements.

Materials Reviewed:

- Division of Pediatric and Maternal Health (DPMH) consult request (May 4, 2017)
- Applicant's proposed labeling included in Module 1.14.1 in NDA 210493 (April 20, 2017)
- Prior DPMH review for IV fosnetupitant/palonosetron (in DARRTS under IND 115191) dated March 10, 2017
- Agreed initial Pediatric Study Plan for fosnetupitant/palonosetron in DARRTS under IND 115191 (June 29, 2016)

Summary:

On April 20, 2017, Helsinn Healthcare SA submitted NDA 210493 seeking marketing approval for Akynzeo for injection (fosnetupitant/palonosetron) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy in adults only. The product will not be approved for use in the pediatric population as studies have not yet been conducted in this population. Accordingly, labeling will state that safety and effectiveness have not been established for pediatric patients.

The Agency issued an Agreed initial Pediatric Study Plan (iPSP) to the applicant on June 29, 2016 which was submitted in this application without any changes. No review issues were raised during this NDA review that impacted the pediatric development program. The PeRC met on November 29, 2017 and agreed with DGIEP's plan to grant a deferral of all pediatric studies in patients' birth to 17 years of age as outlined in the Agreed iPSP because the product is ready for approval in adults. The pediatric postmarketing requirements (PMRs) will be issued in accordance with the Pediatric Research Equity Act (PREA) and will reflect the proposed studies and timelines outlined in the Agreed iPSP.

DPMH reviewed the applicant's draft labeling, assisted with PeRC preparation and development of the pediatric PMRs. DPMH participated in the internal meetings between June and November 2017, and our input will be reflected in the approval letter.

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/s/

ERICA D RADDEN
12/13/2017

MONA K KHURANA
12/13/2017

JOHN J ALEXANDER
12/13/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: December 8, 2017 **Date consulted:** May 4, 2017

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Error Products (DGIEP)

NDA: 210493

Drug: Akynzeo (fosnetupitant/palonosetron) for injection, for intravenous (IV) use
Akynzeo (netupitant and palonosetron) capsules, for oral use

Applicant: Helsinn Healthcare SA

Subject: Pregnancy and Lactation Labeling

Indications (proposed):

- Akynzeo capsules is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
- Akynzeo for injection is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

**Materials
Reviewed:**

- May 4, 2017, DPMH consult request for NDA 210493, DARRTS Reference ID 4093720
- April 20, 2017 and June 1, 2017, Applicant's submission for NDA 210493 for IV fosnetupitant and palonosetron
- April 29, 2014, DPMH review for Aloxi (palonosetron HCl) injection, Miriam Dinatale, D.O., DARRTS Reference ID 3497449
- May 16, 2014, DPMH review for AKYNZEO (netupitant/palonosetron) for NDA 205718 fixed dose combination capsule, Carrie Ceresa, Pharm D., MPH, DARRTS Reference ID 3508235
- April 29, 2015, DPMH review of palonosetron HCl for NDA 207963, Miriam Dinatale, D.O., DARRTS Reference ID 3741833
- March 14, 2016, DPMH review of palonosetron HCl injection for NDA 208109, DARRTS Reference ID 3901563
- January 20, 2016, DPMH review of palonosetron HCl injection for NDA 203050, DARRTS Reference ID 3875380
- August 17, 2017, DPMH review of fosaprepitant dimeglumine for injection, for NDA 210064, DARRTS Reference ID 4140874

Consult Question: “DGIEP requests DPMH *Pediatric and Maternal Health* team’s assistance with the review of this application and its label (PI).”

INTRODUCTION

The Division of Gastroenterology and Inborn Error Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of Akynzeo (fosnetupitant/palonosetron) IV labeling.

REGULATORY HISTORY

On April 20, 2017, Helsinn Healthcare SA submitted a New Drug Application for AKYNZEO (fosnetupitant and palonosetron) IV fixed dose combination for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Fosnetupitant and palonosetron IV is considered a new molecular entity (NME) because fosnetupitant represents a covalently bonded modification to netupitant.¹ The AKYNZEO (fosnetupitant/palonosetron) IV labeling for this NDA and the already approved AKYNZEO (netupitant/palonosetron) capsules labeling for NDA 205718 will have a combined package insert. See below for regulatory history of netupitant and palonosetron currently approved products.

¹ Per DGIEP e-mail reviewed on June 16, 2017: not all “covalently bonded modifications” are NMEs. However, because fosnetupitant is an ester of N-hydroxymethyl-netupitant, and not an ester of the previously approved active moiety, netupitant, it is a new active moiety.

Aloxi (palonosetron HCl) injection NDA 21372

- July 25, 2003, original NDA approval for chemotherapy-induced nausea and vomiting in adults and the prevention of postoperative nausea and vomiting up to 24 hours after surgery in adults.
 - A capsules formulation of Aloxi (palonosetron) was subsequently approved on August 22, 2008 (NDA 22233); however, the product was withdrawn from marketing on September 4, 2012, for reasons not related to safety and effectiveness.

Akynzeo (netupitant/palonosetron) capsules NDA 205718

- October 10, 2014, original NDA approval for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to highly emetogenic chemotherapy.

Palonosetron HCl injection 505(b)(2) NDA approvals

- NDA 208109, July 29, 2016, received tentative approval in adults for moderately emetogenic cancer chemotherapy-prevention of acute and delayed nausea and vomiting associated with initial and repeat courses; highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses; prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery
- NDA 203050, March 1, 2016, approval, same indication as above.
- NDA 207963, August 22, 2016, approval, moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses; highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses.

BACKGROUND

Drug Characteristics²

Netupitant

Netupitant is a selective antagonist of human substance P/neurokinin 1 (NK1) receptors.

- Molecular weight: 578.61 Daltons
- $T_{1/2}$: 80 ± 29 hours (96 after single oral dose administration of Akynzeo)
- C_{max} (ng/mL): 434 (56)
- T_{max} (h):5 (2-12)

Fosnetupitant

Fosnetupitant is a pro-drug for netupitant and is (b) (4) converted *in vivo* to netupitant by metabolic hydrolysis.

- Molecular weight: 761.53 Daltons

(b) (4)

(b) (4)

Palonosetron

Palonosetron is a serotonin subtype 3 (5HT₃) antagonist with strong binding affinity for the 5-HT₃ receptor and little or no affinity for other receptors. 5-HT₃ receptors are located on the nerve terminals of the vagus nerve in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. Nausea and vomiting is triggered by the release of 5-HT₃ in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates the 5-HT₃ receptors located on vagal afferents to initiate the vomiting reflex.^{3,4}

- Molecular weight: 332.87 Daltons
- T_{1/2}: 48 ± 19 hours (44 hours after single oral dose administration of Akynzeo)
- C_{max} (ng/mL): 1.53 (25)
- T_{max} (h): 5(1-12)
- Adverse effects: serotonin syndrome (mental status changes, autonomic instability, neuromuscular symptoms, seizures and gastrointestinal

Chemotherapy-induced nausea and vomiting (CINV)

Nausea and vomiting is a common side effect associated with the administration of chemotherapeutic drugs. Nausea and vomiting can cause weight changes, dehydration, electrolyte imbalances and fatigue. Although nausea and vomiting are related they are also separate events and often one is treated without the other.⁵ Females who experienced severe emesis during pregnancy are believed to be at greater risk for experiencing CINV.⁶ Additionally, women with severe nausea and vomiting during pregnancy may not gain enough weight which can cause fetal growth restriction and lead to a low birth weight infant. See table 1 below for the Institute of Medicine's weight gain recommendations in pregnancy.⁷

³ January 20, 2016, DPMH review of palonosetron HCl injection for NDA 203050, DARRTS Reference ID 3875380

⁴ Drugs@FDA: Aloxi (palonosetron) labeling, Clinical Pharmacology, 12.1: Mechanism of Action, accessed 4 October 2017.

⁵ Navari, R, 2013, Management of Chemotherapy-Induced Nausea and Vomiting, *Drugs*, 73:249–262. doi: 10.1007/s40265-013-0019-1.

⁶ Jordan, K., Sippel, C., Schmoll, H-J, 2007, Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present and Future Recommendations, *The Oncologist*, 12:1143-1150. doi: 10.1634/theoncologist.12-9-1143.

⁷ Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining Guidelines, May, 2009. <https://www.nationalacademies.org/hmd/~media/Files/Report%20Files/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report%20Brief%20-%20Weight%20Gain%20During%20Pregnancy.pdf>

Table 1. Institute of Medicine New Recommendations for Total and Rate of Weight Gain During Pregnancy by Pre-pregnancy BMI (Table S-1, page 2 in publication)⁷

Prepregnancy BMI	Total Weight Gain		Rates of Weight Gain* 2nd and 3rd Trimester	
	Range in kg	Range in lbs	Mean (range) in kg/week	Mean (range) in lbs/week
Underweight (< 18.5 kg/m ²)	12.5-18	28-40	0.51 (0.44-0.58)	1 (1-1.3)
Normal weight (18.5-24.9 kg/m ²)	11.5-16	25-35	0.42 (0.35-0.50)	1 (0.8-1)
Overweight (25.0-29.9 kg/m ²)	7-11.5	15-25	0.28 (0.23-0.33)	0.6 (0.5-0.7)
Obese (≥ 30.0 kg/m ²)	5-9	11-20	0.22 (0.17-0.27)	0.5 (0.4-0.6)

* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

Current State of the Labeling

Table 2. Current pregnancy and lactation approved labeling for netupitant and palonosetron products

Product	Labeling format	Embryo-fetotoxicity	Contraindications	Drug-Drug interactions or pregnancy/contraception requirements	Pregnancy Data		Lactation Data	
					Human	Animal	Human	Animal
Akynzeo (netupitant/palonosetron) capsules NDA 205718	PLR format not PLLR format	None	None	None	None	Yes	None	Yes
Aloxi (palonosetron) injection NDA 21372	PLR format not PLLR format	None	None	None	None	Yes	None	Yes
Palonosetron HCl injection (NDAs 208109, 203050, 207963)	PLR/PLLR format	None	None	None	None	Yes	None	None

*reviewers table

The reader is referred to the section below entitled **Pregnancy: Nonclinical Experience** for details of the animal reproduction studies conducted with netupitant and palonosetron and the section below entitled **Lactation: Nonclinical Experience** for a discussion of palonosetron and the potential for tumorigenicity.

REVIEW

PREGNANCY

Nonclinical Experience

Netupitant

In animal reproduction studies with netupitant, no effects on embryo-fetal development were observed following daily oral administration in pregnant rats during the period of organogenesis at doses up to 3.7 times the human AUC (area under the plasma concentration-time curve) at the recommended single human dose to be given with each cycle of chemotherapy. However, a dose-dependent increase in adverse effects on embryo-fetal development was observed following daily oral administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least 0.2 times the human AUC at the recommended single human dose to be given with each cycle of chemotherapy. Daily oral administration of netupitant in rats up to 3.7 times the human AUC at the recommended human dose during organogenesis through lactation produced no adverse effects in the offspring.

Fosnetupitant

In animal reproduction studies with fosnetupitant, delayed ossification of pubis occurred after intravenous administration in rats during the period of organogenesis at a dose 3 times the human AUC for netupitant (fosnetupitant is rapidly distributed and metabolically eliminated to form netupitant) at the recommended single dose to be given with each cycle of chemotherapy. In pregnant rabbits, an increase in resorptions was observed with daily intravenous administration of fosnetupitant during the period of organogenesis at doses at least 9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single human dose to be given with each cycle of chemotherapy. Daily intravenous administration of fosnetupitant (3 times the human AUC for netupitant at the recommended single human dose to be given with each cycle of chemotherapy) in rats during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development.

Palonosetron

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed following oral administration during the period of organogenesis at doses up to 921 and 1841 times the recommended oral dose in rats and rabbits, respectively.

The reader is referred to the full Pharmacology/Toxicology review by Ke Zhang, Ph.D. and David Joseph, Ph.D., DARRTS.

Review of Literature

Applicant's Review of Literature

The applicant performed a search of published literature using Embase and PubMed without time period limitations. The applicants search parameters can be found in the June 1, 2017, submission to NDA 210493. The applicant concluded that there are no publications in literature regarding the fixed dose combination of netupitant or (fosnetupitant) and palonosetron use in pregnant women.

DPMH's Review of Literature

DPMH performed a search of published literature using Embase and PubMed using the following search parameters, “netupitant and fetal malformations,” “netupitant and spontaneous abortion and miscarriage,” “netupitant and embryofetotoxicity,” “palonosetron and fetal malformations,” “netupitant and spontaneous abortion and miscarriage,” “palonosetron and embryofetotoxicity.” No data was found in the literature search.

Review of Pharmacovigilance Database

The applicant conducted a search of the Helsinn safety database for reports of pregnancy for the oral formulation of AKYNZEO (300 mg netupitant/0.5 mg palonosetron capsules) from January 1, 2006, to May 15, 2017 and for the IV fixed dose formulation of 235 mg fosnetupitant/0.25 mg palonosetron) from January 1, 2013, to May 15, 2017. The following cases were found:

Table 3. Pharmacovigilance Cases from the Helsinn Safety Database

Source	Case	Drug	Timing of Exposure	Outcome
Clinical Development Program Study NETU-11-02	30-year-old female; LMP (b) (6) and pregnancy confirmed on (b) (6) by laboratory sample	Netupitant/palonosetron fixed dose combination single dose	(b) (6)	Healthy female delivered (b) (6); pregnancy uneventful; c-section; babies weight 3.43 kg and height 50 cm; APGAR 10/10; no adverse events
Clinical Development Program Study NETU-07-20	41-year-old female; (b) (6), positive serum pregnancy test	600 mg netupitant/1.5 mg palonosetron	(b) (6)	Healthy female delivered at term (b) (6);
Spontaneous case report; Australia	37-year-old female with ovarian cancer; second trimester of pregnancy	AKYNZEO oral 1 capsule daily for 5 days prior to cisplatin and etoposide	(b) (6) to (b) (6) this was during second trimester of pregnancy	Other medications included cisplatin, etoposide, dexamethasone IV, magnesium, neulasta, metoclopramide; estimated delivery of (b) (6); no outcome data obtained

*reviewers table

Summary

Overall, in animal reproduction studies with netupitant there were no effects seen on embryo-fetal development after daily administration of netupitant given to pregnant rats during organogenesis at 3.7 times the human AUC. In fosnetupitant, delayed ossification of pubis occurred after intravenous administration of fosnetupitant in rats during organogenesis at 3 times the human AUC when given with each cycle of chemotherapy. In palonosetron, no effects were seen on embryo-fetal development in rats and rabbits administered oral palonosetron during organogenesis at dose up to 921 and 1841 the recommended human oral dose, respectively. There are no data on the use of palonosetron or netupitant (or fosnetupitant) during pregnancy in

the published literature. There are three reports of exposure in the applicant's pharmacovigilance database; however, the data are limited and not enough to inform a drug associated risk of adverse pregnancy outcomes.

LACTATION

Nonclinical Experience

In a review by DPMH dated January 20, 2016, by Miriam Dinatale, D.O., it is noted that although rat carcinogenicity studies showed a potential for tumorigenicity, these effects were seen at doses 137 (male rats) and 308 (female rats) times the human exposure at the recommended dose. Since the exposure at which tumors occurred in animals was significantly higher than the human exposure at the recommended dose, the recommendation to avoid breastfeeding due to the potential for tumorigenicity was removed from the lactation subsection of recently approved palonosetron labeling. Since there are no new safety concerns that would support a change in recommendations regarding breastfeeding and the tumorigenicity language, labeling will remain consistent with recently approved palonosetron labeling.

Review of Literature

Applicant's Review of Literature

The applicant performed a search of published literature using Embase and PubMed without time period limitations. The applicant's search parameters can be found in the June 1, 2017, submission to NDA 210493. The applicant concluded that there are no publications in literature regarding the fixed dose combination of netupitant (or fosnetupitant) and palonosetron use in pregnant and lactating women or the effect on either product on male and female fertility.

DPMH's Review of Literature

DPMH conducted a search of *Medication and Mother's Milk*,⁸ the Drugs and Lactation Database (LactMed),⁹ Micromedex¹⁰ and of published literature in PubMed and Embase. No information was found regarding the use of palonosetron, netupitant or fosnetupitant during lactation.

Review of Pharmacovigilance Database

The applicant conducted a search of the Helsinn safety database for reports of breastfeeding for the oral formulation of AKYNZEO (300 mg netupitant/0.5 mg palonosetron capsules) from January 1, 2006, to May 15, 2017 and for the IV fixed dose formulation of 235 mg fosnetupitant/0.25 mg palonosetron) from January 1, 2013, to May 15, 2017. No reports were found.

⁸ Hale, T. *Medication's and Mothers Milk*. Springer Publishing Company, 2017.

⁹ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁰ AKYNZEO. Truven Health Analytics Micromedex Solutions.

http://www.micromedexsolutions.com/micromedex2/librarian/CS/D62240/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/DA171C/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.GoToDashboard?docId=931080&contentSetId=100&title=Netupitant%2FPalonosetron&servicesTitle=Netupitant%2FPalonosetron&brandName=Akynzeo#. Accessed 5 October 2017.

Summary

There are no data on the presence of netupitant (or fosnetupitant) and palonosetron in human milk. In a previous review by DPMH, it is noted that, although rat carcinogenicity studies showed a potential for tumorigenicity, these effects were seen at dose exposures much higher than human exposure. Therefore, since there are no new safety concerns that would support a change in recommendations regarding breastfeeding and the tumorigenicity, the Risk/Benefit statement in the Lactation section of labeling as required under PLLR will state the following: “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for AKYNZEO and any potential adverse effects on the breastfed infant from AKYNZEO or from the underlying maternal condition.”

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Daily oral administration of netupitant in rats at doses up to 30 mg/kg (1.9 times the human AUC in male rats and 3.7 times the human AUC in female rats at the recommended human dose) had no effects on fertility or reproductive performance. Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended human oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.¹¹ The reader is referred to the full Pharmacology/Toxicology review by Ke Zhang, Ph.D. and David Joseph, Ph.D., DARRTS.

Review of Literature

Applicant’s Review of Literature

The applicant performed a search of published literature using Embase and PubMed without time period limitations. The applicants search parameters can be found in the June 1, 2017, submission to NDA 210493. The applicant concluded that there are no publications in literature regarding the fixed dose combination of netupitant or (fosnetupitant) and palonosetron on male and female fertility.

DPMH’s Review of Literature

DPMH conducted a review of published literature in PubMed to evaluate the use of AKYNZEO or its component and its effects on fertility. There are no data on the use of AKYNZEO or its components and effects on fertility.

Summary

Overall, there are no effects on fertility shown in animal reproduction studies and no data in humans available on the effects of AKYNZEO or its components on fertility to inform a potential clinical risk. In addition, pregnancy testing and contraception recommendations are not warranted; (b) (4)

¹¹ Drugs@FDA. Akynzeo package insert. 4/29/2015.

CONCLUSIONS

The Pregnancy and Lactation subsections of AKYNZEO labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of labeling was formatted in the PLLR format to include: “Risk Summary,” and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” subsection of labeling was formatted in the PLLR format to include: the “Risk Summary” section.
- **Patient Counseling Information, Section 17**

The “Patient Counseling Information” section of labeling was updated to correspond with changes made to subsection 8.1 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause fetal harm (8.1).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with AKYNZEO use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes.

In animal reproduction studies with netupitant, no effects on embryo-fetal development were observed following daily oral administration in pregnant rats during the period of organogenesis at doses up to 3.7 times the human AUC (area under the plasma concentration-time curve) at the recommended single dose to be given with each cycle of chemotherapy. However, a dose-dependent increase in adverse effects on embryo-fetal development was observed following daily oral administration of netupitant in pregnant rabbits during the period of organogenesis with doses at least 0.2 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy. Daily oral administration of netupitant in rats up to 3.7 times the human AUC at the recommended dose during organogenesis through lactation produced no adverse effects in the offspring.

In animal reproduction studies with fosnetupitant, delayed ossification of pubis occurred after intravenous administration in rats during the period of organogenesis at a dose 3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy. In pregnant rabbits, an increase in resorptions was observed with daily

intravenous administration of fosnetupitant during the period of organogenesis at doses up to 9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy. Daily intravenous administration of fosnetupitant (3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) in rats during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development.

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed following oral administration during the period of organogenesis at doses up to 921 and 1841 times the recommended oral dose in rats and rabbits, respectively (*see Data*).

Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S., general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Netupitant

Daily oral administration of up to 30 mg/kg netupitant in rats (3.7 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis produced no effects on embryo-fetal development. However, an increased incidence of external and skeletal abnormalities in rabbit fetuses was observed following daily oral administration of netupitant in rabbits at 10 mg/kg/day and higher (0.2 times the human AUC at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis. These abnormalities included positional abnormalities in the limbs and paws, and fused sternbrae. Reduction in fetal rabbit weight occurred at 30 mg/kg/day. Maternal toxicity in rabbits (i.e., loss of bodyweight during the treatment period) was also observed at 30 mg/kg/day. Daily oral administration of up to 30 mg/kg netupitant (3.7 times the human AUC at the recommended dose) in rats during organogenesis through lactation produced no adverse effects in the offspring.

Fosnetupitant

Daily intravenous administration of 39 ^(b)₍₄₎ mg/kg/day fosnetupitant in rats (3 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis produced delayed ossification of pubis. No effects on embryo-fetal development were observed with daily administration of up to 13 ^(b)₍₄₎ mg/kg fosnetupitant in rats (2 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Due to the limited systemic exposure to fosnetupitant in pregnant rats, it is not possible to provide an AUC-based comparison of fosnetupitant exposure in rats and humans. An increase in resorptions was observed with daily intravenous administration of fosnetupitant at 6 ^(b)₍₄₎ mg/kg/day and higher in rabbits (9 times the human AUC for fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during the period of organogenesis. No effects were observed in rabbits at 3 ^(b)₍₄₎ mg/kg/day (5 times the human AUC for

fosnetupitant and 0.4 times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy). Daily intravenous administration of 39 ^(b)₍₄₎ mg/kg fosnetupitant in rats (3 times the AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy) during organogenesis through lactation produced lower bodyweight in offspring at birth through maturation, and delayed physical development (pinna detachment, eye opening, and preputial separation). These effects were associated with maternal toxicity (reduced weight gain and food consumption). No effects occurred in offspring or dams at 13 ^(b)₍₄₎ mg/kg/day (2 ^(b)₍₄₎ times the human AUC for netupitant at the recommended single dose to be given with each cycle of chemotherapy).

Palonosetron

In animal reproduction studies with palonosetron, no effects on embryo-fetal development were observed in pregnant rats given oral doses up to 60 mg/kg/day (921 times the recommended oral dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (1841 times the recommended oral dose based on body surface area) during the period of organogenesis.

8.2 Lactation

Risk Summary

There are no data on the presence of netupitant (or fosnetupitant) or palonosetron in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AKYNZEO and any potential adverse effects on the breastfed infant from AKYNZEO or from the underlying maternal condition

17 PATIENT COUNSELING INFORMATION

Pregnancy

Inform female patients of reproductive potential that AKYNZEO may cause fetal harm and to inform their prescriber of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

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/s/

CARRIE M CERESA
12/08/2017

MIRIAM C DINATALE
12/08/2017

LYNNE P YAO
12/11/2017

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

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

Memorandum

Date: December 8, 2017

To: Charles Line, M.D., Clinical Reviewer
Division of Gastroenterology and Inborn Error Products (DGIEP)

Mary Chung, Regulatory Project Manager (DGIEP)

Joette M Meyer, Associate Director for Labeling (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for Akynzeo (fosnetuptant and palonosetron) for injection, for intravenous use

NDA: 210493

In response to DGIEP's consult request dated May 4, 2017, OPDP has reviewed the proposed product labeling (PI) and Patient Package Insert (PPI) for Akynzeo. This supplement is for a new formulation of Akynzeo, for intravenous use.

PI and PPI: OPDP has reviewed the draft PI received by electronic mail from DMPP on November 29, 2017, and has no comments.

A combined OPDP and DMPP review was completed, and comments on the proposed PPI was sent under separate cover on December 6, 2017.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
12/08/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	December 7, 2017
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 210493
Product Name and Strength:	Akynzeo (fosnetupitant and palonosetron) for injection 235mg/0.25mg
Submission date:	November 28, 2017
Applicant/Sponsor Name:	Helsinn Healthcare, SA
OSE RCM #:	2017-864-1
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, Pharm.D.

1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised carton labeling and container label (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review, OSE RCM #: 2017-864^a.

2 CONCLUSION

The revised carton labeling and container label for Akynzeo is unacceptable from a medication error perspective. As presented, established name is not at least half the size of the proprietary name on both carton labeling and container label.

^aAbraham.S. Label and Labeling Review for Akynzeo (NDA 210493). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Sept 13. 32 p. OSE RCM No.:2017-864

3 RECOMMENDATIONS FOR HELSINN HEALTHCARE, SA

We recommend the following be implemented prior to approval of this NDA:

A. CONTAINER LABEL AND CARTON LABELING:

1. Please ensure that the established name is at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

Appendix A: Label and Labeling Submitted on November 28, 2017

Container label:



Carton labeling:



(b) (4)

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/s/

SHERLY ABRAHAM
12/07/2017

SARAH K VEE
12/07/2017

**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: December 6, 2017

To: Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Error Products (DGIEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Sharon W. Williams, MSN, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, BSN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Meeta Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): AKYNZEO (fosnetupitant and palonosetron)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: NDA 210493

Applicant: Helsinn Healthcare SA

1 INTRODUCTION

On April 20, 2017, Helsinn Healthcare SA submitted for the Agency's review an original New Drug Application (NDA) 210493, for Intravenous Fosnetupitant and Palonosetron Fixed-Dose Combination. AKYNZEO (netupitant and palonosetron) capsules, for oral use are indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

AKYNZEO (fosnetupitant and palonosetron) for injection, for intravenous use is indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy not including anthracycline plus cyclophosphamide chemotherapy.

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 Gastroenterology and Inborn Error Products (DGIEP) on May 4, 2017 for DMPP and OPDP to review the Applicant's proposed combined Patient Package Insert (PPI) for AKYNZEO (netupitant and palonosetron) capsules, for oral use and AKYNZEO (fosnetupitant and palonosetron) for injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft AKYNZEO (netupitant and palonosetron) capsules, for oral use and AKYNZEO (fosnetupitant and palonosetron) for injection, for intravenous use PPI received on April 20, 2017, and received by DMPP on May 4, 2017.
- Draft AKYNZEO (netupitant and palonosetron) capsules, for oral use and AKYNZEO (fosnetupitant and palonosetron) for injection, for intravenous use PPI received on April 20, 2017, and received by OPDP on November 29, 2017.
- Draft AKYNZEO (netupitant and palonosetron) capsules, for oral use and AKYNZEO (fosnetupitant and palonosetron) for injection, for intravenous use Prescribing Information (PI) received on April 20, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on May 4, 2017.
- Draft AKYNZEO (netupitant and palonosetron) capsules, for oral use and AKYNZEO (fosnetupitant and palonosetron) for injection, for intravenous use Prescribing Information (PI) received on April 20, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on November 29, 2017.

3 REVIEW METHODS

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 APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (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)

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/

TWANDA D SCALES
12/06/2017

MEETA N PATEL
12/06/2017

SHARON W WILLIAMS
12/06/2017

LASHAWN M GRIFFITHS
12/06/2017

Clinical Inspection Summary

Date	November 27, 2017
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Charles Line, M.D., Medical Officer, DGIEP
NDA/BLA #	NDA 210493
Applicant	Helsinn Healthcare SA
Drug	fosnetupitant and palonosetron injection
NME (Yes/No)	Yes
Therapeutic Classification	Anti-Emetics/Serotonergics and Others
Proposed Indication	prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy
Consultation Request Date	June 19, 2017
Summary Goal Date	December 10, 2017
Action Goal Date	April 20, 2018
PDUFA Date	April 20, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator (CI) sites and the sponsor were inspected for this application. All CI sites have the classification of no action indicated (NAI) or preliminary NAI. The sponsor has the preliminary classification of NAI. The data generated by this study is acceptable in support of the application.

II. BACKGROUND

The sponsor, Helsinn Healthcare, submitted this NDA for fosnetupitant and palonosetron (fixed dose combination) injection for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Fosnetupitant is a water-soluble phosphorylated prodrug of netupitant, which is rapidly converted to netupitant *in vivo* following IV administration. Netupitant is a novel selective NK₁ receptor antagonist. Palonosetron is a selective 5-HT₃ receptor antagonist that was approved in the U.S. in 2003 in an IV formulation and in 2008 in an oral formulation. The combination of oral netupitant and palonosetron was approved by FDA in October 2014 as Akynzeo[®] capsules. This injectable drug with the new prodrug fosnetupitant will have the same indication as the oral formulation with netupitant.

Drug: fosnetupitant and palonosetron injection

Study– Protocol number and title for all studies that were inspected:

Protocol PALO-15-17 “A Phase 3, Single-dose, Multicenter, Randomized, Double-blind, Parallel Group Study to Assess the Efficacy and Safety of Palonosetron 0.25 mg Administered as a 30-minute IV Infusion Compared to Palonosetron 0.25 mg Administered as a 30-second IV Bolus for the Prevention of Chemotherapy-induced Nausea and Vomiting in Cancer Patients Receiving Highly Emetogenic Chemotherapy”

Number of subjects: 144 subjects

Number of sites: 76

Number of countries where subjects were enrolled: nine

Dates that study was conducted: September 2015 to March 2016

Efficacy endpoint: Complete response defined as no vomiting AND no use of rescue medication.

III. RESULTS (by site):

Name and type of inspected entity/Address	Protocol # /Site #/ # of Subjects	Inspection Dates	Classification
CI: Dr. Michael Schenker Sf. Nectarie Oncology Center Department of Medical Oncology 23A Caracal Str., Craiova, Romania	PALO-15-17 Site 1813/ 25 Subjects	October 9 to 12, 2017	NAI
CI: Dr. Miranda Gogishvili LDT High Technology Medical Center University Clinic 9 Tsinandali str., Tbilisi, Georgia	PALO-15-17 Site 1401/ 24 Subjects	October 16 to 18, 2017	NAI
CI: Dr. Katalin Udud Koranyi National Institute of TBC and Pulmonology 6th Department of Pulmonology Piheno ut 1, H-1121, Budapest, Hungary	PALO-15-17 Site 1608/ 18 Subjects	October 9- 13, 2017	*NAI
Sponsor: Helsinn Healthcare SA Via Pian Scainrolo 9, 6912 Lugano, Switzerland	PALO-15-17	November 21 to 24, 2017	*NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional

letter has been sent to the inspected entity.

1. Dr. Michael Schenker
Sf. Nectarie Oncology Center, Craiova, Romania

For Protocol PALO-15-17 at this site, 26 subjects were screened and 25 subjects were enrolled and completed the study. The records for 21 of the 25 enrolled subjects were reviewed in depth and compared to line listings from the NDA. The FDA field investigator covered subject protection, protocol adherence, and investigational product administration and accountability. The endpoints were verified by inspection of subject diaries. Data generated by this site is acceptable in support of the indication.

2. Dr. Miranda Gogishvili
LDT High Technology Medical Center University Clinic, Tbilisi, Georgia

For Protocol PALO-15-17 at this site, 24 subjects were screened and enrolled, and 23 subjects completed the study. One subject was lost to follow-up after Visit 3. The records for all enrolled subjects were reviewed in depth and compared to line listings from the NDA. The FDA field investigator covered subject protection, protocol adherence, and investigational product administration and accountability. The endpoints were verified by inspection of subject diaries. Data generated by this site is acceptable in support of the indication.

3. Dr. Katalin Udud
Koranyi National Institute of TBC and Pulmonology, Budapest, Hungary

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator and on records and notes exchanged during these communications. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

For Protocol PALO-15-17 at this site, 20 subjects were screened, 18 subjects were enrolled, and 17 subjects completed the study. The records for all enrolled subjects were reviewed in depth and compared to line listings from the NDA. The FDA field investigator covered subject protection, protocol adherence, and investigational product administration and accountability. The endpoints were verified by inspection of subject diaries. Data generated by this site is acceptable in support of the indication.

4. Helsinn Healthcare SA, Lugano, Switzerland

Note: Observations below for this sponsor inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocol PALO-15-17 including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring for the clinical sites, and handling of adverse events and other sponsor/monitor related activities. There was no evidence of underreporting of adverse events. Monitoring was very well performed.

The study appears to have been conducted adequately, and the data generated by this sponsor may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.

Review Division /Division Director/Donna Griebel

Review Division /Medical Team Leader/Anil Rajpal

Review Division /Project Manager/Mary Chung

Review Division/Medical Officer/Charles Line

OSI/Office Director/David Burrow

OSI/DCCE/ Division Director/Ni Khin

OSI/DCCE/Branch Chief/Kassa Ayalew

OSI/DCCE/Team Leader/ Susan D. Thompson

OSI/DCCE/GCP Reviewer/ Susan Leibenhaut

OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

OSI/Database PM/Dana Walters

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/s/

SUSAN LEIBENHAUT
11/27/2017

SUSAN D THOMPSON
11/27/2017

KASSA AYALEW
11/28/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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: September 13, 2017

Requesting Office or Division: Division of Gastrointestinal and Inborn Errors Products (DGIEP)

Application Type and Number: NDA 210493

Product Name and Strength: Akynzeo (fosnetupitant and palonosetron), for injection 235mg/0.25mg

Product Type: Multi-ingredient product

Rx or OTC: Rx

Applicant/Sponsor Name: Helsinn Healthcare, SA

Submission Dates: April 20, 2017
July 19, 2017

OSE RCM #: 2017-864

DMEPA Primary Reviewer: Sherly Abraham, R.Ph.

DMEPA Team Leader: Sarah K. Vee, Pharm.D.

1 REASON FOR REVIEW

This review evaluates the labels and labeling for NDA 210493, Akynzeo (fosnetupitant and palonosetron), a new molecular entity (NME), submitted on April 20, 2017. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information (PI), container label, and carton labeling for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Helsinn Healthcare, SA submitted Akynzeo (fosnetupitant and palonosetron), for the treatment of prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Akynzeo (netupitant and palonosetron) 300 mg/0.5 mg oral capsule was approved under NDA 205718 and indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. on October 10, 2014. On June 12, 2017, the Office of Pharmaceutical Quality (OPQ) determined that Akynzeo (fosnetupitant and palonosetron) for injection is considered to be an NME based on the

following: a) fosnetupitant represents a “covalently bonded modification” to netupitant
b) not all “covalently bonded modifications” are NMEs. However, because fosnetupitant is an ester of N-hydroxymethyl-netupitant, and not an ester of the previously approved active moiety, netupitant, it is considered a new active moiety.

We find the PI acceptable; however, we identified areas in the container label and carton labeling that can be improved to increase the clarity of information to promote the safe use of the product. Specifically, we recommend revising how the proprietary and established names, dosage form, and strength are presented, adding the route of administration and dilution statements, and adding the package type on both the container label and the carton labeling. For carton labeling, we recommend bolding the refrigeration statement. We provide letter-ready recommendations for the Applicant in Section 4.1 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI is acceptable. However, the proposed carton labeling and container labels can be improved to increase the clarity of information to promote the safe use of the product. Please see recommendations for the Applicant in Section 4.1 below:

4.1 RECOMMENDATIONS FOR HELSINN HEALTHCARE, SA

We recommend the following be implemented prior to approval of this NDA:

A. Container Label and Carton Labeling:

1. Presentation of the proprietary and established names, dosage form, and strength should be in the following format. Ensure that the proprietary name, the established name, and the strength statement are the most prominent information on the Principal Display Panel (PDP), taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2) and 21 CFR 201.15(a)(6). For example,

Akynzeo
(fosnetupitant and palonosetron)
For injection
235 mg/0.25 mg per vial

2. Add the route of administration and dilution statement to the PDP below the strength statement per 21 CFR 201.100(b)(3). For example, “Must be reconstituted and further diluted. For intravenous infusion only.”

3. Add the package type, single-dose vial, to the PDP to identify how the medication should be handled and used.

B. Carton Labeling:

1. Bold the statement “(b) (4) **at 2°C-8°C (36°F-46°F).**”. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Akynzeo that Helsinn Healthcare, SA submitted on April 20, 2017 and July 19, 2017.

Table 1. Relevant Product Information for Akynzeo		
Products	Akynzeo (NDA 210493)	Akynzeo (NDA 205718)
Initial Approval Date	N/A	October 10, 2014
Active Ingredients	fosnetupitant and palonosetron	netupitant and palonosetron
Indication	indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy	indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
Route of Administration	intravenous infusion	oral
Dosage Form:	lyophilized powder for injection	capsules
Strength:	235 mg/0.25mg	300 mg/0.5 mg
Dose and Frequency	one single 30 min intravenous infusion 30 minutes prior to emetogenic chemotherapy	one capsule administered approximately 1 hour prior to the start of chemotherapy
How Supplied:	sterile, white to off-white lyophilized powder for reconstitution in single-dose vial.	pack of one capsule in a blister pack of four capsules (two capsule per blister strip)

Storage:	Store at 2° to 8°C (35.6 F to 46.4°F) [see USP Controlled Room Temperature]. Store the reconstituted solution and the final diluted solution at ambient room temperature (b) (4)	Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted from 15 °C to 30 °C (59 °F to 86 °F) [see USP Controlled Room Temperature].
Container closure:	N/A	N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Akynzeo labels and labeling submitted by Helsinn Healthcare, SA on April 20, 2017 and July 19, 2017

- Container label
- Carton labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container label:



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling:

(b) (4)



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHERLY ABRAHAM
09/14/2017

SARAH K VEE
09/14/2017

**Interdisciplinary Review Team for QT Studies Consultation:
QT Study Review**

NDA	210493
Brand Name	AKYNZEO
Generic Name	Fosnetupitant/Palonosetron, IV injection (IV NEPA FDC)
Sponsor	Helsinn Healthcare SA
Indication	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC)
Dosage Form	Intravenous (IV) Infusion
Drug Class	Antiemetic
Therapeutic Dosing Regimen	260 mg fosnetupitant /0.25 mg palonosetron, i.e. 235 mg fosnetupitant free-base /0.25 mg palonosetron, given as a 30 min IV infusion, single dose administration on Day 1 of each chemotherapy cycle
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not known, maximum tested dose is 390 mg fosnetupitant as a single agent administered as a 30 min IV infusion.
Submission Number and Date	001; 4/20/2017
Review Division	DGIEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of intravenous administration by 30 minute infusion of IV NEPA FDC (260 mg fosnetupitant¹ and 0.25 mg palonosetron) is expected based on the totality of the evidence that includes the results from the following four clinical studies (two TQT studies and two studies of IV NEPA FDC):

- A TQT study for IV palonosetron (Aloxi®) showed no clinically significant effect on the QTc interval with a single suprathreshold dose of 2.25 mg palonosetron IV short infusion (Previous QT-IRT review under NDA 21372 dated 08/06/2007 in DARRTS). This dose level provides >9-fold exposure margin over the exposures

¹ Equivalent to 235 mg fosnetupitant free-base

anticipated with therapeutic dosing of 0.25 mg palonosetron given as 30 min IV infusion in IV NEPA FDC product.

- A TQT study for Oral NEPA FDC (Akynzeo®; 300 mg netupitant and 0.5 mg palonosetron) showed no clinically significant effect on the QTc interval with single oral suprathreshold dose of 600 mg netupitant and 1.5 mg palonosetron (Previous QT-IRT review under IND 73493 dated 01/20/2010 in DARRTS). The 600 mg dose of oral netupitant provides similar exposure to netupitant from IV NEPA FDC.
- Study PNET-12-23 was a single center, randomized, Phase I, double-blind, active-controlled, parallel groups study, in which 160 healthy subjects were enrolled: 148 subjects received single ascending IV fosnetupitant (doses from 19.5 mg up to 390 mg with N=8-30 subjects in different dose-groups), and 134 subjects received single dose of oral NEPA FDC. No large (>20 ms) mean increases in baseline-corrected QTcF were observed in the central tendency analysis (Table 7)². None of the subjects in 260 mg IV fosnetupitant dose group (N=30) had QTcF >450 ms or Δ QTcF>30 ms post-dose (Table 9, Table 11). Fosnetupitant is a new molecule in the current submission and has not been studied in any prior TQT studies. The preclinical cardiac safety studies did not identify any potential issues for fosnetupitant. The 1.5-fold exposure margin provided by the 390 mg IV fosnetupitant dose in this study over the 260 mg therapeutic dose adequately covers the highest clinically relevant exposure of fosnetupitant because fosnetupitant clearance (conversion to netupitant) is likely mediated by non-saturable enzymes, such as phosphatases and esterases, distributed throughout the body and none of the intrinsic/extrinsic factors are expected to increase its exposure. Within this exposure margin, the C-QTc assessment did not show a positive relationship for fosnetupitant.
- Study NEPA-15-18 was a multicenter, randomized, phase 3, double-blind, active controlled study in patients with highly emetogenic cancer chemotherapy (HEC). In this study, 202 subjects received oral NEPA FDC and 203 subjects received IV NEPA FDC. No large (>20 ms) mean increases in baseline-corrected QTcF were observed in the central tendency analysis (Table 8)². Similar values for outliers of QTcF and Δ QTcF (Table 10, Table 12) were seen for the two study arms (IV NEPA FDC and oral NEPA FDC). The cardiac safety profile was also similar between these two study arms.

Furthermore, the sponsor has stated that “oral Akynzeo (oral NEPA FDC) has been marketed for 2 years and after more than 14,000 patient exposures with more than 85,000 doses, no QTc reactions have been reported in the post marketing surveillance data.”

The considerations for exposures and QTc effects for the active drug (netupitant) and metabolite moieties (M1, M2, and M3), that are formed from the pro-drug fosnetupitant, are detailed below:

Netupitant: C_{max} of fosnetupitant and netupitant occur at the end of the 30 minute infusion of IV NEPA FDC and mean concentrations of netupitant remained at nearly the same level until 4 h post-infusion. The netupitant C_{max} observed with the therapeutic

² Because there were no placebo and positive controls for QT evaluation in both studies (PNET-12-23 and NEPA-15-18), the data can be used to exclude only large mean QTc effects (20 ms).

dosing of IV NEPA FDC is ~2-fold of that after oral 300 mg netupitant (823 vs. 421 µg/L), but is similar to the netupitant C_{max} observed with suprathapeutic dose (600 mg) of netupitant used in TQT study of oral Akynzeo. Although the previous TQT study of oral Akynzeo does not cover the worst case scenario of possible increase in netupitant exposure up to 1.4-fold that could be expected with hepatic impairment, these exposures are covered by 390 mg IV fosnetupitant (1.5-fold the proposed therapeutic dose of 260 mg fosnetupitant in IV NEPA FDC) that is studied in PNET-12-23, and data from this study did not show a positive C-QTc relationship for netupitant. These results are consistent with the prior TQT study where no positive C-QTc relationship was identified for netupitant.

Netupitant Metabolites M1, M2 and M3: The intensive PK sampling in Study PNET-12-23 showed that the C_{max} for netupitant metabolites M1, M2 and M3 are around 12 h (steady conc. from 8 to 24 h), 2-3 h and 24 h, respectively. Although the ECG sampling in either of the studies (PNET-12-23 and NEPA-15-18) was not adequate to capture the effects near T_{max} of these metabolites, these metabolite exposures with therapeutic dosing of IV NEPA FDC were well covered by suprathapeutic dose of 600 mg netupitant in TQT study for approved oral NEPA FDC (2-fold [54 vs. 26 µg/L], 1.5-fold [228 vs. 156 µg/L] and 1.9-fold [102 vs. 53 µg/L] exposure margin for M1, M2 and M3, respectively). Furthermore, there was no statistically significant positive C-QTc relationship seen with each of these 3 metabolites in the prior TQT study for oral Akynzeo. So, further exploration of C-QTc relationship for these metabolites was not carried out in this review and lack of ECG sampling near T_{max} for these metabolites in the submitted studies (PNET-12-23 and NEPA-15-18) may not impact the overall conclusion.

2 PROPOSED LABEL

The labeling language in the currently proposed label by the sponsor is as follows:

12.2 Pharmacodynamics

Cardiac Electrophysiology

Oral (b) (4) dose netupitant 600 mg and palonosetron 1.5 mg (b) (4) the QTc interval.

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Oral (b) (4) dose of netupitant 600 mg and palonosetron 1.5 mg, or intravenous co-administration by 30 minute infusion of therapeutic dose of fosnetupitant 235 mg and palonosetron 0.25 mg, (b) (4) the QTc interval.

3 BACKGROUND

3.1 PRODUCT INFORMATION

This product is a fixed dose combination of fosnetupitant and palonosetron (IV NEPA FDC; 260 mg fosnetupitant /0.25 mg palonosetron, i.e. 235 mg fosnetupitant free-base

/0.25 mg palonosetron) for IV administration. This FDC was developed as a line extension of the oral FDC (Akynzeo) registered in October 2014 by the FDA. Oral AKYNZEO® (Oral NEPA FDC) is a fixed dose combination of 300 mg netupitant, a substance P/neurokinin1 (NK1) receptor antagonist, and 0.5 mg palonosetron, a serotonin-3 (5-HT3) receptor antagonist. Fosnetupitant is a water soluble phosphorylated pro-drug of netupitant that is rapidly converted to netupitant in vivo.

3.2 MARKET APPROVAL STATUS

Fosnetupitant and palonosetron IV fixed dose combination is not approved for marketing in any country. However, the active moiety (netupitant) in a fixed dose combination with palonosetron is approved as a capsule formulation in the United States and several other countries.

Netupitant is not registered as a single agent. Palonosetron is registered as a single agent under the name ALOXI®, (ALOXI® 0.25 mg solution for intravenous injection, NDA 21-372 and ALOXI® 0.50 mg oral softgel capsules, NDA 22-233), for the prevention of Chemotherapy-Induced Nausea and Vomiting (CINV).

3.3 PRECLINICAL INFORMATION

Refer to Appendix 6.1 for preclinical cardiac safety experience with fosnetupitant.

The following is the preclinical information included in the previous TQT study review for oral Netupitant/Palonosetron combination product:

Source: IB- March 2008:

“The application of netupitant, or its metabolites RO0681133 (M1), RO0713001 (M2) and RO0731519 (M3) (0.1-30 µM) to Chinese Hamster Ovary (CHO) cells expressing recombinant hERG K⁺ channels produces a significant reduction in inward and outward K⁺ currents. From these results, IC₅₀ values of ~ 0.76, 0.84, 43 and 4.4 µM and IC₂₀ values of ~ 0.19, 0.21, 11 and 1.1 µM can be calculated for the block of hERG K⁺ channels by netupitant, and metabolites M1, M2, and M3, respectively. These results indicate that netupitant and its M1, M2, and M3 metabolites could block repolarizing currents through hERG K⁺ channels in vivo if free cardiac concentrations reached levels above ~ 0.19, 0.21, 11 and 1.1 µM, respectively (1011715).

“A number of in-vitro studies are ongoing on the isolated canine ventricular myocytes (“M” mid-myocardial cells), canine Purkinje fibers and canine papillary muscle. The preliminary results are summarized below.

“The effect of netupitant and its metabolites, M1, M2 and M3 on the rapid component of the delayed rectifier potassium current was investigated using isolated canine ventricular myocytes (“M” mid-myocardial cells). Netupitant and its metabolite M1 at 3 µM induced a very slight inhibition (21 ± 1% and 25 ± 2%, respectively) of the rapid component of delayed rectifier potassium current (I_{Kr}) (NETU-07-04, NETU-07-08). M1 was tested up to 30 µM. At this highest concentration the metabolite showed a cytotoxic effect on the myocytes, since the majority of cells collapse rapidly after the beginning of the perfusion (NETU-07-08). Metabolite M2 has no effect on

the rapid component of delayed rectifier potassium current in isolated canine ventricular myocytes up to 30 μM (NETU-07-09). Metabolite M3 at 0.03 μM did not induce any noticeable change in the rapid component of delayed rectifier potassium current (IKr) ($n < 5$). At 3 and 30 μM , metabolite M3 induced $14 \pm 2\%$ and $57 \pm 8\%$ inhibition of IKr tail current, respectively. In conclusion, these results suggest that metabolite M3 only at highest concentration tested (30 μM) induced a significant inhibition of the rapid component of delayed rectifier potassium current (IKr) in isolated canine ventricular myocytes (“M” mid-myocardial cells) (NETU-07-31).

“Netupitant and its major metabolites were investigated for the ability to modify cardiac action potential in isolated canine Purkinje fibers. Under the experimental conditions adopted, netupitant at the concentrations up to 1 μM , M1 at the concentrations up to 0.3 μM , M2 at the concentrations up to 3 μM and M3 at the concentrations up to 3 μM had no statistically significant effect on action potential parameters under either normal (1 Hz) or low (0.33 Hz) stimulation rates (NETU-07-03, NETU-07-10, NETU-07-11 and NETU-07-32).

“Netupitant at 3 μM produced a statistically significant decrease in Action Potential Duration at 50% of repolarization (APD50) under normal (1 Hz) stimulation rate. Under low stimulation rate (0.33 Hz) statistically significant decreases in Action Potential Duration at 50%, 70% and 90% of repolarization were observed. (NETU-07-03). Metabolite M1 at 3 μM caused a statistically significant decrease in Action Potential Duration at 70% and 90% of repolarization (APD70 and APD90) under normal stimulation rate. Under low stimulation rate statistically significant decreases in Action Potential Duration at 50%, 70% and 90% of repolarization were observed. (NETU-07-10). Metabolite M2 only at the highest concentration of 30 μM caused a statistically significant decrease in Action Potential Duration at 50%, 70% and 90% of repolarization (APD50, APD70 and APD90) under normal and low stimulation rates and decreases in the plateau of action potential (APD50). Results on metabolite M3 suggest a statistically significant decrease in Action Potential Duration at 50%, 70% and 90% of repolarization (APD50, APD70 and APD90) only at the highest concentration tested 30 μM . Unfortunately a significant precipitation was observed in the organ bath during the perfusion with metabolite M3 at 30 μM . These results suggest a possible inhibitory effect of netupitant and its metabolites M1, M2 and M3 on sodium and/or calcium currents.

“Results of the studies on isolated canine papillary muscle indicate that netupitant at concentrations up to 3 μM has no statistically significant effect on cardiac action potential parameters under normal stimulation rate (1 Hz) (NETU-07-02). Metabolites M1 and M2 had no statistically significant effect on cardiac action potential parameters under normal stimulation rate at concentrations up to 30 μM (NETU-07-12), (NETU-07-13). Under the experimental conditions adopted, metabolite M3 at concentrations of 0.03 μM had no statistically significant effect on action potential parameters under either normal (1 Hz) stimulation rates. When the perfusion of metabolite M3 was undertaken at 0.3 μM , only a slight but statistically significant increase in action potential parameters at 70% of repolarisation under normal stimulation rate (1 Hz) was observed. At 3 μM and 30 μM , statistically significant increases in Action Potential Duration at 50%, 70% and 90% of

repolarisation (i.e in APD50, APD70 APD90) were observed under normal (1 Hz) stimulation rate. It should be noted that a significant precipitate was observed in the organ bath during the perfusion with metabolite M3 at 30 µM. In conclusion, these results suggest that metabolite M3 at 3 µM and 30 µM induced slight and no concentration-dependent increases in action potential duration (NETU-07-33).”

Regarding this data, the reviewer’s comment stated:

In conscious dogs and in anesthetized whole animals netupitant and its metabolites or palonosetron/netupitant combinations have been associated with bradycardia, hypotension dose-dependent decreases in atrioventricular conduction (increased PR) and in ventricular depolarisation rate (prolonged QRS) and prolonged QT.

3.4 PREVIOUS CLINICAL EXPERIENCE

Refer to Appendix 6.1 for clinical experience with fosnetupitant and IV NEPA FDC.

Both palonosetron and the combination of oral netupitant-palonosetron have been previously subjected to formal ICH E14 Thorough QT Trials.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clinical pharmacology of fosnetupitant, netupitant and palonosetron.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

Previously QT-IRT had reviewed the protocols and subsequent TQT study reports for oral Akynzeo (netupitant/palonosetron) (under IND 73493; dated 01/20/2010 in DARRTS) and IV Aloxi (palonosetron) (under NDA 21372; dated 08/06/2007 in DARRTS). QT-IRT received a consult review under IND 115191 which requested a waiver of a QT/QTc study for IV NEPA FDC. The QT-IRT responded that “*Our final determination of the effects of IV NEPA FDC on the QT/QTc interval will be made when we review the QTc data submitted in the NDA*” (dated 03/01/2017 in DARRTS). Accordingly, in the current submission, the sponsor has submitted the study reports NEPA-15-18 and PNET-12-23 for the study drug, electronic datasets and waveforms to the ECG warehouse.

4.2 QT STUDY

4.2.1 Title

PNET-12-23

A Phase I, double-blind, controlled, parallel groups, unbalanced single ascending dose study to assess the safety of intravenously administered pro-netupitant combined with crossover study extensions to estimate the dose of intravenous pro-netupitant yielding equivalent drug exposure as oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination in healthy male and female volunteers.

NEPA-15-18

A phase 3, multicenter, randomized, double-blind, active control study to evaluate the safety and efficacy of IV pro-netupitant/palonosetron (260 mg/0.25 mg) combination for the prevention of Chemotherapy-induced nausea and vomiting in repeated chemotherapy cycles in patients receiving highly emetogenic chemotherapy

4.2.2 Protocol Number

PNET-12-23
NEPA-15-18

4.2.3 Study Dates

PNET-12-23

Date of first subject enrolled: 09 Jan 2013
Date of last subject completed: 10 Jan 2014

NEPA-15-18

Date of first subject enrolled: 17 Nov 2015
Date of last subject completed: 02 Aug 2016

4.2.4 Objectives

PNET-12-23

Primary objective:

- To assess the safety of pro-netupitant administered as a single intravenous (IV) infusion.

NEPA-15-18

The primary objective of this study was to assess the safety and tolerability of a single dose of intravenous fosnetupitant/palonosetron (260 mg/0.25 mg) fixed-dose combination (IV NEPA FDC) infused over 30 minutes (min), with oral dexamethasone, in initial and repeated cycles of highly emetogenic chemotherapy (HEC).

Both studies carried out ECG measurements for QT characterization.

4.2.5 Study Description

4.2.5.1 Design

PNET-12-23

This single center randomized Phase I study was performed in healthy male and female subjects in different parts: a parallel group single ascending dose (SAD) part with a crossover extension (SAD-CO) (where applicable), a pilot crossover part (P-CO), and a final crossover part (F-CO).

Overview of study parts

A randomized, double-blind (within dose cohorts), 2-period, 2-sequence, crossover design was the basis of each study part. No crossover arm was however performed for low pro-netupitant doses (i.e., doses below 130 mg) in the SAD/SAD-CO part because these doses were investigated mainly for safety reasons.

All parts were performed under double-blind (within dose cohorts), double dummy conditions.

Unbalanced randomization was applied in the SAD/SAD-CO part (4:1 ratio for pro-netupitant vs. oral FDC), while 1:1 randomization was applied in the P-CO and F-CO extensions.

The SAD/SAD-CO part was conducted in dose cohorts of 10 subjects each with single ascending doses. In total, 8 doses (i.e. 19.5, 32.5, 65, 130, 195, 260, 325, 390 mg pro-netupitant) were pre-defined in the clinical study protocol and the crossover extension was planned for doses from 130 mg to 390 mg pro-netupitant (inclusive).

The P-CO part was conducted in dose cohorts of 20 subjects each with the doses selected during the course of the study on the basis of the PK data obtained from the SAD/SAD-CO cohorts. Two doses (i.e. 195 and 260 mg) were selected for the P-CO study extension.

NEPA-15-18

This was a multicenter, multinational, randomized, active-controlled, double-blind, double-dummy, parallel group, stratified study evaluating the safety and efficacy of a single dose of IV NEPA FDC (260 mg/0.25 mg) infused in 30 min, with oral dexamethasone, prior to initial and repeated cycles of HEC. The control group was oral netupitant/palonosetron (300 mg/0.50 mg) fixed-dose combination (Oral NEPA FDC) administered orally 60 min before start of reference HEC.

4.2.5.2 Controls

There was no separate placebo only arm in both the trials. Also, there was no positive control in either of the studies.

4.2.5.3 Blinding

PNET-12-23

The study was performed according to a double-blind double-dummy design (within the dose cohorts). Therefore, the subjects received a placebo capsule together with the active pro-netupitant infusion and a placebo infusion together with the oral active netupitant/palonosetron FDC capsule to guarantee the double-blind nature of the study.

NEPA-15-18

The blinding of the study drugs was guaranteed by the use of identical placebos to the respective active drugs (double-dummy technique).

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

PNET-12-23

This study includes products and doses as below:

- pro-netupitant IV formulation (test)
 - 19.5 mg, 32.5 mg, 65.0 mg, 130.0 mg, 195.0 mg, 260.0 mg, 325.0 mg, and 390.0 mg (SAD/SAD-CO part)

- 195.0 mg and 260.0 mg (P-CO part)
- 234.0 mg and 286.0 mg (F-CO part)
- netupitant and palonosetron FDC oral formulation (reference)
 - 300 mg netupitant and 0.5 mg palonosetron
- placebo capsules as dummy oral treatment
- placebo solution as dummy IV infusion treatment

NEPA-15-18

The control drug, oral netupitant/palonosetron (300 mg/0.50 mg) FDC (Oral NEPA FDC) was to be administered on Day 1 of each cycle.

The test drug, IV fosnetupitant/palonosetron (260 mg/0.25 mg) FDC (IV NEPA FDC) was to be administered as a 30-min infusion of a 50-mL solution on Day 1 of each cycle.

4.2.6.2 Sponsor’s Justification for Doses

PNET-12-23

Selection of starting dose

Based on the results obtained in a 2-week toxicity study in rats (PNET-11-21), the dose level of 13.16 mg/kg/day is the no observed adverse effect level (NOAEL) for systemic effects and the dose level of 39.47 mg/kg/day, which was the highest dose tested in this study, is the NOAEL for local effects. Moreover, a 2-week toxicity study in dogs was also performed (PNET-11-22), and in this study, the dose level of 13.16 mg/kg/day (the highest dose level) was the NOAEL for systemic and for local effects.

Following the FDA guideline “Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers”, the NOAEL was converted to the human equivalent dose (HED), and a dose of 19.5 mg was calculated.

Therefore, based on the above mentioned animal toxicity data, the starting dose for IV administration in human volunteers was proposed to be 19.5 mg pro-netupitant (equivalent on molar basis to 15 mg netupitant, based on a conversion factor rounded to 1.3).

Selection of single ascending doses

Dose escalation above the starting dose of 19.5 mg pro-netupitant was proposed as follows: 32.5 mg, 65 mg, 130 mg, 195 mg, 260 mg, 325 mg, and 390 mg pro-netupitant (equivalent on molar basis to 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg netupitant).

Based on exposure data obtained from oral netupitant 300 mg/palonosetron 0.5 mg FDC studies, together with exposure data obtained in NETU-11-01 study with previous IV netupitant formulation, the oral availability of netupitant in human was estimated as equal to 87%. Therefore, it was expected that an IV dose ranging between 200 mg and 300 mg of netupitant (expected value of 261 mg considering 87% availability factor) would give an equivalent exposure (AUC_{0-inf}) to the oral dose of 300 mg netupitant. This corresponded to a dose of pro-netupitant between 260 mg and 390 mg.

The highest predefined proposed dose in this study was 390 mg pro-netupitant. This dose was defined in accordance with the suggestions of the competent authority and in reference to the specification limits of the active ingredient.

After each cohort of 10 subjects (SAD part) had completed the SAD treatment period, the DSMB assessed the safety (and PK, if relevant) data obtained and determined if dose escalation could proceed to the next predefined dose or if a dose adjustment was necessary.

Selection of doses in the pilot crossover part

Pro-netupitant doses to be tested in the P-CO part depended on the PK data obtained from the previous crossover cohorts (SAD/SAD-CO part from dose 130 mg and previous P-CO cohorts, if any) for which data were already available.

The dose of oral fixed dose combination (FDC) that was equivalent by exposure to netupitant from the current IV pro-drug dose was computed from the last (i.e. the current) estimate of F_{rel} IV. The extended equivalence interval spanned from 80% of the lower 50% confidence limit of this estimate to 125% of its upper 50% confidence limit. If this interval included 300 mg, then the IV pro-netupitant dose was further tested in a P-CO cohort. Otherwise no P-CO cohort was performed with this dose.

Selection of doses in the final crossover part

Pro-netupitant doses to be tested in the F-CO part were determined once all the subjects in the crossover SAD/SAD-CO and P-CO parts completed the study.

After re-estimation of F_{rel} IV, derivation of the target dose, and calculation of the number of subjects needed, half of these subjects were treated at the “estimated target dose – 10%” (i.e., 90% of the estimated target dose) and the other half of the subjects was treated with the “estimated target dose +10%” (i.e., 110% of the estimated target dose), provided that such dose was lower or equal to the highest dose tested and considered safe by the DSMB. In case the 110% of the estimated target dose was above such dose, a lower dose was to be selected for the F-CO part.

NEPA-15-18

The dose of fosnetupitant in the IV NEPA FDC was selected based on the results of a pharmacokinetic (PK) study in healthy volunteers (PNET-12-23). In this study, a dose of 257 mg fosnetupitant was shown to be equivalent in exposure (AUC) to the netupitant dose contained in oral NEPA FDC (i.e., 300 mg netupitant). The dose of IV fosnetupitant was then rounded to 260 mg for further development of the IV NEPA FDC.

The dose of palonosetron selected for the IV NEPA FDC was based on the original palonosetron IV development program. The IV palonosetron dose showing to be effective in the prevention of acute nausea and vomiting associated with HEC, and approved in the US and EU, is the 0.25 mg administered as an IV 30-sec bolus.

Reviewer's Comments:

There are two completed TQT studies demonstrating that netupitant at therapeutic exposures in IV NEPA FDC and palonosetron at suprathreshold exposures had no effect on the QTc interval.

The TQT study with IV palonosetron during the single agent Aloxi program revealed no effect on ECG parameters at doses up to 2.25 mg. In this study, the suprathereapeutic dose of 2.25 mg of palonosetron was infused within 2 min (IV bolus infusion) and provided 9-fold exposure margin over therapeutic dosing of 0.25 mg Aloxi (IV bolus administered as 30 sec infusion). Thus, this study would provide >9-fold exposure margin over the exposures anticipated with therapeutic dosing of 0.25 mg palonosetron given as 30 min IV infusion in IV NEPA FDC product.

The assessments in the current program have adequate exposure margin to cover the highest clinically relevant exposure of fosnetupitant with therapeutic dose, because fosnetupitant clearance (conversion to netupitant) is likely mediated by non-saturable enzymes, such as phosphatases and esterases, distributed throughout the body and none of the intrinsic/extrinsic factors are expected to increase its exposure over those observed in its clinical studies. The study PNET-12-23 did not show a positive C-QTc relationship for fosnetupitant. Moreover, the preclinical cardiac safety studies did not identify any potential issues for fosnetupitant.

The netupitant C_{max} observed with the therapeutic dosing of IV NEPA FDC [Fosnetupitant 260 mg/ palonosetron 0.25 mg] is similar to the netupitant C_{max} observed with suprathereapeutic dose (600 mg) of netupitant used in TQT study of oral Akynzeo combination product (300 mg netupitant/0.5 mg palonosetron; suprathereapeutic dose of 600 mg netupitant /1.5 mg palonosetron was studied in that study). Although the previous TQT study of oral Akynzeo does not cover the worst case scenario of possible increase in netupitant exposure up to 1.4-fold that could be expected with hepatic impairment, these exposures are covered by 390 mg IV fosnetupitant (1.5-fold the proposed therapeutic dose of 260 mg fosnetupitant in IV NEPA FDC) that is studied in dose-escalation study PNET-12-23, and data from this study did not show a positive C-QTc relationship for netupitant.

Moreover, in the Phase 3 study (NEPA-15-18) in more than 400 patients receiving IV NEPA FDC or oral NEPA FDC (oral Akynzeo), the data showed similar cardiac safety profile between the two products, similar values for QTcF and Δ QTcF in by-time and outlier analyses with no clinically significant QTc prolongation signal. Furthermore, the sponsor has stated that “oral Akynzeo has been marketed for 2 years and after more than 14,000 patient exposures with more than 85,000 doses, no QTc reactions have been reported in the post marketing surveillance data.”

4.2.6.3 Instructions with Regard to Meals

PNET-12-23

The administration of the study medication took place after an overnight fasting period of at least 10 h. No food was allowed for at least 4 h after drug administration. On profile days, no breakfast was served. A standardized lunch was given at 4 h after start of infusion, a snack at 7 h and dinner at 10 h after start of infusion.

NEPA-15-18

No dosing instructions were made with regards to meals directly. Instead the timing of the dosing was based around the timing of the chemotherapy.

Reviewer's Comment: No effect of food on PK is expected as this is a product for IV administration.

4.2.6.4 ECG and PK Assessments

PNET-12-23

ECG: At baseline (day -1), then ~0.5-0.67 h (between the end of 30 min infusion and next PK sampling timepoint of 40 min, then at 48 h and 120 h.

PK: PK samples for the analysis of pro-netupitant, netupitant and its 3 main metabolites (M1, M2, M3) were taken at the following times: at predose (within 30 min before the start of infusion), t_{mid} (15 min after start of infusion), t_{end} (30 min after start of infusion), and 40 min, 50 min, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96 and 120 h after the start of infusion (20 samples).

NEPA-15-18

ECG: 12-lead ECGs were to be recorded for each cycle at screening, pre-dose, end of IV study drug infusion of 30 min (i.e., immediately [within 10 min] before the start of the reference chemotherapy) and 5 h (± 1 h) after the oral capsule administration, 24 h (± 2 h) after the oral capsule administration and 120 h (-6/+54 h) after the oral capsule administration.

A digitally recorded ECG was to be transmitted from the site to a central reading facility, where ECG interpretations were to be timely performed by a cardiologist blinded to the treatment received by patients.

PK: No PK Samples were collected in this study.

Reviewer's Comment: Acceptable. In Study PNET-12-23, where IV administration of a range of fosnetupitant doses was studied, the end of infusion timepoint can capture the T_{max} of both fosnetupitant and netupitant. In Study NEPA-15-18, where both IV NEPA FDC and oral NEPA FDA were studied, the end of infusion sampling can capture the T_{max} of both fosnetupitant and netupitant with IV dosing and 5 h sampling can capture the T_{max} of netupitant with oral NEPA FDC dosing. The 48 h and 24 h time points can capture any potential delayed effects in these studies.

The intensive PK sampling in Study PNET-12-23 showed that the C_{max} for netupitant metabolites M1, M2 and M3 are around 12 h (steady conc. from 8 to 24 h), 2-3 h and 24 h, respectively. Although the ECG sampling in either of the studies (PNET-12-23 and NEPA-15-18) was not adequate to capture the effects near T_{max} of these metabolites, as shown in Section 5.3, these metabolite exposures with therapeutic dosing of IV NEPA FDC were well covered by supratherapeutic dose of 600 mg netupitant in TQT study for approved oral NEPA FDC (2-fold [54 vs. 26 $\mu\text{g/L}$], 1.5-fold [228 vs. 156 $\mu\text{g/L}$] and 1.9-fold [120 vs. 53 $\mu\text{g/L}$] exposure margin for M1, M2 and M3, respectively). Further there was no statistically significant positive E-R relationship seen in C-QTc analysis with each of these 3 metabolites in the TQT study (Previous QT-IRT review under IND 73493 for TQT study for oral Akynzeo (netupitant/palonosetron), dated 01/20/2010 in DARRTS).

4.2.6.5 Baseline

PNET-12-23

The sponsor used pre-dose QTc values of each sequence as baselines.

NEPA-15-18

The sponsor used the time=0 of each visit as baselines.

4.2.1 ECG Collection

Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.2 Sponsor's Results

4.2.2.1 Study Subjects

PNET-12-23

In Study PNET-12-23, 160 healthy subjects were enrolled: a total of 148 subjects received one dose of the IV fosnetupitant treatment (ranging from 19.5 mg to 390 mg) and 134 subjects received one dose of the oral 300 mg netupitant/0.5 mg palonosetron treatment. No safety-related changes from baseline were observed in QTcF and no marked difference was observed for either treatment group, including the oral formulation.

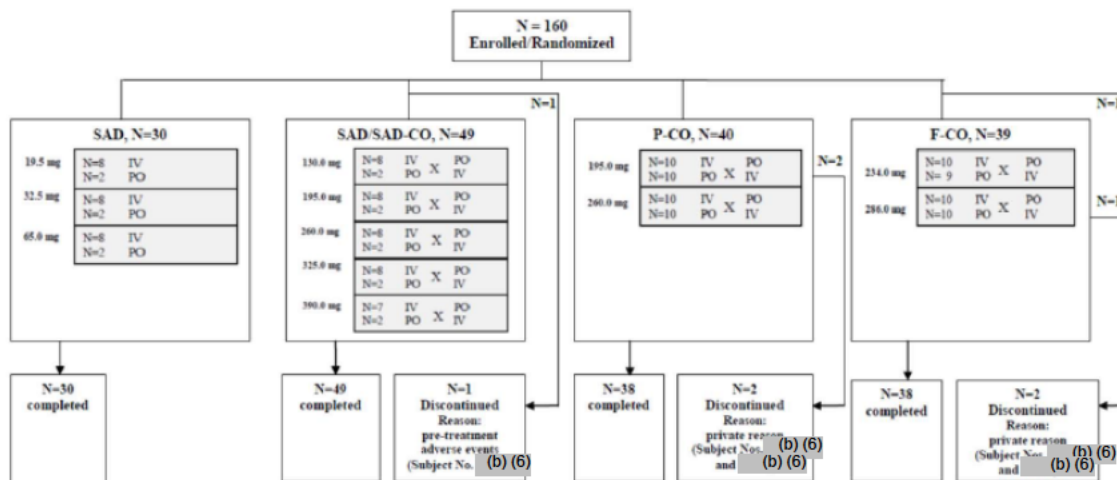
Table 1: Disposition of subjects by cohort

	19.5 mg N=10		32.5 mg N=10		65 mg N=10		180 mg N=10		S-195 mg N=10		P-195 mg N=20		S+P-195 mg N=30	
	IV N=8	Oral N=2	IV N=8	Oral N=2	IV N=8	Oral N=2	IV-Oral N=8	Oral-IV N=2	IV-Oral N=8	Oral-IV N=2	IV-Oral N=10	Oral-IV N=10	IV-Oral N=18	Oral-IV N=12
Randomized	8	2	8	2	8	2	8	2	8	2	10	10	18	12
Treated in Period 1	8	2	8	2	8	2	8	2	8	2	10	10	18	12
Completed up to Day 6 in Period 1	8	2	8	2	8	2	8	2	8	2	10	10	18	12
Treated in Period 2	0	0	0	0	0	0	8	2	8	2	10	10	18	12
Completed up to Day 6 in Period 2	0	0	0	0	0	0	8	2	8	2	10	10	18	12
Completed whole study	8	2	8	2	8	2	8	2	8	2	10	10	18	12
Premature termination	0	0	0	0	0	0	0	0	0	0	0	0	2	2
- Adverse event	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- Private reason	0	0	0	0	0	0	0	0	0	0	0	0	2	2

* Subject (b) (6) was treated with both, oral active and part of IV active in Period 2 (planned treatment: 286 mg IV active)
 N: number of subjects in specified group, n: number of subjects with data available, %: percentage based on number of randomized subjects
 S: single ascending dose (SAD)/ single ascending dose crossover (SAD-CO) part, P: pilot crossover (P-CO) part, F: final crossover (F-CO) part
 IV: intravenous infusion of 19.5 to 390 mg pro-netupitant and administration of placebo capsule
 Oral: oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination (FDC) administration and placebo infusion
 Source: Table 14.1.1.1.1

	234 mg N=20		S-260 mg N=10		P-260 mg N=20		S+P-260 mg N=30		286 mg* N=20		325 mg N=10		390 mg N=10	
	IV-Oral N=10	Oral-IV N=10	IV-Oral N=8	Oral-IV N=2	IV-Oral N=10	Oral-IV N=10	IV-Oral N=18	Oral-IV N=12	IV-Oral N=10	Oral-IV N=10	IV-Oral N=8	Oral-IV N=2	IV-Oral N=8	Oral-IV N=2
Randomized	10	10	8	2	10	10	18	12	10	10	8	2	8	2
Treated in Period 1	10	10	8	2	10	10	18	12	10	10	8	2	7	1
Completed up to Day 6 in Period 1	10	10	8	2	10	10	18	12	10	10	8	2	7	1
Treated in Period 2	10	10	8	2	10	10	18	12	10	10	8	2	7	1
Completed up to Day 6 in Period 2	10	10	8	2	10	10	18	12	10	10	8	2	7	1
Completed whole study	10	10	8	2	10	10	18	12	10	10	8	2	7	1
Premature termination	0	0	0	0	0	0	0	0	0	0	0	0	1	1
- Adverse event	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- Private reason	0	0	0	0	0	0	0	0	0	0	0	0	1	1

* Subject (b) (6) was treated with both, oral active and part of IV active in Period 2 (planned treatment: 286 mg IV active)
 N: number of subjects in specified group, n: number of subjects with data available, %: percentage based on number of randomized subjects
 S: single ascending dose (SAD)/ single ascending dose crossover (SAD-CO) part, P: pilot crossover (P-CO) part, F: final crossover (F-CO) part
 IV: intravenous infusion of 19.5 to 390 mg pro-netupitant and administration of placebo capsule
 Oral: oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination (FDC) administration and placebo infusion
 Source: Table 14.1.1.1.1



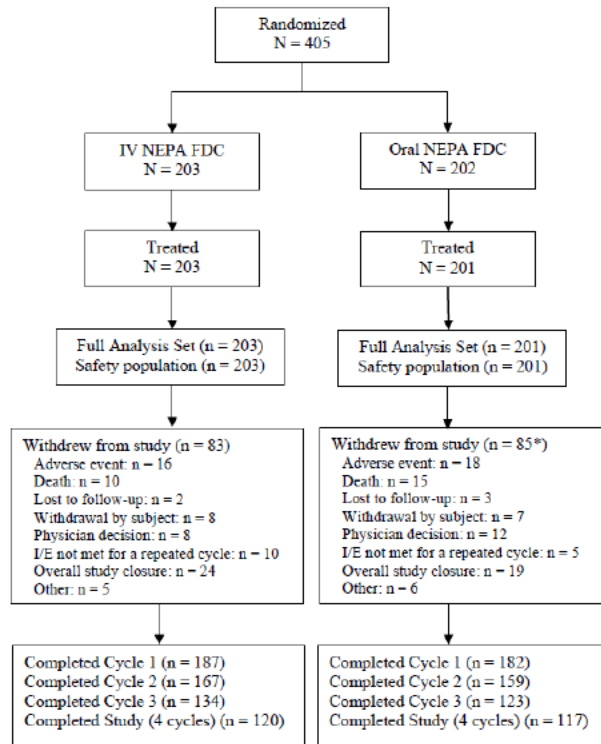
N: number of subjects, SAD: single ascending dose; SAD-CO: single ascending dose crossover, P-CO: pilot crossover, F-CO, final crossover
 IV: intravenous infusion of 19.5 to 390 mg pro-netupitant and administration of placebo capsule
 Oral: oral netupitant 300 mg/palonosetron 0.5 mg fixed dose combination (FDC) administration and placebo infusion
 Source: Table 14.1.1.1.1, Table 14.1.1.1.2, Listing 16.2.1.1, Listing 16.2.1.2

Source: *The Applicant's Clinical Study Report PNET-12-23, Table 10.2-1, Pages 87-89/3498*

NEPA-15-18

A total of 405 patients with HEC (highly emetogenic chemotherapy) were randomized, and 404 (99.8%) received study treatment. A total of 237 (58.5%) patients completed the four study cycles (120 [59.1%] patients in the IV NEPA FDC group, and 117 [57.9%] patients in the Oral NEPA FDC group). The number of patients randomized into each treatment group, patient disposition, and the reasons for early discontinuation from the study are summarized in Table below.

Table 2: Patient Disposition (Population: All Randomized Patients)



Sources: Summary Tables 14.1.1.1 and 14.1.1.2
 Abbreviations: I/E = inclusion/exclusion; IV NEPA FDC = intravenous fosnetupitant/palonosetron fixed-dose combination; N = number of patients in a given group; n = number of patients in a given subgroup; Oral NEPA FDC = oral netupitant/palonosetron fixed-dose combination.
 *Includes patient withdrawn (patient ID (b) (6)) before receiving study drug.

Source: The Applicant's Clinical Study Report NEPA-15-18, Figure 1, Page 77/2086

4.2.2.2 Statistical Analyses

4.2.2.2.1 Primary Analysis

PNET-12-23

In Study PNET-12-23, 160 healthy subjects were enrolled. A total of 148 subjects received one dose of the IV fosnetupitant treatment (ranging from 19.5 mg to 390 mg) and 134 subjects received one dose of the oral 300 mg netupitant/0.5 mg palonosetron treatment. The Applicant concluded that no safety-related changes from baseline were observed in QTcF and no marked difference was observed for either treatment group, including the oral formulation.

Table 3: Change from Baseline (ms) for QTcF by dose, overall IV and overall PO - Study PNET-12-23

QTcF	19.5 mg N=8	32.5 mg N=8	65 mg N=8	130 mg N=10	195 mg N=28	234 mg N=19	260 mg N=30	286 mg N=18
Day 1	2.3 (14.10) [-9.54, 14.04]	0.1 (7.41) [-6.07, 6.32]	0.5 (7.56) [-5.82, 6.82]	-7.0 (14.48) [-17.36, 3.36]	-4.4 (9.11) [-7.96, -0.90]	-6.7 (9.37) [-11.25, -2.22]	-5.8 (8.78) [-9.08, -2.52]	-5.3 (7.91) [-9.21, -1.34]
Day 3	-1.3 (12.15) [-11.41, 8.91]	-2.6 (9.43) [-10.50, 5.25]	3.9 (7.02) [-1.99, 9.74]	-10.7 (15.71) [-21.94, 0.54]	-3.4 (10.85) [-7.56, 0.85]	-2.2 (9.68) [-6.87, 2.45]	0.1 (11.87) [-4.33, 4.53]	0.2 (7.78) [-3.70, 4.03]
Day 6	2.6 (13.88) [-8.98, 14.23]	-1.3 (10.58) [-10.09, 7.59]	6.0 (13.17) [-5.01, 17.01]	5.4 (17.20) [-6.90, 17.70]	1.1 (10.99) [-3.15, 5.37]	1.4 (10.88) [-3.83, 6.67]	-2.3 (12.80) [-7.08, 2.48]	1.7 (9.44) [-2.97, 6.41]

QTcF	325 mg N=10	390 mg N=9	All IV N=148	PO N=134
Day 1	-11.2 (6.94) [-16.17, -6.23]	-7.0 (8.43) [-13.48, -0.52]	-5.0 (9.62) [-6.58, -3.46]	-3.7 (11.98) [-5.73, -1.64]
Day 3	-0.8 (10.89) [-8.59, 6.99]	-1.0 (11.24) [-9.64, 7.64]	-1.7 (10.94) [-3.49, 0.06]	-2.6 (10.10) [-4.35, -0.90]
Day 6	0.5 (11.75) [-7.91, 8.91]	-0.7 (13.92) [-11.37, 10.03]	0.9 (12.03) [-1.06, 2.85]	-0.5 (11.73) [-2.50, 1.50]

Source: FDA's Memo for IND 115191 (DARRTS 03/01/2017), Pages 7/20

NEPA-15-18

NEPA-15-18 was a safety study intended to provide repeat-cycle safety data for up to 4 cycles in at least 100 HEC patients exposed to the IV NEPA FDC. There are no meaningful differences between the IV NEPA and oral NEPA in terms of change from baseline in QT measures, from cycle 1 to 4. Table 4 presented the sponsor's change from baseline for QTcF by treatment and cycle.

Table 4: Sponsor's Change from Baseline (ms) for QTcF by treatment group Study NETU-15-18 by Cycle

QTcF	Cycle 1		Cycle 2		Cycle 3		Cycle 4	
	IV NEPA N=203	PO NEPA N=201	IV NEPA N=179	PO NEPA N=177	IV NEPA N=163	PO NEPA N=150	IV NEPA N=122	PO NEPA N=117
Day 1 (end of Inf)	0.1 (13.3) [-1.7, 2.0]	0.8 (12.7) [-0.9, 2.6]	-1.1 (17.2) [-3.6, 1.5]	1.8 (16.3) [-0.6, 4.2]	0.8 (16.4) [-1.8, 3.3]	1.8 (16.0) [-0.8, 4.4]	-0.8 (18.0) [-4.1, 2.4]	1.1 (15.9) [-1.8, 4.0]
5 hours	8.2 (15.3) [6.1, 10.3]	8.2 (14.8) [6.1, 10.3]	5.5(19.0) [2.6, 8.3]	6.7 (16.7) [4.2, 9.2]	5.3 (16.9) [2.7, 8.0]	6.7 (16.6) [4.0, 9.4]	3.9 (18.2) [0.7, 7.2]	7.3 (18.7) [3.9, 10.8]
24 hours	4.9 (18.8) [2.3, 7.5]	6.7 (17.1) [4.3, 9.1]	2.8 (20.7) [-0.3, 5.8]	6.3 (16.8) [3.7, 8.8]	4.4 (19.8) [1.3, 7.4]	6.8 (17.3) [4.0, 9.6]	4.2 (19.9) [0.6, 7.8]	6.5 (20.4) [2.7, 10.2]
120 hours	-3.0(19.5) [-5.7,-0.3]	-5.2(17.7) [-7.7,-2.8]	-5.8(18.9) [-8.6,-3.0]	-5.2(18.8) [-8.1,-2.4]	-4.2 (17.9) [-7.0,-1.4]	-3.9 (17.6) [-6.8, -1.0]	-4.0 (17.3) [-7.1, 0.9]	-3.3 (20.0) [-7.0, 0.4]

N= number of patients treated in the cycle
Data expressed as mean (SD) and [95% CI]

Source: FDA's Memo for IND 115191 (DARRTS 03/01/2017), Pages 8/20

4.2.2.2 Assay Sensitivity

Not applicable.

4.2.2.3 Categorical Analysis

PNET-12-23

No healthy subject in study PNET-12-23 had QTcB or QTcF change from baseline > 60 ms and no QTcF interval > 500 ms was observed.

NEPA-15-18

There were no cases of new QT interval corrected by Fridericia (QTcF) values >500 ms throughout the study. Only 1 (0.5%) patient in each group had a QTcF change >60 ms throughout the study.

Reviewer's comment: One patient had a Δ QTcF interval of >60 ms at 24 h after treatment with IV NEPA FDC, and 1 patient at the end of infusion, 5 h, 24 h, and 120 h after treatment with Oral NEPA FDC.

4.2.2.3 Safety Analysis

No cases of syncope, seizure, ventricular tachycardia or fibrillation were identified in healthy volunteer or the NEPA-15-19 studies.

NEPA-15-18

TEAEs leading to death were reported for 10 (4.9%) patients in the IV NEPA FDC group and 14 (7.0%) patients in the Oral NEPA FDC group. TEAE leading to study discontinuation were reported for 16 (7.9%) patients in the IV NEPA FDC group and 20 (10.0%) patients in the Oral NEPA FDC group.

Table 5: TEAEs Leading to Death Throughout the Study (Population: Safety)

MedDRA System Organ Class MedDRA Preferred Term	IV NEPA FDC (N=203) n (%)	Oral NEPA FDC (N=201) n (%)
Any TEAE leading to death^a	10 (4.9)	14 (7.0)
Blood and lymphatic system disorders	1 (0.5)	0
Febrile neutropenia	1 (0.5)	0
Cardiac disorders	1 (0.5)	0
Cardiac failure	1 (0.5)	0
Gastrointestinal disorders	2 (1.0)	1 (0.5)
Gastric ulcer haemorrhage	1 (0.5) ^b	0
Ileus	0	1 (0.5)
Intestinal obstruction	1 (0.5)	0
General disorders and administration site conditions	1 (0.5)	6 (3.0)
Death	0	1 (0.5)
Disease progression	0	1 (0.5)
Oedema peripheral	0	1 (0.5)
Sudden death	1 (0.5)	3 (1.5)
Infections and infestations	2 (1.0)	3 (1.5)
Pneumonia	1 (0.5)	1 (0.5)
Pyopneumothorax	1 (0.5)	0
Sepsis	0	2 (1.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	2 (1.0)
Malignant neoplasm progression	0	2 (1.0)
Injury, poisoning and procedural complications	1 (0.5)	0
Accidental overdose	1 (0.5) ^c	0

Renal and urinary disorders	0	1 (0.5)
Nephropathy	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders	1 (0.5)	0
Haemoptysis	1 (0.5)	0
Vascular disorders	1 (0.5)	1 (0.5)
Haemorrhage	1 (0.5)	0
Peripheral embolism	0	1 (0.5)

Sources: Summary Tables 14.3.2.19 and 14.3.2.23

Abbreviations: IV NEPA FDC = intravenous fosnetupitant/palonosetron fixed-dose combination; MedDRA = Medical Dictionary for Regulatory Activities, v.18.0; N = number of patients in a given group, n = number of patients in a given subgroup; Oral NEPA FDC = oral netupitant/palonosetron fixed-dose combination; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

- (a) No study-drug-related TEAT leading to death was reported in this study.
- (b) Patient ID (b) (6) (IV NEPA FDC group) experienced gastric ulcer haemorrhage that was related to dexamethasone.
- (c) Patient ID (b) (6) (IV NEPA FDC group) died of an accidental overdose of diazepam.

Source: Applicant's Clinical Study Report, Table 20

Reviewer's comment: Combined PTs "sudden death" and "death" occurred at low numbers in both arms; however, there were numerically more events in the oral NEPA arm (Akynzeo is an approved product with no QTc prolongation signal in TQT study).

No TEAEs of seizure were recorded. In the SOC central nervous system (CNS) disorders two TEAEs of syncope were identified; one (PT ID N. (b) (6)) was a SAE not related to study drug (Oral NEPA FDC) or dexamethasone. The narrative and CRF are included in the NEPA-15-18 CSR. The other TEAE of syncope was a nonserious event occurring concomitantly with hyponatremia and asthenia in a patient treated with IV NEPA (PT ID N. (b) (6)). Syncope as well as the other events were assessed as not related to the study drug by the Investigator. This patient had also an SAE of atrial fibrillation and discontinued the study due to renal failure. Details for the TEAE syncope are provided in the narrative in Section 7.4 of this SCS, while narrative of SAE and discontinuation due to AE as well as CRF can be found in the CSR.

No TEAE of ventricular fibrillation was observed.

Within the SOC cardiac disorders, a non-serious TEAE of ventricular tachyarrhythmia was reported in one patient (PT ID N. (b) (6)) in the IV NEPA group.

- PT ID N. (b) (6) is a 78-year-old male with lung and respiratory tract cancer. On (b) (6), at Cycle 2 visit 4 (Day 6, 120 h post-dose) a diagnosis of atrial fibrillation and non-sustained ventricular tachycardia was made by the central reviewer. Both abnormalities were assessed as non-serious AEs of CTCAE Grade 2. The Investigator considered the events unlikely related to IV NEPA FDC and possibly related to dexamethasone. These AEs resolved on the same day ((b) (6)). Treatment administered for the reported events included: amiodarone (200 mg PO, qd), bisoprolol (2.5 mg PO qd), dabigatran (110 mg PO bid), dalteparin (5000 IU SC once), digoxin (0.2 mg IV once, then 0.1 mg PO qd), diazepam (5 mg PO once), potassium (2 g PO qd), and torasemide (10 mg PO qd). Concomitantly furosemide (20 mg IV once) was administered for prophylaxis of

cardiovascular events. Overall, these findings did not preclude the continuation of the chemotherapeutic course or continuation of the study drug, and patient completed 4 cycles as planned in the study protocol.

4.2.2.4 Clinical Pharmacology

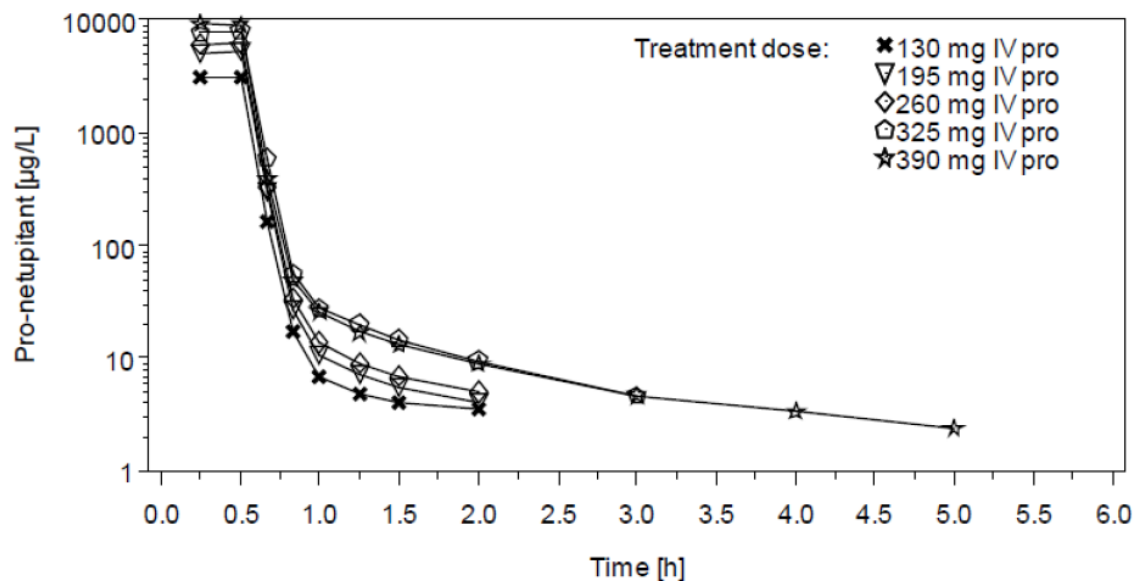
4.2.2.4.1 Pharmacokinetic Analysis

The PK results presented in this section are based on data from Study PNET-12-23 alone as there was no PK data collected in Study NEPA-15-18.

Study PNET-12-23 evaluated a range of doses from 19.5 mg to 390 mg fosnetupitant (pro-netupitant) via IV infusion and oral NEPA FDC (netupitant 300 mg/palonosetron 0.5 mg). In this study, plasma concentrations of fosnetupitant, netupitant and netupitant metabolites M1, M2, and M3 were measured. The PK profiles for all these relevant moieties (fosnetupitant, netupitant, M1, M2, and M3) are presented in Figure 1-Figure 5 below.

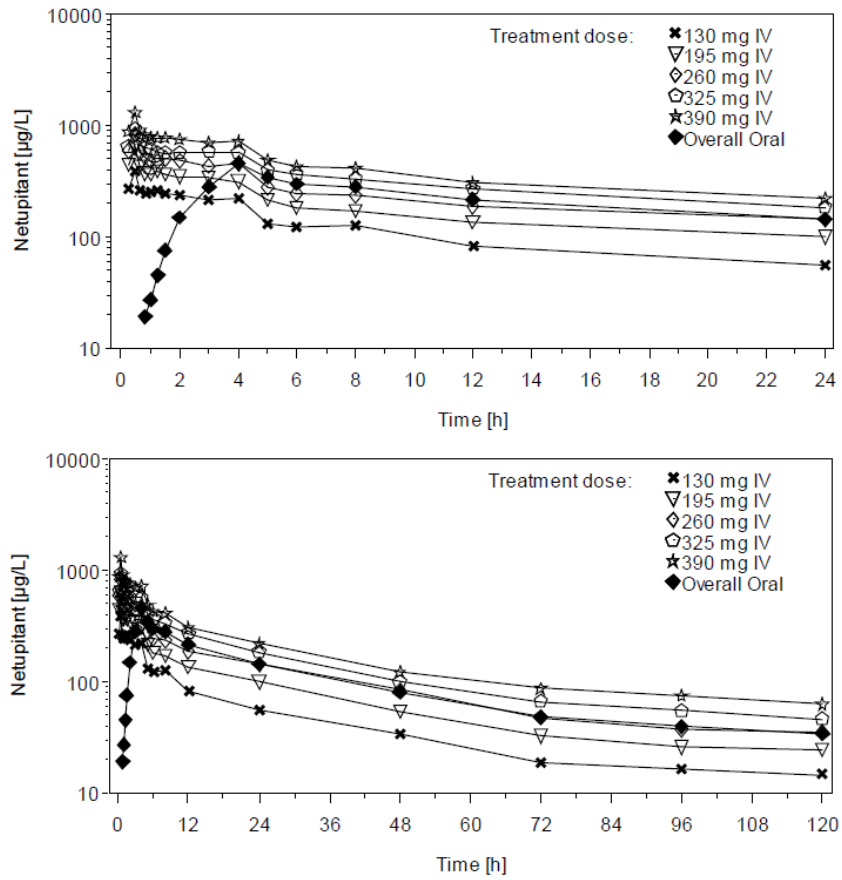
Reviewer's comment: The reviewer's analysis in Section 5.3 presents the detailed comparison of concentrations for various moieties in this study and in prior TQT study for oral NEPA FDC (previous QT-IRT review under IND 73493, dated 01/20/2010 in DARRTS).

Figure 1: Arithmetic mean concentration-time profile of fosnetupitant after infusion of 130 mg to 390 mg fosnetupitant (SAD-CO and P-CO)



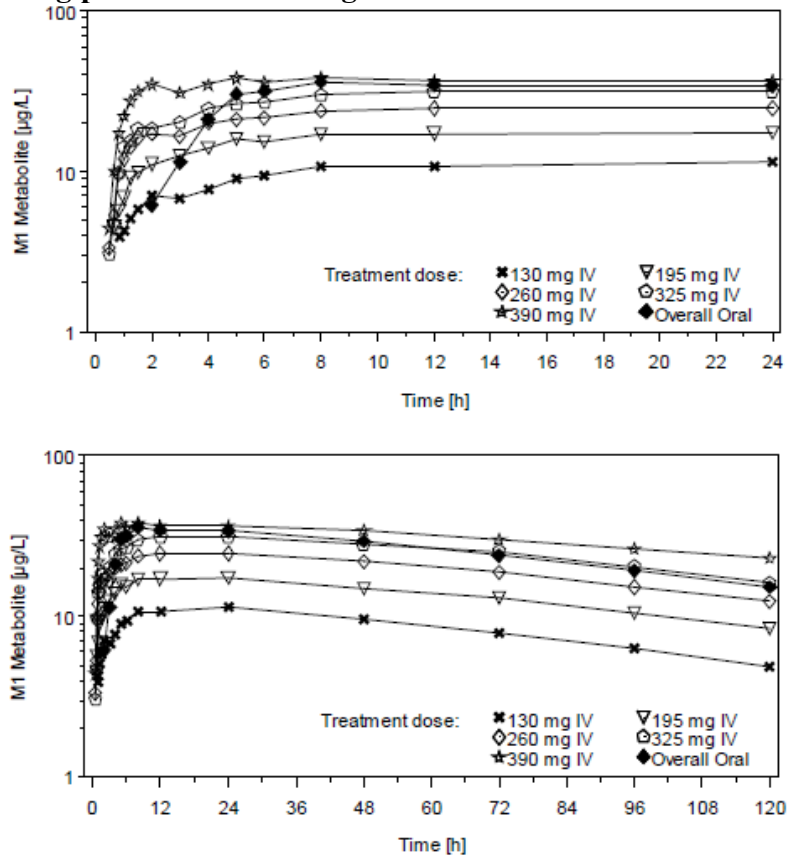
Source: Applicant's Clinical Study Report PNET-12-23, page 102

Figure 2: Arithmetic mean concentration-time profile of netupitant after infusion of 130 mg to 390 mg fosnetupitant (SAD-CO and P-CO) or after oral administration of netupitant 300 mg/palonosetron 0.5 mg



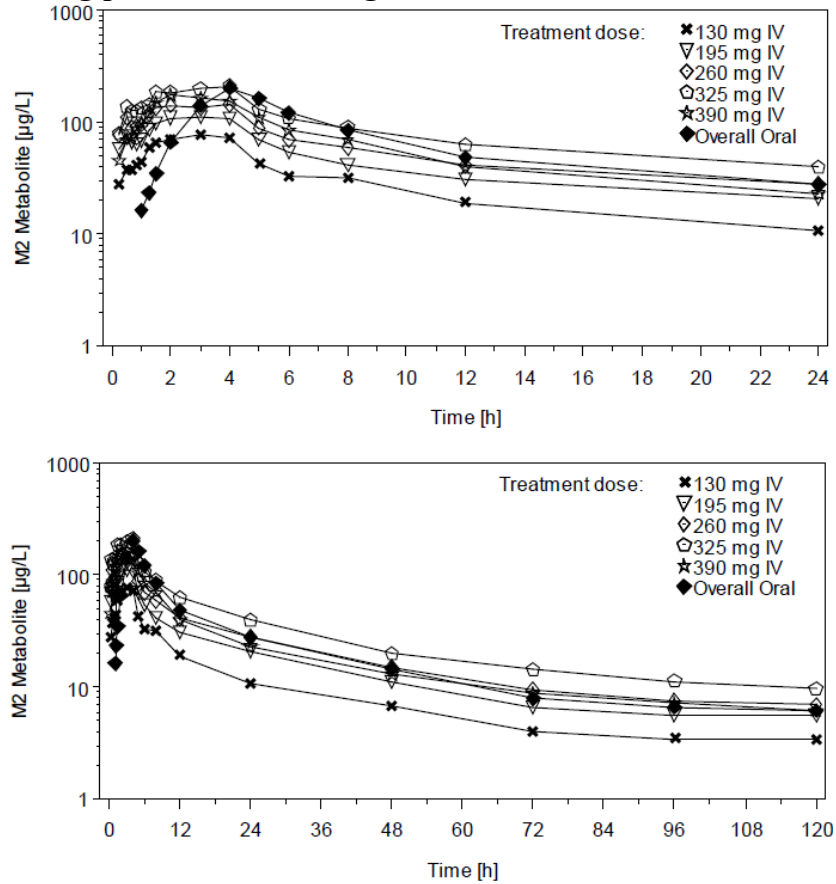
Source: Applicant's Clinical Study Report PNET-12-23, page 105

Figure 3: Arithmetic mean concentration-time profile of M1 after infusion of 130 mg to 390 mg fosnetupitant (SAD-CO and P-CO) or after oral administration of netupitant 300 mg/palonosetron 0.5 mg



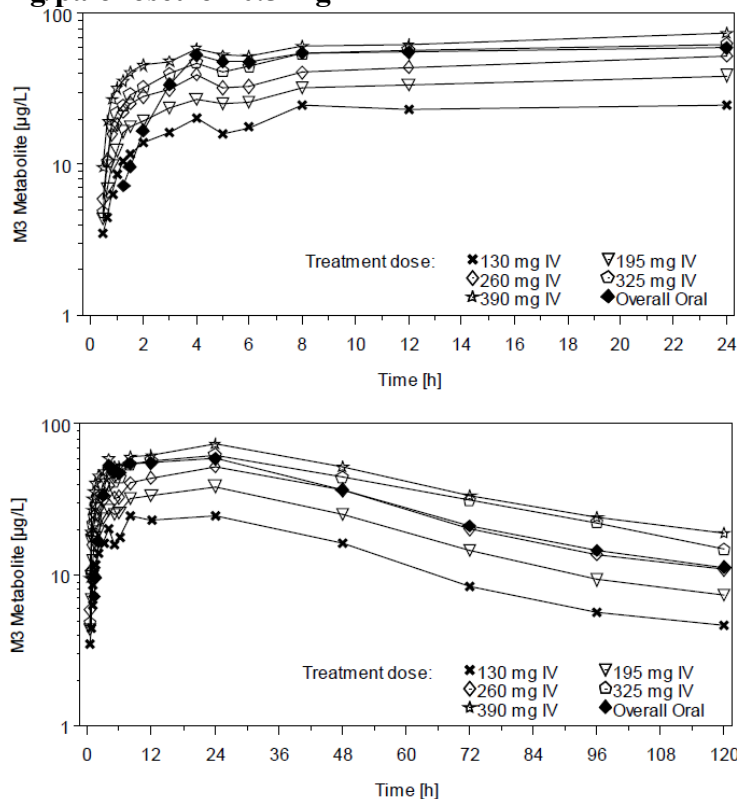
Source: Applicant's Clinical Study Report PNET-12-23, page 108

Figure 4: Arithmetic mean concentration-time profile of M2 after infusion of 130 mg to 390 mg fosnetupitant (SAD-CO and P-CO) or after oral administration of netupitant 300 mg/palonosetron 0.5 mg



Source: Applicant's Clinical Study Report PNET-12-23, page 110

Figure 5: Arithmetic mean concentration-time profile of M3 after infusion of 130 mg to 390 mg fosnetupitant (SAD-CO and P-CO) or after oral administration of netupitant 300 mg/palonosetron 0.5 mg

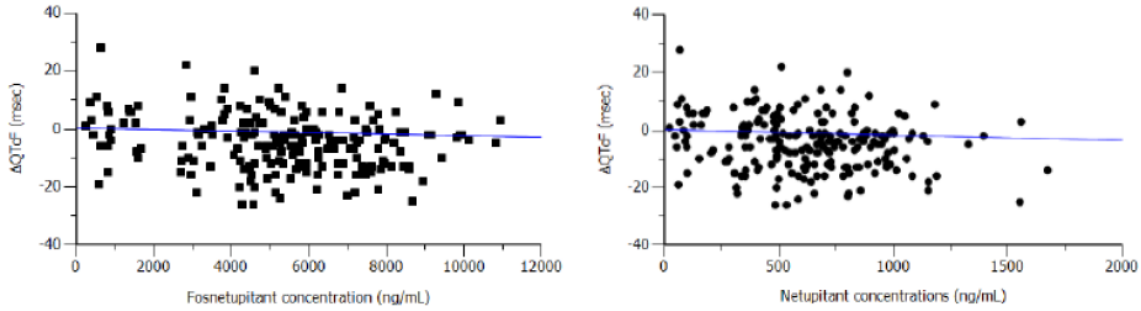


Source: Applicant's Clinical Study Report PNET-12-23, page 112

4.2.2.4.2 Exposure-Response Analysis

The applicant conducted regression for change from baseline QTcF against both fosnetupitant and netupitant concentrations for data pooled across studies PNET-12-23 and PNET-13-63. The results of the regression analysis are shown in Figure 6 and Table 6 and suggest no trend for QT prolongation with increasing fosnetupitant or netupitant concentrations. This analysis is additionally supported by the results of the thorough QT study NETU-07-20, and was reviewed previously by the IRT under IND73493.

Figure 6: Pooled PK/PD data from Studies PNET-12-23 and PNET-13-63. Change of QTcF, PR and QRS from baseline vs. fosnetupitant (left plots) and netupitant (right plots) concentrations at the end of infusion



Source: FDA’s Memo for IND 115191 (DARRTS 03/01/2017), Pages 9/20

Table 6: Linear regression analysis (wt=1/Y2) between change of ECG intervals from baseline vs. fosnetupitant or netupitant concentrations at the end of infusion. Pooled data from Studies PNET-12-23 and PNET-13-63

PK/PD	Parameter	Units	Estimate	SE	95% CI Lower	95% CI Upper
ΔQTcF vs. Fosnetupitant Conc.	Intercept	msec	0.4082703	0.4718242	-0.5222151	1.3387556
	Slope	msec/ng/mL	-0.0002617	0.0000814	-0.0004221	-0.0001013
ΔQTcF vs. Netupitant Conc.	Intercept	msec	0.2693052	0.4414433	-0.6012660	1.1398764
	Slope	msec/ng/mL	-0.0019219	0.0006130	-0.0031309	-0.0007129

Source: FDA’s Memo for IND 115191 (DARRTS 03/01/2017), Pages 9/20

Reviewer’s Analysis: A plot of ΔQTcF vs. fosnetupitant and netupitant concentrations is presented in Section 5.3 by the reviewer.

5 REVIEWERS’ ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The reviewers used the same QT/RR correction method (QTcF) that is used by the sponsor for their primary QTc analysis. There were no large mean changes in HR (>10 bpm) with any of the treatments, so the choice of this correction method is reasonable.

5.2 STATISTICAL ASSESSMENTS

In the reviewer’s analyses presented in this section, for NEPA-15-18 study, the reviewer used pre-dose value at first visit (time=0 for first dose) as the baseline for all post-dose measurements across all visits, while the sponsor had used the pre-dose value (time=0) in each visit as the baseline for this study. This can result in some differences in the categorical and central tendency values for ECG parameters in sponsor’s vs. reviewer’s analyses.

5.2.1 QTc Analysis

5.2.1.1 The Central Tendency Analysis for IV NEPA FDC and Oral NEPA FDC

The primary endpoint is the change from baseline of QTcF. The descriptive statistics are listed in Table 7 - Table 8. Tables present the summary statistics (mean and standard deviation) and the 90% confidence interval for the mean change from baseline (Δ QTcF). For Study PNET-12-23, the largest upper bounds of the 2-sided 90% CI for IV fosnetupitant (doses of 19.5 mg, 65 mg, 130 mg) exceeded 10 ms (see Table 7). This may be the result of small sample size for these dose cohorts. For Study NEPA-15-18, the largest upper bounds of the 2-sided 90% CI for IV NEPA FDC at Cycle 1 (Time=5 h) reached 10 ms and for Oral NEPA FDC at Cycle 4 (Time=5 h) exceeded 10 ms (see Table 8).

Table 7: Descriptive Statistics Results of Δ QTcF for IV fosnetupitant doses (260 mg and higher) and oral 300 mg netupitant/0.5 mg palonosetron by Time (PNET-12-23)

Treatment	Time (h)	N	Mean	Std Dev	90% CI for Mean
260 mg	0.5	30	-5.9	8.8	(-8.6, -3.2)
	48	30	0.0	11.5	(-3.6, 3.6)
	120	30	-2.4	12.9	(-6.4, 1.6)
286 mg	0.5	18	-8.9	10.9	(-13.3, -4.4)
	48	18	-3.4	10.5	(-7.7, 0.8)
	120	18	-1.9	9.2	(-5.7, 1.9)
325 mg	0.5	10	-12.0	6.1	(-15.5, -8.5)
	48	10	-1.6	11.3	(-8.2, 5.0)
	120	10	-0.3	11.7	(-7.1, 6.5)
390 mg	0.5	9	-8.4	7.9	(-13.3, -3.6)
	48	9	-2.4	8.7	(-7.8, 3.0)
	120	9	-2.1	11.4	(-9.2, 5.0)
Oral NEPA FDC	0.5	134	-2.6	13.1	(-4.5, -0.7)
	48	133	-1.5	10.1	(-3.0, -0.1)
	120	133	0.7	11.6	(-0.9, 2.4)

Table 8: Descriptive Statistics Results of Δ QTcF for IV NEPA FDC and Oral NEPA FDC by Cycle and Time (NEPA-15-18)

Treatment	Cycle	Time (h)	N	Mean	Std Dev	90% CI for Mean
IV NEPA FDC	1	0.5	201	0.1	13.3	(-1.4, 1.7)

Treatment	Cycle	Time (h)	N	Mean	Std Dev	90% CI for Mean
		5	202	8.2	15.3	(6.4, 10.0)
		24	205	4.9	18.7	(2.8, 7.1)
		120	205	-2.8	19.3	(-5.1, -0.6)
	2	0.5	176	-1.1	17.2	(-3.2, 1.1)
		5	175	5.5	19.0	(3.1, 7.8)
		24	177	2.8	20.7	(0.2, 5.3)
		120	179	-5.9	18.9	(-8.2, -3.5)
	3	0.5	162	0.8	16.4	(-1.3, 2.9)
		5	163	5.3	16.9	(3.2, 7.5)
		24	162	4.4	19.8	(1.8, 6.9)
		120	161	-3.6	18.6	(-6.0, -1.2)
	4	0.5	122	-0.8	18.0	(-3.5, 1.9)
		5	122	3.9	18.2	(1.2, 6.7)
		24	122	4.2	19.9	(1.2, 7.2)
		120	120	-4.0	17.3	(-6.6, -1.4)
Oral NEPA FDC	1	0.5	199	0.8	12.7	(-0.6, 2.3)
		5	199	8.2	14.8	(6.5, 9.9)
		24	199	6.7	17.1	(4.7, 8.7)
		120	198	-5.2	17.7	(-7.3, -3.2)
	2	0.5	174	1.8	16.3	(-0.3, 3.8)
		5	173	6.7	16.7	(4.6, 8.8)
		24	171	6.4	16.8	(4.3, 8.5)
		120	171	-5.2	18.8	(-7.6, -2.9)
	3	0.5	149	1.8	16.0	(-0.4, 4.0)
		5	149	6.7	16.6	(4.5, 9.0)
		24	149	6.8	17.3	(4.4, 9.1)
		120	145	-3.9	17.6	(-6.3, -1.5)
	4	0.5	115	1.1	15.9	(-1.3, 3.6)
		5	116	7.3	18.7	(4.5, 10.2)
		24	116	6.5	20.4	(3.3, 9.6)
		120	116	-3.3	20.0	(-6.4, -0.2)

Note: The reviewer used pre-dose value at first visit (time=0 for first dose) as the baseline for all post-dose measurements across all visits for this table, while the sponsor had used the pre-dose value (time=0) in each visit as the baseline for this analysis.

5.2.1.1 Assay Sensitivity Analysis

Not applicable.

5.2.1.2 Categorical Analysis

Table 9 and Table 10 list the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 . No subject's QTcF is above 500 ms for studies NEPA-15-18 and PNET-12-23.

Table 9: Categorical Analysis for QTcF (PNET-12-23)

Treatment Group	Total N	Value $\leq$ 450 ms	450 ms $<$ Value $\leq$ 480 ms	480 ms $<$ Value $\leq$ 500 ms	Value $>$ 500 ms
19.5 mg	8	8 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
32.5 mg	8	8 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
65 mg	8	8 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
130 mg	10	9 (90.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)
195 mg	28	27 (96.4%)	1 (3.6%)	0 (0.0%)	0 (0.0%)
234 mg	19	19 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
260 mg	30	30 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
286 mg	18	18 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
325 mg	10	10 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
390 mg	9	8 (88.9%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
Oral NEPA FDC	133	129 (97.0%)	4 (3.0%)	0 (0.0%)	0 (0.0%)

Table 10: Categorical Analysis for QTcF (NEPA-15-18)

Treatment Group	Total N	Value $\leq$ 450 ms	450 ms $<$ Value $\leq$ 480 ms	480 ms $<$ Value $\leq$ 500 ms	Value $>$ 500
IV NEPA FDC	203	163 (80.3%)	35 (17.2%)	5 (2.5%)	0 (0.0%)
Oral NEPA FDC	200	149 (74.5%)	50 (25.0%)	1 (0.5%)	0 (0.0%)

Note: The reviewer used pre-dose value at first visit (time=0 for first dose) as the baseline for all post-dose measurements across all visits for this table, while the sponsor had used the pre-dose value (time=0) in each visit as the baseline for this analysis.

Table 11 and Table 12 list the categorical analysis results for Δ QTcF. One subject's change from baseline is above 90 ms in study NEPA-15-18.

Table 11: Categorical Analysis of Δ QTcF (PNET-12-23)

Treatment Group	Total N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	60 ms<Value $\leq$ 90 ms	Value>90 ms
19.5 mg	8	8 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
32.5 mg	8	8 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
65 mg	8	7 (87.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
130 mg	10	8 (80.0%)	2 (20.0%)	0 (0.0%)	0 (0.0%)
195 mg	28	28 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
234 mg	19	18 (94.7%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
260 mg	30	30 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
286 mg	18	18 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
325 mg	10	10 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
390 mg	9	9 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oral NEPA FDC	133	131 (98.5%)	2 (1.5%)	0 (0.0%)	0 (0.0%)

Table 12: Categorical Analysis of Δ QTcF (NEPA-15-18)

Treatment Group	Total N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	60 ms<Value $\leq$ 90 ms	Value>90 ms
IV NEPA FDC	203	144 (70.9%)	57 (28.1%)	2 (1.0%)	0 (0.0%)
Oral NEPA FDC	200	147 (73.5%)	52 (26.0%)	0 (0.0%)	1 (0.5%)

Note: The reviewer used pre-dose value at first visit (time=0 for first dose) as the baseline for all post-dose measurements across all visits for this table, while the sponsor had used the pre-dose value (time=0) in each visit as the baseline for this analysis.

5.2.2 HR Analysis

The change from baseline in HR was evaluated using similar methods as described for QTc in Section 5.2.1. The descriptive statistics are listed in Table 13 - Table 14. Table 15 and Table 16 present the categorical analysis of HR for studies PNET-12-23 and NEPA-15-18, respectively. There was no subject who experienced HR interval greater than 100 bpm in study PNET-12-23. Ninety two subjects experienced HR interval greater than 100 bpm who received IV NEPA FDC and Oral NEPA FDC in patient population (NEPA-15-18).

Table 13: Descriptive Statistics Results of Δ HR for IV fosnetupitant doses (260 mg and higher) and oral 300 mg netupitant/0.5 mg palonosetron by Time (PNET-12-23)

Treatment	Time (h)	N	Mean	Std Dev	90% CI for Mean
260 mg	0.5	30	-7.3	10.2	(-10.5, -4.1)
	48	30	-1.8	9.9	(-4.9, 1.3)
	120	30	-3.5	11.6	(-7.1, 0.1)
286 mg	0.5	18	-7.7	8.2	(-11.1, -4.3)
	48	18	-1.7	8.0	(-4.9, 1.6)
	120	18	0.5	6.3	(-2.1, 3.1)
325 mg	0.5	10	-5.5	5.6	(-8.8, -2.2)
	48	10	1.6	7.8	(-2.9, 6.1)
	120	10	-3.2	5.4	(-6.3, -0.1)
390 mg	0.5	9	-8.4	5.3	(-11.7, -5.1)
	48	9	-3.2	9.2	(-8.9, 2.5)
	120	9	-5.3	10.9	(-12.1, 1.4)
Oral NEPA FDC	0.5	134	-5.3	8.0	(-6.4, -4.1)
	48	133	-1.9	8.3	(-3.1, -0.7)
	120	133	-3.9	8.2	(-5.1, -2.7)

Table 14: Descriptive Statistics Results of Δ HR for IV NEPA FDC and Oral NEPA FDC by Cycle and Time (NEPA-15-18)

Treatment	Cycle	Time (h)	N	Mean	Std Dev	90% CI for Mean
IV NEPA FDC	1	0.5	201	-2.7	7.9	(-3.6, -1.8)
		5	203	4.3	9.9	(3.2, 5.5)
		24	205	-0.4	10.8	(-1.6, 0.8)
		120	205	1.3	13.7	(-0.3, 2.8)
	2	0.5	176	-1.1	11.1	(-2.5, 0.2)
		5	176	5.3	13.5	(3.6, 6.9)
		24	177	1.6	13.8	(-0.2, 3.3)
		120	179	3.1	14.6	(1.3, 4.9)
	3	0.5	162	-0.4	10.5	(-1.8, 1.0)
		5	163	5.8	13.2	(4.1, 7.5)
		24	162	3.5	13.2	(1.8, 5.2)
		120	161	2.6	13.6	(0.8, 4.3)

Treatment	Cycle	Time (h)	N	Mean	Std Dev	90% CI for Mean
	4	0.5	122	1.0	12.1	(-0.8, 2.9)
		5	122	5.9	13.1	(4.0, 7.9)
		24	122	3.6	13.7	(1.6, 5.7)
		120	120	4.2	14.4	(2.1, 6.4)
Oral NEPA FDC	1	0.5	199	-2.5	7.3	(-3.3, -1.6)
		5	199	3.1	9.7	(2.0, 4.2)
		24	199	-1.1	11.0	(-2.4, 0.2)
		120	198	-0.4	12.6	(-1.9, 1.1)
	2	0.5	174	-3.2	12.2	(-4.8, -1.7)
		5	173	3.0	13.2	(1.4, 4.7)
		24	171	0.0	12.8	(-1.6, 1.6)
		120	171	0.5	14.7	(-1.3, 2.4)
	3	0.5	149	-2.7	11.6	(-4.3, -1.2)
		5	149	3.6	13.1	(1.8, 5.3)
		24	149	1.6	13.4	(-0.2, 3.4)
		120	145	0.5	13.7	(-1.4, 2.3)
	4	0.5	115	-2.4	11.6	(-4.2, -0.6)
		5	116	2.6	12.3	(0.7, 4.4)
		24	116	1.8	13.6	(-0.3, 3.9)

Table 15: Categorical Analysis for HR (PNET-12-23)

Treatment Group	Total N	HR ≤ 100 bpm	HR >100 bpm
19.5 mg	8	8 (100%)	0 (0.0%)
32.5 mg	8	8 (100%)	0 (0.0%)
65 mg	8	8 (100%)	0 (0.0%)
130 mg	10	10 (100%)	0 (0.0%)
195 mg	28	28 (100%)	0 (0.0%)
234 mg	19	19 (100%)	0 (0.0%)
260 mg	30	30 (100%)	0 (0.0%)
286 mg	18	18 (100%)	0 (0.0%)
325 mg	10	10 (100%)	0 (0.0%)
390 mg	9	9 (100%)	0 (0.0%)
Oral NEPA FDC	133	133 (100%)	0 (0.0%)

Table 16: Categorical Analysis for HR (NEPA-15-18)

Treatment Group	Total N	HR ≤ 100 bpm	HR >100 bpm
IV NEPA FDC	203	156 (76.8%)	47 (23.2%)
Oral NEPA FDC	200	155 (77.5%)	45 (22.5%)

5.2.3 PR Analysis

The change from baseline in PR was evaluated using similar methods as described for QTc Section 5.2.1. The descriptive statistics are listed in Table 17 - Table 18. Table 19 and Table 20 present the categorical analysis of PR for studies PNET-12-23 and NEPA-15-18, respectively. Fourteen subjects experienced PR interval greater than 200 ms in fosnetupitant doses from 195 mg up to 390 mg, and oral 300 mg netupitant/0.5 mg palonosetron (PNET-12-23). Sixty nine subjects experienced PR interval greater than 200 ms in the IV NEPA FDC and Oral NEPA FDC group (NEPA-15-18).

Table 17: Descriptive Statistics Results for ΔPR for IV fosnetupitant doses (260 mg and higher) and oral 300 mg netupitant/0.5 mg palonosetron by Time (PNET-12-23)

Treatment	Time (h)	N	Mean	Std Dev	90% CI for Mean
260 mg	0.5	30	7.1	8.1	(4.6, 9.6)
	48	30	2.9	13.2	(-1.2, 7.0)
	120	30	1.5	9.3	(-1.4, 4.4)
286 mg	0.5	18	7.1	11.6	(2.4, 11.9)
	48	18	2.3	10.6	(-2.0, 6.7)
	120	18	-0.1	9.9	(-4.2, 4.0)
325 mg	0.5	10	7.8	7.6	(3.4, 12.2)
	48	10	1.0	9.2	(-4.4, 6.4)
	120	10	-1.2	9.4	(-6.7, 4.3)
390 mg	0.5	9	9.8	9.6	(3.9, 15.7)
	48	9	5.1	11.7	(-2.1, 12.4)
	120	9	7.1	10.5	(0.6, 13.6)
Oral NEPA FDC	0.5	134	5.2	10.6	(3.7, 6.7)
	48	133	0.5	9.9	(-0.9, 1.9)
	120	133	0.4	9.2	(-0.9, 1.7)

Table 18: Descriptive Statistics Results of Δ PR for IV NEPA FDC and Oral NEPA FDC by Cycle and Time (NEPA-15-18)

Treatment	Cycle	Time (h)	N	Mean	Std Dev	90% CI for Mean
IV NEPA FDC	1	0.5	201	2.6	12.2	(1.2, 4.0)
		5	203	2.6	12.8	(1.1, 4.1)
		24	204	0.8	14.2	(-0.9, 2.4)
		120	203	-10.9	16.6	(-12.8, -9.0)
	2	0.5	174	2.1	17.8	(-0.1, 4.3)
		5	173	1.8	17.1	(-0.3, 4.0)
		24	175	0.5	17.5	(-1.7, 2.7)
		120	174	-11.8	17.3	(-14.0, -9.6)
	3	0.5	161	3.3	16.3	(1.2, 5.4)
		5	161	2.6	16.3	(0.5, 4.7)
		24	161	-0.4	17.1	(-2.7, 1.8)
		120	160	-9.8	17.9	(-12.1, -7.4)
	4	0.5	121	3.1	16.3	(0.6, 5.5)
		5	121	0.9	18.0	(-1.8, 3.6)
		24	122	0.7	19.2	(-2.2, 3.5)
		120	120	-12.2	18.0	(-14.9, -9.5)
Oral NEPA FDC	1	0.5	199	2.9	12.8	(1.4, 4.4)
		5	199	3.5	13.8	(1.9, 5.1)
		24	199	1.3	14.4	(-0.4, 3.0)
		120	198	-10.1	14.1	(-11.8, -8.5)
	2	0.5	174	3.8	13.1	(2.1, 5.4)
		5	173	3.8	14.9	(1.9, 5.7)
		24	171	0.6	14.9	(-1.3, 2.5)
		120	171	-12.1	15.6	(-14.0, -10.1)
	3	0.5	149	4.0	17.3	(1.6, 6.3)
		5	149	3.5	12.8	(1.8, 5.3)
		24	149	-0.7	14.5	(-2.6, 1.3)
		120	145	-10.3	13.3	(-12.1, -8.4)
	4	0.5	115	2.9	15.2	(0.5, 5.2)
		5	116	4.1	16.2	(1.6, 6.6)
		24	116	0.5	15.8	(-1.9, 2.9)
		120	116	-9.5	14.8	(-11.8, -7.2)

Table 19: Categorical Analysis for PR (PNET-12-23)

Treatment Group	Total N	PR ≤ 200 ms	PR >200 ms
19.5 mg	8	8 (100%)	0 (0.0%)
32.5 mg	8	8 (100%)	0 (0.0%)
65 mg	8	8 (100%)	0 (0.0%)
130 mg	10	10 (100%)	0 (0.0%)
195 mg	28	27 (96.4%)	1 (3.6%)
234 mg	19	18 (94.7%)	1 (5.3%)
260 mg	30	29 (96.7%)	1 (3.3%)
286 mg	18	17 (94.4%)	1 (5.6%)
325 mg	10	8 (80.0%)	2 (20.0%)
390 mg	9	8 (88.9%)	1 (11.1%)
Oral NEPA FDC	133	126 (94.7%)	7 (5.3%)

Table 20: Categorical Analysis for PR (NEPA-15-18)

Treatment Group	Total N	PR ≤ 200 ms	PR >200 ms
IV NEPA FDC	203	170 (83.7%)	33 (16.3%)
Oral NEPA FDC	200	164 (82.0%)	36 (18.0%)

5.2.4 QRS Analysis

The change from baseline in QRS was evaluated using similar methods as described for QTc Section 5.2.1. The descriptive statistics are listed in Table 21 -Table 22. Table 23 and Table 24 present the categorical analysis of QRS for studies PNET-12-23 and NEPA-15-18, respectively. Twenty six subjects experienced QRS interval greater than 110 ms in fosnetupitant doses from 19.5 mg up to 390 mg, and oral 300 mg netupitant/0.5 mg palonosetron (PNET-12-23). Thirty-five subjects experienced QRS interval greater than 110 ms in IV NEPA FDC and Oral NEPA FDC group (NEPA-15-18).

Table 21: Descriptive Statistics Results of ΔQRS for IV fosnetupitant doses (260 mg and higher) and oral 300 mg netupitant/0.5 mg palonosetron by Time (PNET-12-23)

Treatment	Time (h)	N	Mean	Std Dev	90% CI for Mean
260 mg	0.5	30	0.2	6.9	(-1.9, 2.3)
	48	30	0.3	6.8	(-1.9, 2.4)
	120	30	-0.9	6.9	(-3.1, 1.2)
286 mg	0.5	18	-1.7	6.6	(-4.4, 1.0)

Treatment	Time (h)	N	Mean	Std Dev	90% CI for Mean
	48	18	-2.7	5.7	(-5.0, -0.3)
	120	18	-3.0	6.4	(-5.6, -0.4)
325 mg	0.5	10	-3.4	7.8	(-7.9, 1.1)
	48	10	0.0	9.0	(-5.2, 5.2)
	120	10	-3.0	9.5	(-8.5, 2.5)
390 mg	0.5	9	-4.0	13.2	(-12.2, 4.2)
	48	9	-4.2	7.3	(-8.8, 0.3)
	120	9	-2.7	8.1	(-7.7, 2.4)
Oral NEPA FDC	0.5	134	-0.7	6.4	(-1.6, 0.2)
	48	133	-0.9	6.2	(-1.8, 0.0)
	120	133	-0.5	7.5	(-1.6, 0.6)

Table 22: Descriptive Statistics Results of Δ QRS for IV NEPA FDC and Oral NEPA FDC (NEPA-15-18)

Treatment	Cycle	Time (h)	N	Mean	Std Dev	90% CI for Mean
IV NEPA FDC	1	0.5	201	0.3	7.2	(-0.5, 1.1)
		5	203	0.2	6.9	(-0.6, 1.0)
		24	205	1.8	7.1	(1.0, 2.6)
		120	205	0.4	7.0	(-0.4, 1.3)
	2	0.5	176	-0.7	8.1	(-1.7, 0.3)
		5	176	-0.0	8.2	(-1.0, 1.0)
		24	177	0.4	8.4	(-0.7, 1.4)
		120	179	-0.8	7.9	(-1.8, 0.1)
	3	0.5	162	0.2	8.7	(-0.9, 1.3)
		5	163	-1.2	8.3	(-2.3, -0.1)
		24	162	0.7	9.0	(-0.4, 1.9)
		120	161	-0.8	8.4	(-1.9, 0.3)
	4	0.5	122	-1.3	8.8	(-2.6, 0.0)
		5	122	-1.5	8.4	(-2.7, -0.2)
		24	122	-0.3	8.5	(-1.6, 1.0)
		120	120	-1.7	9.2	(-3.1, -0.3)
Oral NEPA FDC	1	0.5	199	1.0	7.2	(0.2, 1.9)
		5	199	0.5	7.3	(-0.4, 1.3)

Treatment	Cycle	Time (h)	N	Mean	Std Dev	90% CI for Mean
		24	199	2.0	7.9	(1.1, 2.9)
		120	198	1.0	7.7	(0.1, 1.9)
	2	0.5	174	0.1	7.6	(-0.8, 1.1)
		5	173	-0.3	7.6	(-1.3, 0.6)
		24	171	1.7	7.7	(0.7, 2.7)
		120	171	-0.3	8.5	(-1.4, 0.8)
	3	0.5	149	-0.6	7.3	(-1.6, 0.4)
		5	149	-1.8	7.4	(-2.8, -0.8)
		24	149	0.9	8.1	(-0.2, 2.0)
		120	145	-1.7	7.6	(-2.7, -0.6)
	4	0.5	115	0.1	7.3	(-1.0, 1.2)
		5	116	-0.2	7.9	(-1.4, 1.0)
		24	116	1.2	8.0	(-0.1, 2.4)
		120	116	-0.2	7.6	(-1.4, 0.9)

Table 23: Categorical Analysis for QRS (PNET-12-23)

Treatment Group	Total N	QRS ≤ 110 ms	QRS > 110 ms
19.5 mg	8	8 (100%)	0 (0.0%)
32.5 mg	8	7 (87.5%)	1 (12.5%)
65 mg	8	8 (100%)	0 (0.0%)
130 mg	10	10 (100%)	0 (0.0%)
195 mg	28	25 (89.3%)	3 (10.7%)
234 mg	19	16 (84.2%)	3 (15.8%)
260 mg	30	29 (96.7%)	1 (3.3%)
286 mg	18	17 (94.4%)	1 (5.6%)
325 mg	10	7 (70.0%)	3 (30.0%)
390 mg	9	8 (88.9%)	1 (11.1%)
Oral NEPA FDC	133	120 (90.2%)	13 (9.8%)

Table 24: Categorical Analysis for QRS (NEPA-15-18)

Treatment Group	Total N	QRS ≤ 110 ms	QRS > 110 ms
IV NEPA FDC	203	187 (92.1%)	16 (7.9%)
Oral NEPA FDC	200	181 (90.5%)	19 (9.5%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The PK and exposure-response results presented in this section are based on data from Study PNET-12-23. There was no PK data collected in Study NEPA-15-18.

Study PNET-12-23 evaluated a range of doses from 19.5 mg to 390 mg fosnetupitant (pro-netupitant) via IV infusion and oral NEPA FDC (netupitant 300 mg/palonosetron 0.5 mg). In this study, plasma concentrations of fosnetupitant, netupitant and netupitant metabolites M1, M2, and M3 were measured.

The Table 25 below presents the collated values of T_{max} and geometric mean C_{max} for:

- proposed therapeutic dose of 260 mg fosnetupitant in IV NEPA FDC (from PNET-12-23)
- highest IV infusion dose of 390 mg fosnetupitant (from PNET-12-23)
- approved oral NEPA FDC which contains 300 mg netupitant (from PNET-12-23)
- supratherapeutic dose of 600 mg oral netupitant studied in prior TQT study for oral NEPA FDC.

Table 25: Comparison of PK Parameters (C_{max} and T_{max})

	Fosnetupitant IV infusion (0.5 h)	Oral NEPA FDC
Fosnetupitant	$T_{max} \sim 0.4$ h $C_{max} \sim 6363$ µg/L (260 mg), 9515 µg/L (390 mg)	
Netupitant	Nearly steady conc. from 0.5 to 4 h $T_{max} \sim 0.5$ h $C_{max} \sim 823$ µg/L (260 mg), 1287 µg/L (390 mg)	$T_{max} \sim 4$ h $C_{max} \sim 421$ µg/L (300 mg) ~ 648 µg/L (mean 816) (600 mg)
M1	Steady conc. from 8 to 24 h $T_{max} \sim 12$ h $C_{max} \sim 26$ µg/L (260 mg), 42 µg/L (390 mg)	$T_{max} \sim 8$ h $C_{max} \sim 37$ µg/L (300 mg) ~ 54 µg/L (600 mg)

M2	T _{max} ~ 2-3 h C _{max} ~ 156 µg/L (260 mg), 176 µg/L (390 mg)	T _{max} ~ 4 h C _{max} ~ 188 µg/L (300 mg) ~ 228 µg/L (600 mg)
M3	T _{max} ~ 24 h C _{max} ~ 53 µg/L (260 mg), 73 µg/L (390 mg)	T _{max} ~ 12 h C _{max} ~ 62 µg/L (300 mg) ~ 102 µg/L (600 mg)

Source: Applicant's Clinical Study Report PNET-12-23, Tables 11.1-4 through 11.1-8 and previous QT-IRT review for oral NEPA FDC (under IND 7349, dated 01/20/2010 in DARRTS).

The intensive PK sampling in Study PNET-12-23 showed that the C_{max} for netupitant metabolites M1, M2 and M3 are around 12 h (steady conc. from 8 to 24 h), 2-3 h and 24 h, respectively. Although the ECG sampling in either of the studies (PNET-12-23 and NEPA-15-18) was not adequate to capture the effects near T_{max} of these metabolites, these metabolite exposures with therapeutic dosing of IV NEPA FDC were well covered by suprathreshold dose of 600 mg netupitant in TQT study for approved oral NEPA FDC (2-fold [54 vs. 26 µg/L], 1.5-fold [228 vs. 156 µg/L] and 1.9-fold [102 vs. 53 µg/L] exposure margin for M1, M2 and M3, respectively). Furthermore, there was no statistically significant positive E-R relationship seen in C-QTc analysis with each of these 3 metabolites in the TQT study (Previous QT-IRT review under IND 73493 for TQT study for oral Akynzeo (netupitant/palonosetron), dated 01/20/2010 in DARRTS). Thus, further exploration of E-R relationship for these metabolites was not carried out in this review.

The PK data also demonstrated that the C_{max} of fosnetupitant and netupitant occur at the end of the 30 minute infusion of IV NEPA FDC, indicating the fast formation of netupitant from its prodrug. Mean concentrations of netupitant remained at nearly the same level until 4 h post-infusion and declined slowly thereafter. Netupitant C_{max} after the IV 260 mg fosnetupitant (therapeutic dose in IV NEPA FDC) was ~2-fold of that after oral 300 mg netupitant (823 vs. 421 µg/L). Also this netupitant C_{max} after the IV 260 mg fosnetupitant was similar to the C_{max} achieved with suprathreshold oral dose (600 mg) of netupitant previously studied as a part of TQT study for oral Akynzeo (suprathreshold dose of 600 mg netupitant /1.5 mg palonosetron studied in that study). Although the previous TQT study of oral Akynzeo does not cover the worst case scenario of possible increase in netupitant exposure up to 1.4-fold that could be expected with hepatic impairment, these exposures are covered by 390 mg IV fosnetupitant (1.5-fold the proposed therapeutic dose of 260 mg fosnetupitant in IV NEPA FDC) that is studied in Study PNET-12-23. So the relationship between ΔQTcF and netupitant concentrations is explored in this review in order to take into account these higher exposure levels.

Further, this review also focused on the new moiety of fosnetupitant, which has not been studied in any prior TQT studies. The preclinical cardiac safety studies did not identify any potential issues for fosnetupitant. The assessments in the current program have adequate exposure margin to cover the highest clinically relevant exposure of fosnetupitant with therapeutic dose, because fosnetupitant clearance (conversion to

netupitant) is likely mediated by non-saturable enzymes, such as phosphatases and esterases, distributed throughout the body and none of the intrinsic/extrinsic factors are expected to increase its exposure over the observed therapeutic exposures in its clinical studies.

The exposure-response relationship between ΔQTcF and fosnetupitant concentrations and between ΔQTcF and netupitant concentrations is visualized in Figure 7 and Figure 8, respectively, with no evident positive C-QTc relationship. The results for netupitant are consistent with the prior TQT study where no positive C-QTc relationship was identified for netupitant.

Figure 7: ΔQTcF vs. Fosnetupitant Concentration

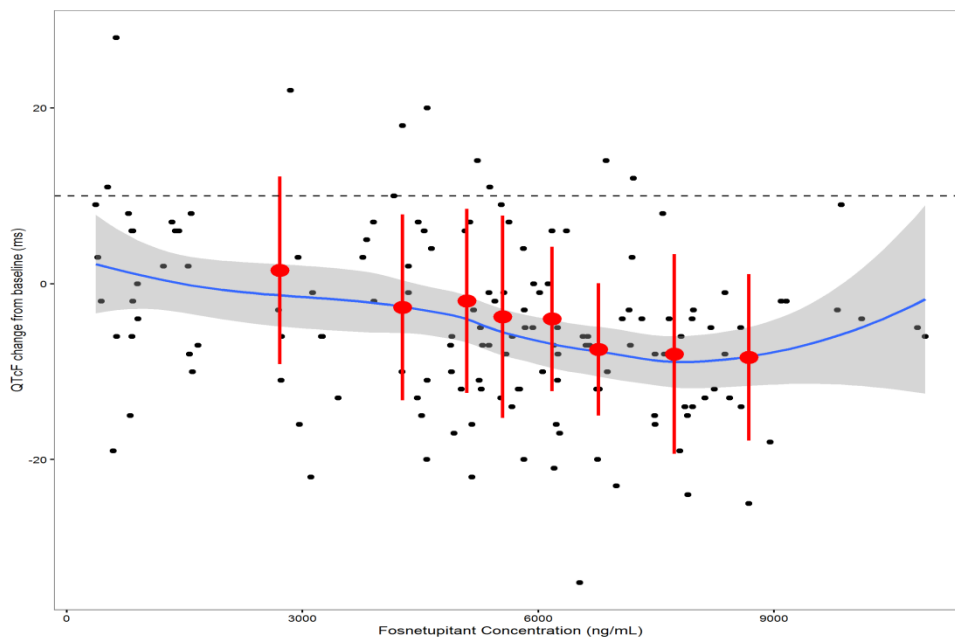
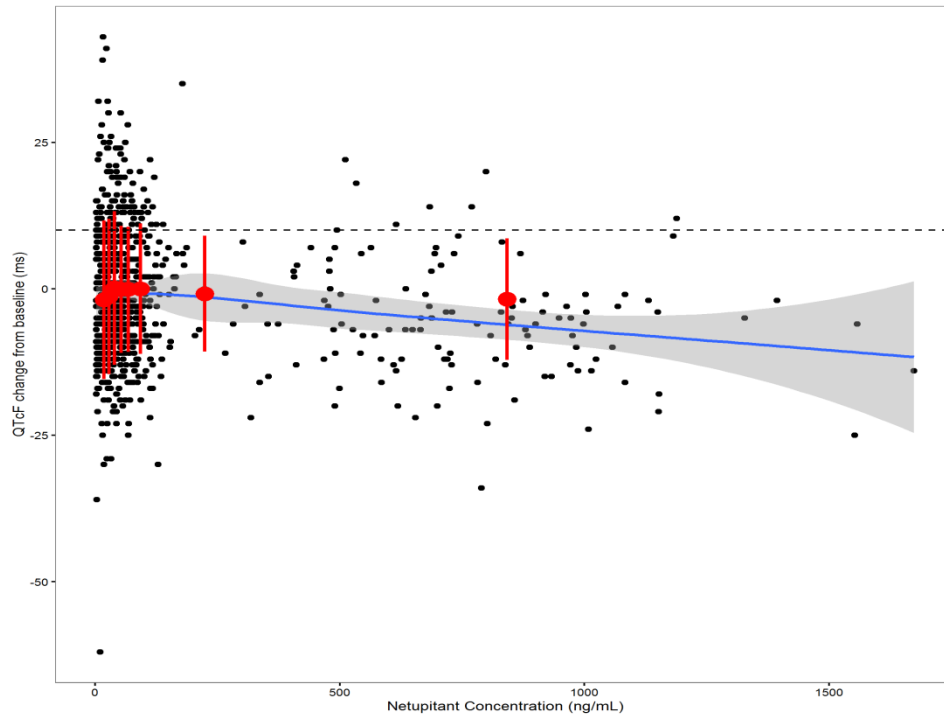


Figure 8: Δ QTcF vs. Netupitant Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) were previously described in Section 4.2.2.3 Safety Analysis.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in these two studies appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effect on PR or QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	260mg fosnetupitant (235mg fosnetupitant free-base) / 0.25mg palonosetron given as a 30-minute intravenous infusion													
Maximum tolerated dose	In rats, the maximum tolerated dose (MTD) after intravenous repeated administration was 78.94 mg/kg/day (equivalent to 60 mg/kg/day of netupitant) due to a slight decrease in body weight, a slight increase in the weight of liver and some local changes at the injection site (Study PNET-11-06, Appendix 18). In dogs, after intravenous repeated administration, the dose level of 39.47 mg/kg/day (equivalent to 30 mg/kg/day of netupitant) was considered the MTD due to the effects on body weight (a slight reduction) and food consumption (marked reduction up to 70%) (Study PNET-11-07, Appendix 18).													
Principal adverse events	Cancer Patients A total of 404 chemotherapy naïve cancer patients were treated in up to 4 consecutive cycles in the Ph III, double-blind, randomized, multicentre safety study NEPA-15-18. A total of 203 patients received the fixed dose combination (FDC) of fosnetupitant 260mg/palonosetron 0.25mg as 30-minute infusion (IV NEPA) and 201 patients received the oral netupitant/palonosetron (300mg/0.5mg) FDC (oral NEPA FDC), each in addition to oral dexamethasone. Throughout the study, the most frequent TEAE was neutropenia reported in 30.0% of patients in the IV NEPA FDC group and 28.9% of patients in the oral NEPA FDC group. Other frequently reported TEAEs were anemia (16.3% and 18.9% of patients, respectively), alopecia (15.8% and 14.4% of patients, respectively), constipation (10.3% and 12.9% of patients, respectively), and leukopenia (10.3% and 10.9% of patients, respectively). Healthy Volunteers In the two healthy volunteer studies conducted with fosnetupitant as a single agent, the most frequently reported TEAE after both administration routes was headache (all IV doses: 8.1% of subjects; oral: 15.7% of subjects) in PNET-12-23 (Single IV ascending dose study from 19.5 mg up to 390 mg versus oral NEPA FDC) and flushing (17.9% with dexamethasone alone, 30%, 35% and 27.8% after 130, 195 and 260 mg fosnetupitant plus dexamethasone, respectively) in PNET-13-63 (DDI study).													
Maximum dose tested	Single Dose	- 260mg fosnetupitant / 0.25mg palonosetron FDC administered as 30-minute intravenous infusion (Ph I Study NEPA-15-19 in cancer patients). - 390mg fosnetupitant single agent administered as 30-minute intravenous infusion (Ph I Study PNET-12-23 in healthy subjects).												
	Multiple Dose	260mg fosnetupitant / 0.25mg palonosetron FDC administered as 30-minute intravenous infusion in up to 4 consecutive chemotherapy cycles 21 to 35 days apart (Ph III Study NEPA-15-18).												
Exposures Achieved at Maximum Tested Dose	Single Dose	In cancer patients, after a single 30-minute intravenous infusion of 260mg fosnetupitant/0.25mg palonosetron FDC, C_{max} and AUC_{inf} of fosnetupitant, netupitant generated <i>in vivo</i> from fosnetupitant hydrolysis and palonosetron were the following: <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Study NEPA-15-19 Patients, n=24</th> <th style="text-align: center;">C_{max}</th> <th style="text-align: center;">AUC_{inf}</th> </tr> </thead> <tbody> <tr> <td>Fosnetupitant, mean (CV%)</td> <td style="text-align: center;">3478.33 ng/mL (44.80)</td> <td style="text-align: center;">1400.98 h.ng/mL</td> </tr> <tr> <td>Netupitant, mean (CV%)</td> <td style="text-align: center;">589.54 ng/mL (27.97)</td> <td style="text-align: center;">15588.49 h.ng/mL</td> </tr> <tr> <td>Palonosetron, mean (CV%)</td> <td style="text-align: center;">823 pg/mL (35.08)</td> <td style="text-align: center;">36066.22 h.pg/mL</td> </tr> </tbody> </table>	Study NEPA-15-19 Patients, n=24	C_{max}	AUC_{inf}	Fosnetupitant, mean (CV%)	3478.33 ng/mL (44.80)	1400.98 h.ng/mL	Netupitant, mean (CV%)	589.54 ng/mL (27.97)	15588.49 h.ng/mL	Palonosetron, mean (CV%)	823 pg/mL (35.08)	36066.22 h.pg/mL
		Study NEPA-15-19 Patients, n=24	C_{max}	AUC_{inf}										
Fosnetupitant, mean (CV%)	3478.33 ng/mL (44.80)	1400.98 h.ng/mL												
Netupitant, mean (CV%)	589.54 ng/mL (27.97)	15588.49 h.ng/mL												
Palonosetron, mean (CV%)	823 pg/mL (35.08)	36066.22 h.pg/mL												
In healthy volunteers (HVs), after a single 30-minute intravenous infusion of 390mg fosnetupitant, C_{max} and AUC_{inf} of fosnetupitant and														

		netupitant generated <i>in vivo</i> from fosnetupitant hydrolysis were the following:																				
		<table border="1"> <thead> <tr> <th>Study PNET-12-23 HVs, n=9</th> <th>C_{max}</th> <th>AUC_{inf}</th> </tr> </thead> <tbody> <tr> <td>Fosnetupitant, mean (CV%)</td> <td>9562 ng/mL (10.53)</td> <td>4353 h.ng/mL (10.53)</td> </tr> <tr> <td>Netupitant, mean (CV%)</td> <td>1310 ng/mL (19.44)</td> <td>23923 h.ng/mL (19.44)</td> </tr> </tbody> </table>	Study PNET-12-23 HVs, n=9	C _{max}	AUC _{inf}	Fosnetupitant, mean (CV%)	9562 ng/mL (10.53)	4353 h.ng/mL (10.53)	Netupitant, mean (CV%)	1310 ng/mL (19.44)	23923 h.ng/mL (19.44)											
Study PNET-12-23 HVs, n=9	C _{max}	AUC _{inf}																				
Fosnetupitant, mean (CV%)	9562 ng/mL (10.53)	4353 h.ng/mL (10.53)																				
Netupitant, mean (CV%)	1310 ng/mL (19.44)	23923 h.ng/mL (19.44)																				
Multiple Dose		No PK data are available with multiple fosnetupitant dose administration as the drug is intended for single dose administration on Day 1 only of each chemotherapy cycle.																				
Range of linear PK		Fosnetupitant: from 19.5 to 390mg IV, single agent (Study PNET-12-23). Palonosetron: from 0.3 to 90 µg/kg IV, single agent (Package Insert).																				
Accumulation at steady state		No PK data are available for multiple dose administration of IV NEPA FDC as the drug combination is intended for single dose administration on Day 1 of each chemotherapy cycle.																				
Metabolites		Fosnetupitant is rapidly hydrolyzed <i>in vivo</i> to generate netupitant, the only primary metabolite. Netupitant is then metabolized by CYP3A4 giving rise to secondary metabolites M1 (desmethyl-netupitant), M2 (netupitant-N-oxide), and M3 (OH-methyl-netupitant). The profile of activity of netupitant, M1, M2 and M3 is summarized below (Study 1006030): <table border="1"> <thead> <tr> <th></th> <th>Netupitant</th> <th>M1</th> <th>M2</th> <th>M3</th> </tr> </thead> <tbody> <tr> <td>pKi hNK1 (M)</td> <td>9</td> <td>9</td> <td>9</td> <td>9.1</td> </tr> <tr> <td>ED₅₀ gerbil foot-tapping, i.p. (mg/kg)</td> <td>1.5</td> <td>5.4</td> <td>> 10</td> <td>1.2</td> </tr> <tr> <td>ED₅₀ gerbil foot-tapping, p.o. (mg/kg)</td> <td>0.5</td> <td>2.4</td> <td>< 10 70% inh. at 10 mg/kg</td> <td>Not tested</td> </tr> </tbody> </table> Palonosetron is metabolized to N-oxide-palonosetron (M9) and 6-S-hydroxy-palonosetron (M4). These metabolites are substantially inactive, each having less than 1% of the 5HT₃ receptor antagonist activity of palonosetron.		Netupitant	M1	M2	M3	pKi hNK1 (M)	9	9	9	9.1	ED ₅₀ gerbil foot-tapping, i.p. (mg/kg)	1.5	5.4	> 10	1.2	ED ₅₀ gerbil foot-tapping, p.o. (mg/kg)	0.5	2.4	< 10 70% inh. at 10 mg/kg	Not tested
	Netupitant	M1	M2	M3																		
pKi hNK1 (M)	9	9	9	9.1																		
ED ₅₀ gerbil foot-tapping, i.p. (mg/kg)	1.5	5.4	> 10	1.2																		
ED ₅₀ gerbil foot-tapping, p.o. (mg/kg)	0.5	2.4	< 10 70% inh. at 10 mg/kg	Not tested																		
Absorption	Absolute/Relative Bioavailability	Fosnetupitant / palonosetron FDC is administered intravenously. Therefore absolute bioavailability of combined drugs is complete (100%).																				
	t _{max}	After a single 30-min intravenous infusion of 260mg fosnetupitant alone in HVs (Study PNET-12-23) or in combination with 0.25mg palonosetron in cancer patients (Study NEPA-15-19), the median t_{max} (range) values for fosnetupitant, the primary metabolite netupitant, the secondary metabolites M1, M2, M3 and palonosetron (patients only) are given in the table below: <table border="1"> <thead> <tr> <th>t_{max} (h) Median (range)</th> <th>Study PNET-12-23 HVs, n=30</th> <th>Study NEPA-15-19 Patients, n=24</th> </tr> </thead> <tbody> <tr> <td>Fosnetupitant</td> <td>0.50 (0.25 - 0.52)</td> <td>0.53 (0.52 - 0.62)</td> </tr> <tr> <td>Netupitant</td> <td>0.50 (0.50 - 4.00)</td> <td>0.56 (0.52 - 4.00)</td> </tr> <tr> <td>Metabolite M1</td> <td>12.00 (2.00 - 48.02)</td> <td>12.00 (2.00 - 192.00)</td> </tr> <tr> <td>Metabolite M2</td> <td>3.00 (0.50 - 4.00)</td> <td>2.00 (2.00 - 4.00)</td> </tr> <tr> <td>Metabolite M3</td> <td>24.00 (4.00 - 48.00)</td> <td>12.00 (2.00 - 24.10)</td> </tr> </tbody> </table>	t _{max} (h) Median (range)	Study PNET-12-23 HVs, n=30	Study NEPA-15-19 Patients, n=24	Fosnetupitant	0.50 (0.25 - 0.52)	0.53 (0.52 - 0.62)	Netupitant	0.50 (0.50 - 4.00)	0.56 (0.52 - 4.00)	Metabolite M1	12.00 (2.00 - 48.02)	12.00 (2.00 - 192.00)	Metabolite M2	3.00 (0.50 - 4.00)	2.00 (2.00 - 4.00)	Metabolite M3	24.00 (4.00 - 48.00)	12.00 (2.00 - 24.10)		
t _{max} (h) Median (range)	Study PNET-12-23 HVs, n=30	Study NEPA-15-19 Patients, n=24																				
Fosnetupitant	0.50 (0.25 - 0.52)	0.53 (0.52 - 0.62)																				
Netupitant	0.50 (0.50 - 4.00)	0.56 (0.52 - 4.00)																				
Metabolite M1	12.00 (2.00 - 48.02)	12.00 (2.00 - 192.00)																				
Metabolite M2	3.00 (0.50 - 4.00)	2.00 (2.00 - 4.00)																				
Metabolite M3	24.00 (4.00 - 48.00)	12.00 (2.00 - 24.10)																				

		Palonosetron	Not available	0.58 (0.52 - 6.00)																	
Distribution	Vd/F or Vd	After a single 260mg 30-min intravenous infusion of fosnetupitant single agent, mean Vd (%CV) for fosnetupitant in healthy subjects is 124.2 L (60.94) (Study PNET-12-23, n=30). After a single 30-min intravenous infusion of 260mg fosnetupitant / 0.25mg palonosetron FDC, mean Vd (%CV) values for fosnetupitant and palonosetron in cancer patients are 295.79 L (180.73) and 593.89 L (40.21), respectively (Study NEPA-15-19, n=24).																			
	% bound	Fosnetupitant and palonosetron plasma protein binding was determined by equilibrium dialysis. For fosnetupitant, mean (CV%) % bound was 92.14% (1.80) at 1 µM and 94.86% (0.50) at 10 µM, overall mean value 93.5% (Study PNET-15-90). Approximately 62% of palonosetron is bound to plasma proteins (Study CL 6204, Package Insert).																			
Elimination	Route	Primary elimination route for fosnetupitant is metabolism. The prodrug is rapidly and completely hydrolyzed to netupitant by non-CYP450 hydrolytic enzymes. Netupitant is then primarily eliminated by CYP3A4 mediated metabolism with formation of the main metabolites M1, M2 and M3. After oral administration of radiolabeled netupitant, 86.5% of administered radioactivity was excreted via the feces in 30 days post-dose. Primary elimination route for palonosetron is via the kidneys. After a single intravenous dose of radiolabeled palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine, with unchanged palonosetron representing approximately 40% of the administered dose. Other elimination routes for fosnetupitant are unknown. After oral administration of radiolabeled netupitant, 4.7% of administered radioactivity was excreted in urine in 30 days post-dose. Palonosetron is eliminated by CYP2D6 mediated metabolism with formation of two primary metabolites: N-oxide-palonosetron (M9) and 6-S-hydroxy-palonosetron (M4).																			
	Terminal t½	After a single 30-min intravenous infusion of 260mg fosnetupitant alone in HVs (Study PNET-12-23) or in combination with 0.25mg palonosetron in cancer patients (Study NEPA-15-19), the mean t_{1/2} (CV%) values for fosnetupitant, the primary metabolite netupitant, the secondary metabolites M1, M2, M3 and palonosetron (patients only) are given in the table below: <table border="1"> <thead> <tr> <th>t_{1/2} (h) Mean (CV%)</th> <th>Study PNET-12-23 HV5, n=30</th> <th>Study NEPA-15-19 Patients, n=24</th> </tr> </thead> <tbody> <tr> <td>Fosnetupitant</td> <td>0.956 (57.80)</td> <td>0.75 (53.5)</td> </tr> <tr> <td>Netupitant</td> <td>36.05 (18.90)</td> <td>143.73 (50.49)</td> </tr> <tr> <td>Metabolite M1</td> <td>89.34 (53.06)</td> <td>159.54 (45.52)</td> </tr> <tr> <td>Metabolite M2</td> <td>36.09 (68.62)</td> <td>136.40 (78.49)</td> </tr> <tr> <td>Metabolite M3</td> <td>47.32 (48.04)</td> <td>111.40 (48.59)</td> </tr> </tbody> </table>			t _{1/2} (h) Mean (CV%)	Study PNET-12-23 HV5, n=30	Study NEPA-15-19 Patients, n=24	Fosnetupitant	0.956 (57.80)	0.75 (53.5)	Netupitant	36.05 (18.90)	143.73 (50.49)	Metabolite M1	89.34 (53.06)	159.54 (45.52)	Metabolite M2	36.09 (68.62)	136.40 (78.49)	Metabolite M3	47.32 (48.04)
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Metabolite M3	47.32 (48.04)	111.40 (48.59)																			

		Palonosetron	Not available	58.42 (46.56)									
		Netupitant $t_{1/2}$ estimates in PNET-12-23 were shorter compared to previous studies with oral NEPA (e.g., NEPA-10-11, NEPA-10-12, NEPA-11-02, NEPA-11-23) and in the IV study NEPA-15-19. This apparent discrepancy is justified by the time interval in which the apparent terminal half-life was calculated, i.e., up to 120 h in study PNET-12-23 and up to longer times (up to 240 h) in the other studies.											
	CL/F or CL	After a single 30-min intravenous infusion of 260mg fosnetupitant alone in HVs (Study PNET-12-23) or in combination with 0.25mg palonosetron in cancer patients (Study NEPA-15-19), the mean CL (CV%) values for fosnetupitant and palonosetron (patients only) are given in the following table: <table border="1"> <thead> <tr> <th>CL (L/h) Mean (CV%)</th> <th>Study PNET-12-23 HV's, n=30</th> <th>Study NEPA-15-19 Patients, n=24</th> </tr> </thead> <tbody> <tr> <td>Fosnetupitant</td> <td>90.05 (14.73)</td> <td>249.08 (108.30)</td> </tr> <tr> <td>Palonosetron</td> <td>Not available</td> <td>7.61 (33.96)</td> </tr> </tbody> </table>			CL (L/h) Mean (CV%)	Study PNET-12-23 HV's, n=30	Study NEPA-15-19 Patients, n=24	Fosnetupitant	90.05 (14.73)	249.08 (108.30)	Palonosetron	Not available	7.61 (33.96)
CL (L/h) Mean (CV%)	Study PNET-12-23 HV's, n=30	Study NEPA-15-19 Patients, n=24											
Fosnetupitant	90.05 (14.73)	249.08 (108.30)											
Palonosetron	Not available	7.61 (33.96)											
Intrinsic Factors	Age	No data evaluating the effect of age on the PK of fosnetupitant are available. A study in the pediatric population is planned. Based on a population PK study, age was not found to be a significant covariate for netupitant and palonosetron PK after oral administration of netupitant-palonosetron FDC (Study NETU-10-02). In study NETU-10-12 the effect of age on the PK parameters of netupitant was investigated after oral administration of netupitant-palonosetron FDC. In elderly subjects, netupitant and palonosetron C_{max} increased by 36% and 10%, respectively, whereas AUC_{inf} increased by 25% and 37%, respectively as compared to younger adults. A study in the pediatric population with the oral netupitant-palonosetron FDC is in progress (Protocol NEPA-15-31). A previous study in pediatric cancer patients following intravenous infusion of palonosetron at 20 μg/kg over 15 min showed in age groups between 2 and <17 years an exposure (AUC_{inf}) approximately 3-fold higher than that achieved in adult cancer patients after intravenous infusion of 0.25mg palonosetron (Study PALO-10-20, Package Insert).											
	Sex	Study PNET-12-23 showed that in healthy subjects receiving a single 260mg fosnetupitant infusion, fosnetupitant mean C_{max} and AUC_{inf} were superimposable in females (n=13) and in males (n=19), their mean ratio being 1.006 and 1.009, respectively (less than 1% difference). As far as released netupitant is concerned, mean C_{max} and AUC_{inf} were 16% and 4% higher in females than in males, respectively. Study NEPA-15-19 showed that in cancer patients receiving a single 260mg fosnetupitant / 0.25mg palonosetron infusion, fosnetupitant mean C_{max} and AUC_{inf} were slightly higher in females (n=13), 19% and 22%, respectively, than in males (n=11). On the other hand, C_{max} and AUC_{inf} of netupitant released from fosnetupitant were superimposable in females and males, mean ratios being 1.07 and 0.99, respectively.											

		Palonosetron mean C_{max} was similar in females and males (ratio M/F = 1.01) and mean AUC_{inf} was slightly higher, i.e., 26%, than in males. A <i>post-hoc</i> analysis (Study NEPA-13-11) of pooled data from 3 studies with oral netupitant 300mg/palonosetron 0.5mg FDC (NETU-09-07, NETU-11-02 and NETU-11-23), indicated that netupitant C_{max} and AUC_{0-t} were 35.29% and 2.35% greater in females than in males, respectively. Mean palonosetron C_{max} and AUC_{0-t} were 30.53% and 39.88% higher in females than in males, respectively.
	Race	No data assessing the effect of race on the PK of fosnetupitant are available. However, no impact of race can be predicted considering that the hydrolytic enzymes involved in the rapid biotransformation of the prodrug into netupitant do not belong to the CYP450 superfamily and, likely, are not subject to genetic polymorphism (e.g., phosphatases, esterases). The effect of race on netupitant PK is also unlikely based on the following theoretical considerations and experimental results. Netupitant is primarily metabolized by CYP3A4. With the exception of alleles *1B in Afro-americans and *19 in Indo-Pakistans, genetic polymorphism of CYP3A4 may occur in a small proportion of the population across all of the affected alleles, with either no influence on enzyme activity or its reduction. In a recent study in 18 Chinese healthy subjects (study NEPA-14-02) receiving an oral administration of 300mg netupitant / 0.5mg palonosetron FDC, mean C_{max} and AUC_{inf} of netupitant in Chinese were marginally higher, i.e., 17% and 10%, respectively, than those observed in the Caucasian population after administration of oral NEPA FDC (Study NETU-11-02, 22 fasted HVs). Palonosetron is primarily metabolized by CYP2D6, known to be a polymorphic CYP isoform. Racial and ethnic studies of drug metabolism have shown substantial inter-population differences in the polymorphic distribution of CYP2D6 activity. A study conducted in CYP2D6 poor (PM) and extensive metabolizers (EM) after administration of a single IV dose of 0.75 mg palonosetron showed similar values of C_{max} (PM/EM=0.98) and AUC_{inf} (PM/EM=0.85) for the two groups (Study PALO-99-39). Also, intravenous palonosetron PK was characterized in 24 healthy Japanese subjects over the dose range of 3 – 90 μg/kg. Total body clearance was 25% higher in Japanese subjects compared to Caucasians. Finally, in Chinese healthy subjects (study NEPA-14-02) receiving an oral administration of 300mg netupitant / 0.5mg palonosetron FDC, mean C_{max} and AUC_{inf} of palonosetron were higher, i.e., 42% and 68%, respectively, than those observed in the Caucasian population after administration of oral NEPA FDC (Study NETU-11-02, 22 fasted HVs).
	Hepatic & Renal Impairment	No studies have been performed with fosnetupitant in hepatic and renal impairment. However, no change in the PK profile of fosnetupitant can be predicted in both hepatic and renal impairment because the prodrug is not expected to be excreted through the urine and it is likely metabolized by non-saturable enzymes systems, such as phosphatases and esterases, largely distributed throughout the body and not only in the liver. Netupitant and palonosetron PK was investigated in hepatic

		impairment after oral netupitant/palonosetron FDC administration (study NETU-10-10). In patients with mild or moderate hepatic impairment, mean AUC_{inf} of netupitant was 67% and 86% higher, respectively, than in healthy subjects, and the mean C_{max} for netupitant was 40% and 41% higher, respectively than in healthy subjects. In patients with mild or moderate hepatic impairment, mean AUC_{inf} of palonosetron was 33% and 62% higher, respectively, than in healthy subjects, and the mean C_{max} for netupitant was 14% higher and unchanged, respectively as compared to healthy subjects. In light of the negligible renal excretion of netupitant and its metabolites (4.7% of the administered dose), no specific PK studies have been performed in renal impairment. In a population PK analysis, mild and moderate renal impairment did not significantly affect the pharmacokinetics of netupitant in cancer patients. After a single IV bolus of palonosetron 0.75 mg to the patients over 30 seconds, mild to moderate renal impairment did not significantly affect palonosetron PK parameters, whereas AUC_{inf} increased by approximately 28% in patients with severe renal impairment relative to healthy subjects (Study PALO-99-35).
Extrinsic Factors	Drug interactions	Fosnetupitant is administered intravenously and is efficiently hydrolyzed by non-saturable enzymatic systems, such as phosphatases and esterases, abundantly distributed throughout the body. Therefore no interactions are expected between fosnetupitant itself and concomitant drugs known to be inhibitors or inducers of CYP450 enzymes that could alter fosnetupitant PK behavior. In <i>in vitro</i> studies using human liver microsomes (study PNET-15-49), fosnetupitant showed weak inhibition towards some CYP450 isoforms, e.g., CYP2C9 (IC_{50}=27.9 μM), CYP2C19 (IC_{50}=46.1 μM), CYP2C8 (IC_{50}=56.7 μM). Also, fosnetupitant showed weak inhibition towards transporters, i.e., P-gp (IC_{50}=50 μM), OATP1B1 (IC_{50} 19.1 μM), OATP1B3 (IC_{50}=17.37 μM) (study PNET-15-27). A PBPK modeling study (Study PNET-16-29) indicated, based on <i>in vitro</i> K_i estimates, physicochemical properties and <i>in vivo</i> PK data for fosnetupitant, no <i>in vivo</i> interaction between fosnetupitant and CYP2C9, CYP2C19, OATP1B1, OATP1B3 and P-gp substrates is expected. This prediction is justified by the short permanence of fosnetupitant in the systemic circulation determined by a high systemic prodrug clearance. The elevated fosnetupitant concentrations observed in a very short timeframe at the end of the infusion appeared to have no significant impact on the PK profile of drug substrates of relevant CYP450 isoforms and transporters weakly inhibited <i>in vitro</i> by fosnetupitant. For the same reason, no drug interactions are expected between fosnetupitant as substrate of OATP1B1 and OATP1B3 and inhibitors of these two transporters. However, metabolism of fosnetupitant generates netupitant, which has been found to be a moderate CYP3A4 inhibitor. Hence, an <i>in vivo</i> drug interaction study was performed

	between fosnetupitant, administered as a single IV infusion of 130, 195 and 260mg over 30 minutes and dexamethasone, a CYP3A4 probe substrate (Study-13-63). On Day 1, dexamethasone C_{max} did not increase when given with a single administration of 260mg fosnetupitant (adjusted geometric mean ratio = 0.97) whereas AUC_{0-24} showed a 50% increase. On Day 4, dexamethasone C_{max} and AUC_{0-24} increased 1.7- and 2.4 fold, respectively, when given with a single administration of 260mg fosnetupitant. Another study demonstrated that CYP3A4 inhibition lasts up to 6 days from the single oral netupitant administration (Study NEPA-14-39). <i>In vivo</i> interaction studies have also been performed with oral netupitant/palonosetron FDC co-administered with CYP3A4 drug substrates. <i>Dexamethasone (Study NETU-06-07)</i>. After co-administration of a single dose of netupitant (300 mg) with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg b.i.d. from Day 2 to Day 4), mean C_{max} and AUC_{0-24} of dexamethasone were increased by 1.1 and 1.7-fold, respectively, on Day 1 and up to 1.7 and 2.4-fold on Day 4 as compared to exposure after dexamethasone alone. Increased dexamethasone exposure as a consequence of CYP3A4 inhibition lasted up to Day 6 (Study NEPA-14-39). <i>Midazolam (Study NP16599)</i>. When co-administered with netupitant 300 mg, the mean C_{max} and AUC of midazolam after single dose oral administration of 7.5 mg midazolam was 36% and 126% higher, respectively. <i>Erythromycin (Study NP16599)</i>. When 500 mg erythromycin was co-administered with netupitant 300 mg, the systemic exposure of erythromycin was highly variable and the mean C_{max} and AUC of erythromycin were increased by 92% and 56%, respectively. <i>Oral Contraceptives (Study NETU-10-08)</i>. A single oral dose of netupitant/palonosetron FDC, when given with a single oral dose of 60 µg ethinyl estradiol and 300 µg levonorgestrel, increased the AUC of levonorgestrel by 46%, whereas C_{max} was unchanged. No significant effect on C_{max} and AUC of ethinyl estradiol was observed. The point estimates of C_{max} and AUC_{inf} were 1.05 and 1.12, respectively. <i>Chemotherapeutic Agents (docetaxel, etoposide, cyclophosphamide) (Study NETU-10-09)</i>. With co-administration of oral netupitant/palonosetron FDC, the mean C_{max} and AUC_{inf} of docetaxel were 49% and 35% higher, respectively, whereas mean C_{max} and AUC_{inf} of etoposide were increased by 10% and 28%, respectively compared to when co-administered with palonosetron alone. Mean C_{max} and AUC for cyclophosphamide after co-administration with oral netupitant/palonosetron FDC was 27% and 20% higher compared to when co-administered with palonosetron alone. <i>Digoxin (Study NETU-07-01)</i>. The effect of P-gp inhibition exerted by netupitant was studied on the PK of the probe substrate digoxin by co-administration of netupitant 450 mg. No significant effect were observed on the systemic exposure and urinary excretion of digoxin

		The effects of CYP3A4 inducers and inhibitors on the PK of netupitant and palonosetron were assessed. <i>Rifampicin (Study NETU-10-11).</i> A single oral dose of netupitant/palonosetron FDC was administered with rifampicin, a strong CYP3A4 inducer, following once daily administration of 600 mg rifampicin for 17 days. Co-administration of rifampicin decreased the mean C_{max} and AUC_{inf} of netupitant by 62% and 82%, respectively, compared to those after netupitant/palonosetron alone. Co-administration of rifampicin decreased the mean C_{max} and AUC_{inf} for palonosetron by 15% and 19%, respectively. <i>Ketoconazole (Study NETU-10-11).</i> A single oral dose of netupitant/palonosetron FDC was administered with ketoconazole, a strong CYP3A4 inhibitor, following once daily administration of 400 mg ketoconazole for 12 days. Co-administration with ketoconazole increased mean C_{max} and AUC_{inf} of netupitant by 25% and 140%, respectively, compared to after administration of netupitant/palonosetron FDC alone. The mean C_{max} and AUC_{inf} of palonosetron were 15% and 10% higher, respectively, when co-administered with ketoconazole. Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. <i>In vitro</i> studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and, CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Coadministration of 0.25 mg I.V. palonosetron and 20 mg I.V. dexamethasone in healthy subjects revealed no PK drug-interactions between palonosetron and dexamethasone. In an interaction study in healthy subjects where palonosetron 0.25 mg (I.V. bolus) was administered on day 1 and oral aprepitant for 3 days (125 mg/80 mg/80 mg), the pharmacokinetics of palonosetron were not significantly altered (AUC: no change, C_{max}: 15% increase). A study in healthy volunteers involving single-dose I.V. palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction. An <i>in vitro</i> interaction study was done to assess the substrate or inhibitor properties of palonosetron (PALO-15-28) for transporters. Palonosetron resulted to be substrate of P-gp and a weak inhibitor of the MATE1, MATE2-K, OCT1, OCT2 and OAT3. Application of principles and basic models described in the DDI guidance (2012), indicated no <i>in vivo</i> relevance of these interactions.
	Food Effects	Not-applicable because the drug is administered by intravenous infusion
Expected High Clinical Exposure Scenario	Using the proposed intravenous dose of 260mg fosnetupitant in combination with 0.25mg palonosetron, no specific worst case scenarios that create the conditions for relevant changes in exposure can be envisioned for the following reasons: - fosnetupitant has an extremely high systemic clearance likely mediated by non-saturable enzymes, such as phosphatases and esterases, largely	

	distributed throughout the body; - fosnetupitant is immediately and rapidly hydrolyzed to netupitant; - fosnetupitant has dose-proportional pharmacokinetics in a wide dose range; - no drug interactions that could overexpose patients to the prodrug are expected; - no change in the PK profile of fosnetupitant could be expected in both hepatic and renal impairment; - no gender effect has been shown in studies in healthy subjects and cancer patients; - limited inter-individual PK parameter variability has been observed in all the PK studies performed with fosnetupitant; - IV NEPA FDC is going to be administered in controlled conditions by healthcare professionals, as a single dose. Possible increase of netupitant exposure due to drug interactions with strong inhibitors of the CYP3A4-mediated metabolism or hepatic impairment, are covered by safety data at supratherapeutic doses, as discussed in the oral Akynzeo® dossier.
Preclinical Cardiac Safety	Based on the rapid conversion of fosnetupitant to netupitant the cardiac safety of fosnetupitant relies on a comprehensive cardiac safety program performed for oral Akynzeo® (Appendix 18). <i>In vitro studies.</i> Effect of Fosnetupitant on hERG Current (IKr) was assessed <i>in vitro</i> (Study PNET-12-06). Fosnetupitant up to 30 µM had no effects on the delayed rectifier potassium current (IKr) encoded by hERG. <i>In vivo studies.</i> Cardiovascular function was assessed <i>in vivo</i> in telemetered dogs in a 2-week study with IV fosnetupitant (Study PNET-12-35). Fosnetupitant was administered at 1.32, 3.95 and 13.16 mg/kg/day (equivalent to 1, 3 and 10 mg/kg/day of netupitant). All electrocardiographic tracings recorded during the study did not show any abnormality which could be considered treatment-related. The intravenous administration of combination fosnetupitant/palonosetron 1.32/1 mg/kg/day, 13.2/6 and 3.95/3 for 2 weeks (NEPA-13-76) did not induce any effect on arterial blood pressure, heart rate and body temperature in a study in telemetered dogs. Alterations in atrio-ventricular conduction, ventricular depolarisation and repolarisation characterised by increases in PR, PQ, QT interval and QRS complex durations, ST segment, QT corrected QTc and QTshift were observed in the high-dose group (13.2/6 mg/kg/day) at Day 14. There were no effects on QT at low (1.32/1 mg/kg/day) and mid-dose (3.95/3 mg/kg/day) levels at any time during the study. Changes in QT and QRS complex were due to the main netupitant metabolite, M1. In the 4-week toxicology study PNET-13-27, the cardiovascular effects of fosnetupitant were assessed in conscious dogs dosed at 1.316, 3.95 or 13.16 mg/kg/day, equivalent to 1, 3 and 10 mg/kg/day of netupitant, by intravenous route once daily for 4 weeks. Electrocardiographic tracings recorded during the dosing period did not show any abnormality which could be considered to be treatment-related. In the 4-week toxicology study NEPA-13-52, dogs were treated with fosnetupitant/palonosetron at doses of 0/0, 1.32/1, 3.95/3, or 13.16/10/6 mg/kg/day for 4 weeks. Palonosetron was administered at 10 mg/kg/day during 14/13 days (males /females, respectively); due to convulsive episodes the dose level was then reduced to 6 mg/kg/day until the end of the study. Intravenous administration of the combination of fosnetupitant-palonosetron caused transient and reversible increased heart rate at mid dose (females only) and at high dose (both sexes) levels. These changes were associated with a transient and reversible increase, without dose-related effect, in QTc (QTcF and QTcV) intervals at the high dose level (male and female animals) and at the mid dose (males only).

Clinical Cardiac Safety	<u>Cancer Patients</u> In NEPA-15-18 (HEC study), 203 cancer patients received IV NEPA FDC and 201 patients received oral NEPA FDC, up to 4 chemotherapy cycles. Exposures to IV NEPA FDC were as follows: 187 patients with 1 exposure, 179 pts with 2 exposures, 163 pts with 3 exposures and 122 pts with 4 exposures. In Study NEPA-15-18, the following adverse events potentially suggestive of proarrhythmic effect as per ICH E14 were reported: <i>in the IV NEPA FDC group</i> • cardiac failure: 1 patient (0.5%); • extra systoles: 1 patient (0.5%); • tachycardia: 1 patient (0.5%); • ventricular tachyarrhythmia: 1 patient (0.5%); • sudden death: 1 patient (0.5%); • syncope: 1 patient (0.5%); • ECG QT prolongations: 3 patients (1.5%). <i>In the oral NEPA FDC group,</i> • cardiac failure: 1 patient (0.5%); • tachycardia: 4 patients (2.0%); • sudden death: 3 patients (1.5%); • syncope: 1 patient (0.5%); • ECG QT prolongations: 2 patients (1.0%). Across all cycles, no patient had a QTcF > 500 msec with a baseline value < 500 msec. In each group, there was one patient (0.5%) with a change from baseline > 60 msec. <u>Healthy Volunteers</u> Two studies were performed in healthy subjects (PNET-12-23 and PNET-13-63), with a total of 178 subjects (PNET-12-23; 148 subjects and PNET-13-63; 30 subjects) exposed to at least one dose of IV fosnetupitant within the range 19.5 mg to 390 mg. Crossover design was applied in both studies. Subjects exposed to the relevant fosnetupitant dose in PNET-12-23 study were: 19.5mg (8 subjects); 32.5mg (8); 65mg (8); 130mg (10); 195mg (28); 234mg (19); 260mg (30); 286mg (18); 325mg (10); 390mg (9). In PNET-13-63, study subjects were exposed to 130mg fosnetupitant (20 subjects), 195mg fosnetupitant (20 subjects) and 260mg fosnetupitant (18 subjects). No cardiac safety events as per ICH E14 guidance were reported. No subjects in either trial had QTcB or QTcF changes from baseline > 60 msec and no new QTcB or QTcF interval > 500 msec was observed.

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/s/

JUSTIN C EARP
08/28/2017

DHANANJAY D MARATHE
08/28/2017

MOH JEE NG
08/28/2017

MOHAMMAD A RAHMAN
08/28/2017

MICHAEL Y LI
08/28/2017

CHRISTINE E GARNETT
08/28/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 210493 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Akynzeo Established/Proper Name: fosnetupitant and palonosetron Dosage Form: injection Strengths: Route(s) of Administration: intravenous		
Applicant: Helsinn Healthcare SA Agent for Applicant (if applicable): August Consulting, Inc.		
Date of Application: April 20, 2017 Date of Receipt: April 20, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: April 20, 2018		Action Goal Date (if different):
Filing Date: June 19, 2017		Date of Filing Meeting: June 8, 2017
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	☐ 351(a) ☐ 351(k)	

Review Classification:		☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher		
The application will be a priority review if: • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted				
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐			
Part 3 Combination Product? ☐	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)			
☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 115191				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☐	☒		On 6/15/17 and 6/19/17, the document room staff has been requested to update the review timeline.
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	☐	☐		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted questions below:	☐	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		

Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☐		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☐		
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below:	☐	☐		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If no, include template language in the 74-day letter. Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)] Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.	☐	☐		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	☐	☒		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	☐	☐	☒	
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: 5 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☒	☐	☐	
NDA only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic)			
	☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☐	☒		
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	☐	☐	☒	
Forms and Certifications <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	☒	☐		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	☒	☐		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	☐	☒		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSL/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	 DPMH Maternal PLLR related IR issued 5/17/17; sponsor response received 6/2/17.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☐	☐	☒	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☐ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	☒	☐	☐	QT IRT consult issued 5/10/17.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): February 4, 2015; December 9, 2014	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): November 30, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? Date(s):	☐			

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 8, 2017

BACKGROUND:

Helsinn Healthcare submitted a new 505(b)(1) NDA 210493 Akynzeo (fosnetupitant and palonosetron) inj. This is the I.V. formulation of the approved Akynzeo (netupitant and palonosetron) capsule (approved 10/10/14).

- Proposed indication:
 - Akynzeo for injection is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.
 - Akynzeo is a (b)(4) combination of palonosetron and netupitant (b)(4) or fosnetupitant, (b)(4); palonosetron prevents nausea and vomiting during the acute phase and netupitant/fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.
- Clinical program (phase 3 studies):
 - PALO-15-17: ph3 non-inferiority study to demonstrate efficacy/safety of a single dose of I.V. palonosetron 0.25 mg 30 minute infusion (compared with I.V. palonosetron 0.25 mg 30 second bolus (as per the approved Aloxi (palonosetron) label))(440 patients total).
 - NEPA-15-18: ph3 safety study comparing I.V. Akynzeo vs. Oral Akynzeo to demonstrate safety of higher Cmax of netupitant I.V. (400 patients total).
- An agreed iPSP was issued under referenced IND 115191 fosnetupitant and palonosetron inj. on 6/29/16.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mary Chung	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Anil Rajpal		Y
Division Director/Deputy	Donna Griebel (DD), Joyce Korvick (DDS)		Y
Office Director/Deputy			
Clinical	Reviewer:	Aisha Johnson	Y
	TL:	Anil Rajpal	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Pharmacology	Reviewer:	Elizabeth Shang	N
	TL:	Insook Kim	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Min Min	Y
	TL:	Yeh-Fong Chen	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ke Zhang	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Hitesh Shroff	N
	RBPM:	Oumou Barry	N
• Drug Substance	Reviewer:	Joe (Joseph) Leginus	N
• Drug Product	Reviewer:	Caroline Strasinger (coverage for ATL)	Y
• Process	Reviewer:	Li Shan Hsieh	N
• Microbiology	Reviewer:	Lisa Shelton	Y
• Facility	Reviewer:	Michael Klupal	Y
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Twanda Scales	N
	TL:	Marcia Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Meeta Patel	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Sherly Abraham	Y
	TL:	Sarah Vee	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	N
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	Millie (Mildred) Wright (DPMH, RPM)		Y
	Carrie Ceresa (DPMH, Maternal Health)		Y
	Nicholas Miles (OSE, SRPM)		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The application is not the first in its class and did not raise significant safety or efficacy issues.
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	Not applicable
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz (Director, Office of Drug Evaluation III)	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): September 7, 2017	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H CHUNG
06/19/2017

BRIAN K STRONGIN
06/19/2017