CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Review

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA	NDA 205718
Applicant Name	Helsinn Healthcare SA
Date of Submission	September 26, 2013 Received: September 27, 2013
PDUFA Goal Date	September 27, 2014
Proprietary Name / Established (USAN) Name	Akynzeo netupitant and palonosetron
Dosage Forms / Strength	capsule/ netupitant 300 mg and palonosetron 0.5 mg
Proposed Indication(s)	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including highly emetogenic chemotherapy
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Nancy Snow, DO/ Ruyi He, MD
Statistical Review	Yeh-Fong Chen, PhD/Freda Cooner, PhD
CMC	Raymond Frankewich, PhD/Hitesh Shroff, Ph.D./Nina Ni, Ph.D
ONDQA Biopharmaceutics	Assadollah Norry, PhD/Tapash Ghosh, PhD/Richard Lostritto, PhD
Pharmacology Toxicology Review	Ke Zhang, PhD/David Joseph, PhD
Clinical Pharmacology Review	Dilara Jappar, PhD/Insook Kim, PhD/Sue-Chih Lee, PhD Jingyu Yu, PhD/Nitin Mehrotra, PhD
CDTL Review	Ruyi He, MD
PMHS MHT	Erica Radden, MD/Hari Cheryl Sachs, MD/Lynne Yao, MD Carrie Ceresa, Pharm D, MPH/Jeanine Best, MSN, RN, PNP/Lynne Yao, MD
OSI	Susan Liebenthal, MD
CSS	Katherine Bonson, PhD/Silvia Calderon, PhD/Michael Klein, PhD

OND=Office of New Drugs
OSI=Office of Scientific Evaluation
PMHS=Pediatric and Maternal Health Staff
MHT= Maternal Health Team
CDTL=Cross-Discipline Team Leader
CSS=Controlled Substance Staff

APPEARS THIS WAY ON ORIGINAL

Division Director Review

1. Introduction

The applicant has submitted an NDA for an oral fixed combination product that consists of two antiemetics, the 5HT3 inhibitor palonosetron 0.5 mg (which has been previously approved in the US as a single agent, but never marketed in the US) and an NK-1 inhibitor netupitant 300 mg (which is a new molecular entity). There are multiple 5HT3 inhibitors approved for prevention of chemotherapy induced nausea and vomiting (CINV). This class (5HT3 inhibitor) is generally associated with efficacy in the first 24 hours after chemotherapy, i.e., the "acute phase". There is currently only one approved NK-1 inhibitor in the U.S., Emend, which has been approved in both oral and intravenous (IV) dosage forms. NK-1 inhibition is are particularly important for prevention of nausea and vomiting during the delayed phase. The delayed phase is generally defined as the time period between 24 and 120 hours post chemotherapy.

Akynzeo is a single capsule that contains: 3 smaller tablets (100 mg each) of netupitant and a single capsule of palonosetron 0.5 mg. In order to address the combination rule, the applicant submitted 3 major efficacy trials, each designed to demonstrate the contribution of each component to overall product efficacy. The applicant intended the development plan to address efficacy for prevention of CINV in both moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC), in both the acute and delayed phases. The development plan was subject to multiple meetings between the applicant and FDA. Discussions were complicated by the approved indication for oral palonosetron and the sponsor's desire to use (b) (4) These negotiations are summarized in Section 2 Background of this review.

The Akynzeo development plan was based on the regulatory approach to CINV drug development used for previously approved antiemetics. Late in its development, the FDA raised the issue that future product labeling could be impacted by ASCO 2011 guideline[1] changes in the emetogenicity category (from MEC to HEC) for anthracyclines (including doxorubicin, epirubicin, idarubicin and daunorubicin) administered in combination with cyclophosphamide. The chemotherapy administered in the single "MEC" trial conducted to support Akynzeo's approval for a MEC indication enrolled women receiving anthracycline plus cyclophosphamide chemotherapy.

All disciplines have recommended approval, and I concur with their recommendations. My review will focus on major review issues.

[1] Basch E, Prestrud A, Hesketh P, et al. Antiemetics; American Society of Clinical Oncology Clinical Practice Guideline Update. JCO. 2011. Vol 29:4189-4198.

2. Background

Please refer to the Clinical and CDTL reviews for a comprehensive summary of the regulatory history. In this section, I will cover:

1) The general approach that has been utilized to establish effectiveness of antiemetics for CINV
2) The labeled indications that have been granted to reflect trial outcomes
3) Considerations regarding the impact of changes in emetogenicity designation for anthracycline plus cyclophosphamide combination chemotherapy (from MEC to HEC) on antiemetic indications for CINV.

4) The previously documented evidence base for the effectiveness of oral palonosetron, which impacted the clinical development plan design, given the need to address the Combination Rule.

After presenting this information for context, I will summarize the key discussions between FDA and the sponsor regarding the Akynzeo clinical development plan.

Regulatory issues related to the general approach to antiemetic drug development. Antiemetic drug development for CINV has generally included clinical trials dedicated to studying effectiveness of the proposed product in the setting of HEC (usually, cisplatin-based chemotherapy) and trials dedicated to the setting of MEC (most recently, these trials have enrolled patients who were treated with anthracycline and cyclophosphamide chemotherapy). The indications have evolved to stating the product prevents chemotherapy induced nausea and vomiting in MEC and/or HEC, depending on the outcome of the trials in each of these two settings. A summary of this MEC/HEC labeling history follows below. The reader is also referred to Dr. J. Korvick's October 2005 review supporting the approval of Emend for MEC, as it provides a more detailed summary of this history.

The first 5HT3 inhibitor, intravenous ondansetron, was approved in **January 1991,** with a very general indication statement, "Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy," which did not contain the MEC/HEC terminology, even though studies were conducted in the settings of cisplatin and cyclophosphamide 500 mg to 600 mg/m^2. There was also no reference to "MEC" and "HEC" in the ondansetron Clinical Studies section. However, the oral ondansetron label, approved in **December 1992**, did contain specific indication statements regarding HEC and MEC.

Although the labeled indication from the **1993** approval of IV granisetron was general, with a qualifier, "Prevention of nausea and or vomiting associated with emetogenic cancer therapy, including high dose cisplatin," the Clinical Studies section includes cisplatin studies and a subsection called "moderately emetogenic chemotherapy study" that specifically describes MEC as carboplatin, cisplatin 20-50 mg/m^2 and cyclophosphamide >600mg/m^2.

Oral dolasetron was approved in **September 1997** with the indication, "prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy." The clinical development program for the oral dosage form focused on MEC chemotherapy regimens. The

chemotherapy in one trial was cyclophosphamide and/or doxorubicin. The chemotherapy in the second trial was not described in the label. Intravenous dolasetron was also approved in **September 1997** with the indication "prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin." The NDA also included a single MEC study. The Clinical Studies section includes a header "Cyclophosphamide Based Chemotherapy" and describes the study as primarily enrolling women receiving "moderately emetogenic chemotherapy such as cyclophosphamide based regimens."

Intravenous palonosetron was approved in **July 2003**, with indications specifically identifying HEC and MEC. Approximately half of the patients in the MEC trial were treated with doxorubicin and approximately 10% with epirubicin. Oral palonosetron was approved in **August 2008**, with an indication limited to MEC. Approximately half of the patients in the trial were treated with doxorubicin and another 10% with epirubicin. Due to its long half-life, the clinical development plan included evaluation in both the acute and delayed phases post chemotherapy. The intravenous palonosetron indication refers to efficacy in both the delayed and acute phases post MEC chemotherapy. However, in the setting of HEC, it is only approved for the acute phase. In contrast, oral palonosetron does not carry an indication for the delayed phase. The results of secondary analysis of delayed phase in the noninferiority trial that supported the approval of oral palonosetron for MEC did not demonstrate that oral palonosetron (0.5mg) was noninferior to IV palonosetron (0.25mg).

Aprepitant, which was approved in **March 2003**, is the only approved NK-1 inhibitor. The indication was "prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin." Patients in both clinical trials received cisplatin based chemotherapy (>50 mg/m^2). Approval of a MEC indication occurred in **October 2005**, "prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy." The label describes a single MEC trial that enrolled almost exclusively women, who were treated with anthracycline plus cyclophosphamide combination regimens. The approval of aprepitant constituted the first references to "acute" and "delayed" "phases", although the ondansetron label's Clinical Studies section refers to multi-day dosing and its Dosage and Administration instructions for MEC state that treatment should continue with BID dosing "for 1-2 days after completion of chemotherapy."

Initially, drug development plans for products intended to prevent delayed nausea and vomiting utilized a primary endpoint of overall phase, which encompasses the full 0-120 hour period, with secondary endpoints for each component, acute phase (first 24 hours) and delayed phase (25-120 hours). The Division has transitioned to recommending that delayed phase is the appropriate primary endpoint period for a product intended to prevent delayed nausea and vomiting.

This history is summarized in the table below.

Table 1. Summary of CINV Indications Granted for Various 5-HT3 Inhibitor and NK-1 Inhibitors

5HT3	Dosage form	HEC/MEC	Acute/Delayed
Zofran (ondansetron)		HEC and MEC	Acute Plus: Day 2 and 3 dosing instructions for MEC only.
Anzemet (dolasetron)	IV and PO	IV = "Prevention of [CINV], including high dose cisplatin" PO = MEC	acute based on Clinical Studies Section says first 24 hours
Kytril (granisetron)		"Prevention of [CINV], including high dose cisplatin" Clinical Studies Section includes a MEC trial.	acute based on Clinical Studies Section says 24 hours.
Aloxi (palonosetron)	IV	HEC	Acute
		MEC	Acute and Delayed
	PO	MEC	Acute
NK1			
Emend	PO and IV	HEC	Acute and Delayed
		MEC	"prevention of nausea and vomiting" Clinical Studies Section refers to "overall phase, 0-120 hours". Individual analyses for acute, delayed not statistically significant in one of two MEC studies.

Impact of changes in emetogenicity designation for anthracycline plus cyclophosphamide from MEC to HEC on indications for antiemetics for CINV.

Given the changes in the designation of anthracycline plus cyclophosphamide regimens to "HEC" and the enrollment limited to patients receiving anthracycline plus cyclophosphamide chemotherapy in Akynzeo's dedicated "MEC" trial, the Division considered whether it is appropriate to approve a general CINV indication if a product has only shown efficacy in a development program limited to HEC chemotherapy trials. It seemed reasonable to assume that a product that is effective in HEC would be effective in MEC. The approval history of antiemetics was evaluated to identify examples of products in which efficacy could only be established in the setting of HEC, i.e., the product specifically failed in MEC trials while at the same time "winning" in HEC.

The product labels of Emend (NK-1 inhibitor) and various 5HT3 inhibitors, including Zofran, Aloxi (palonosetron), Anzemet (dolasetron) and Kytril (granisetron) were reviewed and only two products were identified with an indication limited to MEC, i.e., oral dolasetron and oral

Aloxi. Each of those products was only studied in the MEC setting. The review was further complicated by the fact that there are limitations in the HEC/MEC indications related to specific periods of prevention of CINV, i.e., acute vs. delayed phases, based on whether the phase was studied and whether efficacy was established. This issue was relevant to two products, palonosetron and Emend.

The IV palonosetron indication refers to efficacy in both the delayed and acute phases post MEC chemotherapy. However, in the setting of HEC, it is only approved for the acute phase. In contrast, oral palonosetron, which does not carry a HEC indication, has a MEC indication limited to the acute phase. Therefore, for IV palonosetron, efficacy in MEC was actually broader than in HEC (including delayed phase).

Emend carries an indication for both the acute and delayed phases of HEC, but only general wording regarding MEC, i.e., no specific reference to acute and delayed phases for MEC. At the time of initial approval, the primary endpoint for the only MEC study was "overall phase", i.e., the full 0-120 hours post chemotherapy (approximate N= 430 per arm). However, the numerically favorable trends in each secondary endpoint, the acute and delayed phases, were not statistically significant. The individual acute and delayed phase efficacy analyses were statistically significant in the HEC trial. This resulted in the initial differential labeling between HEC and MEC. However, a subsequent study submitted for review post-approval also evaluated Emend in MEC (approximate N=430 per arm), and that second study showed statistically significant improvements in efficacy relative to the control in each of the analyses, acute and delayed phases; the indication was not revised to reflect this.

After considering the trials that supported the specific indications that appeared limited to MEC, the Division concluded we lack persuasive evidence that a product that is effective in HEC would not also be expected to be effective in the setting of MEC. It should be noted that even though the anthracyline/cyclophosphamide (AC) combination was changed from MEC to HEC in the Guidelines, the information provided to support the change suggests that this regimen is not as emetogenic as cisplatin chemotherapy. The lower limit for inclusion in the HEC category is causing vomiting in 90% of patients not treated with antiemetic prophylaxis. However, as stated in the ASCO Guidelines, (www.asco.org/guidelines/antiemetics) the Update Committee changed the emetogenicity category for AC after considering placebo controlled data which indicated 85% of patient treated with AC would be expected to vomit in the absence of antiemetic prophylaxis.

It is of key importance for an antiemetic development program to establish whether a new product is effective in the setting of cisplatin chemotherapy, and it seems reasonable to expect that a product that has been shown to be effective for CINV HEC, should be effective for CINV MEC. The Division concluded that the early more general (historic) approach to CINV labeling that utilized a general statement combined with a qualifier such as, "indicated for the prevention of nausea and vomiting associated with cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy" would be appropriate if a product has been shown to be effective in the setting of cisplatin based chemotherapy. If the product has not been studied in the setting of cisplatin based chemotherapy, or the product failed to demonstrate effectiveness in that setting but was effective in the setting of less emetogenic

drugs, the labeled indication would then need to clearly specify the setting in which it has been shown to be effective, and a limitation of use that states the product has not been studied or was not effective in the setting of cisplatin based chemotherapy could be considered. The latter would be important if the clinical trials supporting approval were limited to AC regimens. Similarly, if the product is only effective in non-anthracycline/cyclophosphamide and non-HEC chemotherapy, the product label would need to specify that information.

The differences in delayed phase efficacy observed in the IV palonosetron trials between the MEC and HEC settings should be considered in assessing future development plans that might propose (b) (4). The differences observed in delayed phase efficacy of IV palonosetron between the HEC (cisplatin) and MEC trials (which primarily enrolled women with breast cancer and the most common chemotherapy regimen studied was likely AC) suggest that these regimens should be studied separately in order to clearly define the full extent of efficacy in the setting of cisplatin chemotherapy.

An additional consideration regarding the Guidelines and labeling relates to the concomitant antiemetic medications administered in the clinical trials supporting product approval. Emend was the first and only product to mention in the Dosage and Administration section that the product should be administered with a 5-HT3 antagonist and a corticosteroid. The Emend label gives specific instructions for dexamethasone dosing on Days 1 and Days 2-4 post chemotherapy in the setting of "HEC". The MEC dexamethasone instructions state it should be administered on Day 1 only (how it was administered in the clinical trials). Similar dexamethasone schedules were utilized in the trials submitted to support this NDA. The ASCO Guidelines state that for HEC, an NK-1 inhibitor should be administered with a 5HT3 on day 1 only and with dexamethasone on days 1-3 or Days 1-4. For MEC, the Guidelines do not recommend use of an NK-1 inhibitor. Instead they recommend palonosetron (due to its long half-life) combined with dexamethasone administered Days 1-3, a dexamethasone regimen that does not appear in approved product labels.

Impact of oral/IV palonosetron labeled indications on Akynzeo's clinical development plan. The proposed combination product combines the NK-1 inhibitor netupitant with the applicant's 5HT3 inhibitor, oral palonosetron. Because the proposed fixed combination contained a product that had been previously approved for specific CINV indications, the established efficacy of oral palonostron had to be considered in determining the trials necessary to support the approval of a product that combines it with a new NK-1 inhibitor. *The applicant proposed to develop the combination product for both HEC and MEC indications, and both acute and delayed phases in each of HEC and MEC.* The previously approved NK-1 inhibitor, Emend, was approved based on add-on studies in combination with a 5HT-3 inhibitor (and dexamethasone).

There were two major issues to address in designing a development plan with this scope of indications for a fixed combination that included oral palonosetron 0.5 mg: 1) oral palonosetron is not indicated for HEC, so the contribution of oral palonosetron to prevention of CINV in the HEC setting would need to be established, and 2) questions were raised regarding whether it would be necessary to establish the role of palonosetron for even the

acute MEC setting in the presence of the NK-1, in light of evidence from Emend trials that NK-1 inhibition increased acute phase response. Additional complexities arose from the sponsor's desire to [redacted] (b) (4) in studies designed to establish the contribution of netupitant. The difference in palonosetron doses [redacted] (b) (4) was anticipated to diminish the ability to delineate the contribution of each product to the combination. The summary of the interactions between the sponsor and FDA regarding the clinical development plan follows below.

Summary of communication between FDA and sponsor regarding the Akynzeo clinical development plan.

At the April 5, 2006, pre-IND meeting, the sponsor asked for comment on whether their plan to not include a netupitant alone arm in their phase 2 dose finding study (netupitant added on to oral palonosetron 0.5 mg in the setting of HEC) would fall short of adequately addressing the Combination Rule. They had concerns that an NK-1 alone arm may be inadequate treatment in the setting of HEC. The Division agreed to the plan. (Note: this refers to Study NETU-07-07, ultimately the key trial submitted to support the HEC indication.)

The sponsor also asked whether it would be adequate to establish noninferiority of oral 0.5 mg palonosetron [redacted] (b) (4) in the setting of MEC to support its use in combination with netupitant in both MEC and HEC settings. The Agency response was limited to saying that it would depend on the data from the noninferiority study, and the HEC/MEC issue was not addressed. FDA ultimately raised this issue as a concern at the End of phase 2 meeting.

In the July 20, 2009 End of Phase 2 meeting, the sponsor proposed the following studies to support Akynzeo approval for acute and delayed CINV in HEC and MEC:

For HEC: 1) Study NETU-07-07 (phase 2 dose finding study of netupitant added to oral palonosetron 0.50 mg, *which is not approved for HEC*) [redacted] (b) (4)

For MEC: 1) NETU-08-18: superiority trial comparing oral palonosetron 0.5 mg plus netupitant combination versus [redacted] (b) (4) palonosetron [redacted] (b) (4) (*the different palonosetron doses raised issues for interpreting netupitant's contribution to treatment effect*).

The meeting minutes reflect that the FDA stated that "more work will be needed for the HEC indication since oral palonosetron is not approved for this indication"**.**

The sponsor asked FDA to confirm that an individual netupitant monotherapy study is not needed to fulfill the Combination Rule requirement. The meeting minutes state, "FDA confirmed that the sponsor's phase 2 study confirmed that netupitant was effective for the proposed indication." However, the Division had not yet reviewed the data and the results would need to be confirmed in NDA review.

The sponsor specifically asked about their plan to bridge the phase 2 study NETU-07-07 "combination test articles" to the phase 3 fixed-dose combination capsule, which would be further bridged to the to-be-marketed fixed-dose combination capsule. FDA stated that for the *in vivo* bioavailability study intended to bridge the phase 2 and 3 trials, the sponsor's plan to (b) (4) the BE criteria for C_{max} based on (b) (4) would be an NDA review issue. The FDA described the requirements for successfully bridging the phase 3 and to-be-marketed formulations, as outlined in the SUPAC guidance. FDA stated that the manufacturing site change determination (regarding "Level") is made on a case by case basis", and FDA lacked adequate information to agree with the sponsor's proposal that the manufacturing site change was a Level (b) (4) and the equipment equivalency was a Level (b) (4) (See Section 3 CMC/Biopharmaceutics of this review.)

The Division told the sponsor that the multi-cycle trial would need to be longer than the proposed 3 cycles, given that netupitant and its metabolites had been detected in dog myocardium. The sponsor agreed not to put an upper limit on cycle numbers and agreed to include additional cardiovascular safety monitoring in the clinical trials, e.g. troponin levels.

Note that in this meeting, the Division agreed that the general design of the proposed MEC study NETU-08-18 was adequate to support approval for MEC, provided the combination demonstrated superiority to (b) (4) palonosetron. The difference in palonosetron doses was raised as a significant concern. The Division agreed to a primary endpoint of overall phase (0-120 hours), with the acute and delayed phases as secondary endpoints, in part because the approved NK-1 Emend was approved based on superiority in the overall phase.

(b) (4)

Also on October 12, 2009, a **SPA request** was submitted for a **MEC study,** NETU-08-18. The sponsor proposed (b) (4)

(b) (4). The Division issued a **SPA No Agreement letter for this request on November 27, 2009**.

1. Similar concerns were expressed regarding the different doses of palonosetron in the two arms. The Division recommended an oral palonosetron control arm.
2. The Division noted that palonosetron is only approved for the acute phase of MEC, and that the eventual product labeling would need to state that the contribution of the palonosetron to the fixed combination in MEC is for the acute phase (0-24 hours). The proposed trial would not establish efficacy of palonosetron in the delayed and overall phases.
3. The above cardiovascular safety monitoring recommendations were repeated.

On **January 22, 2010,** the FDA and sponsor met to discuss the SPA no agreement letters**.** The sponsor proposed the following revised clinical development program:

(b) (4)

NETU 10-10 (New HEC study proposal: Noninferiority trial of 0.5 mg oral palonosetron compared to 0.25 mg IV palonosetron in the setting of HEC, with primary endpoint Complete Response in the acute phase) The sponsor proposed that this study would establish the contribution of the oral palonosetron to the combination with netupitant.

NETU-07-07 (HEC dose finding trial already completed)

NETU-08-18 (MEC trial proposed in the MEC SPA request)

In this meeting:

1. The Division stated it would review the development plan with the Office of Medical Policy (OMP).
2. Regarding the proposed palonosetron (IV vs. oral) HEC noninferiority study (NETU-10-10),
    a. Division stated this trial might serve as an appropriate alternative to adding oral palonosetron arms (third study arm) to other trials to establish the contribution of oral palonosetron to the combination.
    b. Division indicated the proposed 15% noninferiority margin might be accepted, as it had been accepted with past applications; however, further internal discussion was required. FDA pointed out that the prior palonosetron approval based on a noninferiority assessment utilized an adjusted confidence interval due to reliance on a single study. The sponsor stated the adjustment in that trial was due to testing multiple palonosetron doses. FDA reiterated its confidence interval adjustment recommendation.
    c. Division expressed concern about whether a HEC study could be conducted without including an NK-1 inhibitor.

(b) (4)

4. FDA stated, "We agree that the NETU-07-07 study design isolates the effect of netupitant. However, we will need to review the final study results and statistical analysis plan for NETU-07-07 before we can provide comment on whether 300 mg of netupitant was superior in the overall, acute, and delayed phases of CINV-HEC."
5. Regarding MEC study NETU-08-18, the division reiterated its recommendation for an oral palonosetron control arm, but stated it would review this with OMP.
6. The Division agreed with a proposal to eliminate 12-hour troponin samples..

These issues were subsequently discussed with leadership from OMP, and the Division followed OMPs recommendations. This included requiring the applicant to establish the role of oral palonosetron in treatment of HEC, which could be done by performing a noninferiority trial comparing oral palonosetron to IV palonosetron. In addition, the Division wouldn't require an NK-1 only arm to establish the additional contribution of the 5HT3 to prevention of nausea and vomiting. OMP leadership also encouraged the Division and applicant to consider the phase 2 dose finding trial NETU 07-07 an adequate and well controlled trial that had the potential for providing substantial evidence of netupitant's effectiveness in HEC, i.e., a second HEC study wouldn't be necessary.

A **letter dated March 8, 2010** conveyed the advice from the OMP meeting:

1. "Trials PALO-10-XX and NETU-07-07 will be acceptable to support the proposed fixed-dose combination capsule for the prevention of acute and delayed CINV-HEC, provided that we are able, after our review of the trial data, to confirm the outcome you have reported for NETU-07-07, and if the outcome of PALO-10-XX is also positive. Trial (b) (4) does not appear to be necessary.

2. Trial NETU-08-18, which proposes (b) (4) is not acceptable to support the fixed-dose combination capsule for the prevention of acute and delayed CINV-MEC. For trial NETU-08-18 to support the proposed indication, the protocol should be revised to include an active comparator arm of 0.5 mg oral palonosetron HCl. This arm can either be a third arm or replace the proposed (b) (4) arm. Additionally, the primary endpoint can be tested either as a co-primary endpoint consisting of acute and delayed phases, or tested hierarchically with the delayed phase first followed by acute and overall phases, to control Type I error."

The sponsor responded with a follow-up question regarding whether (b) (4) if NETU-07-07 was found non-supportive, presuming NETU-10-XX was successful in establishing noninferiority. The Agency replied in a **letter on March 17, 2010**: "We have concerns regarding reliance on (b) (4) If you have concerns that NETU-07-07 may not be supportive, we again recommend that that (b) (4)

On **March 30, 2010, another SPA request** was submitted for the **MEC** protocol for study NETU-08-18. **A SPA No Agreement** was issued on **May 14, 2010**. Although the sponsor had (b) (4), the FDA couldn't agree with specific aspects of the statistical analysis plan, including a proposal to (b) (4) The Agency couldn't agree, (b) (4)

On **May 4, 2010, a SPA request** was submitted for the sponsor's new palonosetron noninferiority trial (PALO-10-01), which compared oral palonosetron 0.5 mg with IV palonosetron 0.25 mg in HEC. A **SPA no agreement letter** was issued on **June 18, 2010**. The Agency agreed on some aspects of the proposed protocol and disagreed on others.

1. FDA agreed with the primary endpoint of complete response in the first 24 hours.
2. FDA agreed with a 15% noninferiority margin "based on past usage"; however, it recommended type I error should be controlled at a two-sided 1% level, for the results to be considered robust.
3. Sponsor asked for reassurance that the noninferiority study in combination with the phase 2 dose finding study NETU-07-07 would adequately support approval for HEC, in light of the NETU-07-07 population. The sponsor stated: "Completed single cycle study NETU-07-07 was entirely conducted in Russia and the Ukraine and therefore there will be no US patients treated with the combination in the HEC setting in the planned NDA. If PALO-10-01 is successful and if FDA finds the efficacy analyses in FDA's ongoing review of the NETU-07-07 study report to be acceptable, study NETU-07-07 is planned to serve as the sole pivotal trial for purposes of supporting HEC efficacy and safety… (in conjunction with MEC study NETU-08-18 in the planned NDA). NETU-07-07 demonstrated statistical superiority of the combination 300/0.5 mg dose group versus oral palonosetron 0.5 mg alone in the overall (p=0.004), acute (p=0.007) and delayed (p=0.018) phases." FDA replied NETU-07-07 will be acceptable as the sole efficacy trial in acute and delayed CINV-HEC, provided the reviews of NETU-07-07 and PALO-10-01 conclude the data support efficacy and there are sufficient data beyond cycle 4.
4. Sponsor asked about the ability to label for efficacy of repeat cycles in HEC, given that NETU-07-07 was not a repeat dose study. FDA stated, "With regards to repeat cycles, from an efficacy standpoint, this labeling in HEC will rely on the observation in the MEC study. From a safety standpoint, the repeat cycle labeling claim will need to be obtained from HEC and/or MEC."

A **meeting was held July 15, 2010** to discuss the **SPA no agreement** letter issued for **MEC study** NETU-08-18. The sponsor clarified that although most patients would be expected to be treated a maximum of 4 cycles, there would be no treatment limit and some patients would receive more than 4 cycles. In addition, they proposed a new repeat cycle trial that would enroll both HEC and MEC patients receiving unlimited consecutive repeat cycles, NETU-10-29. The Division stated it expected to review more than 100 patients who had been treated

with at least 6 cycles of the combination, for the purposes of safety evaluation, ideally in the setting of a control arm.

Subsequently, **two SPA requests** were submitted on **September 21, 2010**, for:

1) **MEC** trial NETU-08-18 comparing the combination to oral palonosetron
2) **HEC** noninferiority study of palonosetron oral vs. IV

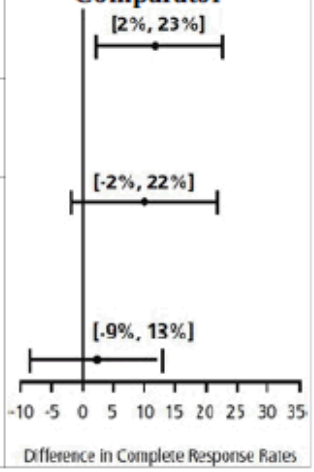
The Agency issued **SPA agreement letters** to each request on **November 3, 2010**. FDA agreed the repeat cycle efficacy demonstrated in NETU-08-18 could support labeling repeat cycle efficacy in both MEC and HEC. FDA agreed to the 15% noninferiority margin for the HEC palonosetron trial, based on the sponsor's plan to use a 99% confidence interval.

Establishing noninferiority margins in CINV antiemetic clinical development has been difficult due to the paucity of placebo-controlled information. In addition, the responder definitions in available placebo controlled trials are not consistent with the definition the Division now considers relevant. The IV palonosetron label indicates the adult acute phase CINV indication for HEC and MEC hinged on noninferiority analyses utilizing a -15% lower bound of the confidence interval for the difference in response between palonosetron and the comparator, utilizing a 2-sided 97.5% confidence interval. The lower bound exceeded -10 in all three trials; in one MEC trial (ondansetron control) it exceeded zero. (Both MEC trials enrolled 70-80% females receiving breast cancer chemotherapy, suggesting AC was the "MEC" regimen.) The following table is reproduced from the IV palonosetron label:

Table 2: Intravenous palonosetron noninferiority analyses

Table 3: Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N[a]	% with Complete Response	*p*-value[b]	97.5% Confidence Interval ALOXI minus Comparator[c]
Moderately Emetogenic	1	ALOXI 0.25 mg	189	81	0.009	[2%, 23%]
		Ondansetron 32 mg I.V.	185	69		
	2	ALOXI 0.25 mg	189	63	NS	[-2%, 22%]
		Dolasetron 100 mg I.V.	191	53		
Highly Emetogenic	3	ALOXI 0.25 mg	223	59	NS	[-9%, 13%]
		Ondasetron 32 mg I.V.	221	57		



a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than -15% demonstrates non-inferiority between ALOXI and comparator.

The Statistical Reviewer for the IV palonosetron NDA summarized the applicant's meta-analysis supporting their proposed noninferiority margin. She identified 4 key trials that compared ondansetron to placebo, which are summarized in the table below. The difference in response rates for ondansetron vs. placebo ranged from 47-70% for MEC. The HEC trial difference was 14% and was exceeded by lowest bound of the confidence interval for the comparison of IV palonosetron to ondansetron or dolasetron.

Table 3: Summary of placebo controlled 5HT3 inhibitor efficacy data

Table 7. Response rates in comparative trials

Study	Active treatment	Response in placebo	Response in active	Difference in rates	Emeto-genicity
Beck et al, 1993	Ondansetron	15/81 (19%)	52/79 (66%)	47%	Moderate
Cubeddu et al, 1990	Ondansetron	0/10 (0%)	7/10 (70%)	70%	Moderate
Cubeddu et al, 1990	Ondansetron	0/14 (0%)	2/14 (14%)	14%	High
Cubeddu et al, 1994	Ondansetron	9/73 (12%)	47/71 (66%)	54%	Moderate

She also considered the placebo response rates from individual studies in the meta-analysis, which ranged 0-50%, with a mean of 17 and standard deviation of 16. For HEC, the placebo mean was 7 with a standard deviation of 10. She summarized her evaluation of the historical data in the context of the palonosetron efficacy results as follows: "….an examination and meta-analysis of results from the anti-emetic literature was carried out. In the few studies where ondansetron or dolasetron was directly compared to placebo, the active treatment reliably out-performed placebo to a greater extent than the difference between treatments in the trials in this application. ….The magnitude of the differences found or modeled in the meta-analysis also was large enough to justify a conclusion of noninferiority of palonosetron in the current trials."

The noninferiority margin of -15% utilized in the IV palonosetron application has been selected by sponsors of other 5HT3 antagonist development plans for their noninferiority analyses. (See reviews of the granisetron patch for review discussions regarding challenges posed by establishing a noninferiority margin. In that review, the confidence intervals around the complete responses observed were also examined relative to the maximum placebo response that may be expected.)

In another **letter dated November 19, 2010**, the Agency responded to questions regarding the Akynzeo repeat course safety study NETU-10-29. The Agency recommended stratified randomization by chemotherapy type (HEC/MEC), and strongly recommended making "every effort to enroll patients who are receiving repeat dose anthracycline containing therapy" to provide repeated dose safety data in the setting of cardiotoxic chemotherapy.

In the April 16, 2013 pre-NDA meeting, FDA noted that NETU 08-18, the sole MEC efficacy trial, utilized AC chemotherapy and discussed the reclassification of AC regimens to HEC with the sponsor. FDA stated that if Aknyzeo was approved, the indication would describe the regimens actually studied in the program. The Division stated it is moving beyond "HEC" and "MEC" classifications. FDA also advised the sponsor that its justification for (b) (4) would be a review issue. FDA noted that if there were few patients with

renal impairment in the clinical dataset, a post marketing study to assess pharmacokinetics in renally impaired subjects would be considered.

3. CMC/Biopharmaceutics

The CMC reviewers determined the applicant had provided sufficient information to assure the identity, strength, purity and quality of the drug product. The Office of Compliance made a recommendation of "Acceptable" for the manufacturing facilities. The reviewers ultimately concurred with final labeling after revision. The CMC and Biopharmaceutics reviewers have recommended approval, and I concur.

The fixed combination product is composed of:

- Three intermediate netupitant tablets (100 mg each)
- One intermediate palonosetron (b) (4) capsule (0.5mg)
- One size 0 hard gelatin capsule consisting of a white body with black imprint "HE1" and a caramel cap.

A certificate from the capsule manufacturer confirmed the gelatin in the capsule meets the recommendations of the FDA (b) (4) Guidance.

The CMC reviewers identified 4 excipients present in the final dosage form that were not listed in the FDA inactive ingredient database for further evaluation by both the CMC and the Pharmacology/Toxicology reviewers. Ultimately, they determined that two of the excipients were in fact in the database and the amount present in the drug product is far lower than the maximum amount cited in the Database (see addendum reviews). They determined there was no safety issue associated with the levels present of either of the two remaining excipients, based on a number of data sources, including the Joint FAO/WHO Expert Committee on Food Additives, the European Food Safety Authority Scientific Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food published findings of safety of sucrose esters of fatty acids, a CFR citation for sodium stearyl fumarate listing it as an entitled Food Additive Permitted for Direct Addition to Food for Human Consumption.

The capsule formulation for netupitant changed between phases 1 and 2. The reviewer stated that the phase 2 capsule formulation "was the basis of the tablet formulation proposed for commercialization and was used in the pivotal Phase 3 trials." The clinical and registration batch manufacturing sites differed, and the applicant provided a "tabular comparison of equipment used at the different sites and a detailed comparison of processing parameters during the manufacturing of INT clinical and registration batches," in accordance with the Q8(R2) Pharmaceutical Development, Manufacturing Process Development guidance. In addition, a bioequivalence study was performed to establish equivalence between the tablet product made by (b) (4) and the tablet made by HPB. The study was reviewed by the ONDQA Biopharmaceutics reviewers. (See below.)

Regarding the finished drug product specification impurities, the CMC reviewer noted that the elemental impurity level acceptance criteria were appropriately set and were less than allowed by USP <232>.

Regarding the impurities identified for netupitant, the CMC reviewer noted that the drug substance specification listed two process impurities, (b) (4) and one

degradation product, [redacted] but none of the other identified degradation products [redacted] were specified. The CMC reviewer noted that for the latter 3 degradation products, which were not specified in the finished drug product specification, none were identified above [redacted] through 24 months of storage, which justified not monitoring these 3. The degradation product [redacted] was observed in the drug product under forced stress conditions and was identified as the main degradation product to be observed during stability. The CMC reviewer noted that the limit set for [redacted] was justified in accordance with ICHQ3A, based on the maximum daily dose of netupitant. Ames testing for two specified impurities, [redacted] revealed no evidence of mutagenic effect. The netupitant drug substance was subjected to *in vivo* and *in vitro* testing, including Ames test, mouse lymphoma tests and micronucleus test in rat bone marrow. The Ames test concluded no evidence of mutagenic effect. The mouse lymphoma cell mutation assay and rat micronucleus test were negative. Additionally, a deductive estimate of risk from existing knowledge (DEREK) assessment was performed on all the potential impurities structurally related to netupitant and no genotoxic alert structure was found. Based on these assessments, the reviewers determined that the impurity limits based on ICH Q3B were acceptable.

Regarding the impurities for the palonosetron component of the drug product, the CMC reviewer noted that the limit for the specified impurity [redacted] was based on the qualification threshold in ICH Q3B for a drug with a maximum daily dose of <10 mg, and that it is the same limit for the currently marketed Aloxi Capsules, which is an identical palonosetron dose. [redacted]. The CMC reviewer noted that since these 3 are process impurities they do not need to be specified impurities in the Akynzeo drug product specification, in accordance with ICH Q3B. An additional degradation product of palonosetron was identified in this submission, [redacted], and it is not monitored in Akynzeo or in the Aloxi capsule marketed product. The CMC reviewer stated in his review, "Since it is not monitored in either the drug substance or in Aloxi capsules, it appears that it has not been observed in any significant amount in the drug substance or drug product on stability." To further evaluate this, he noted that this impurity would be detected as "Single Unspecified Impurities" in the summary results, and examination of those results revealed that "no impurity above LOQ was detected after 24 months storage." Because it does not appear in significant amounts on stability, the CMC reviewers determined that the applicant's decision to not treat it as a specified impurity was justified.

ONDQA Biopharmaceutics. The applicant submitted two bioequivalence studies to provide a bridge between the late phase 1 formulation, phase 3 formulation and the to-be marketed formulation.

Study NETU-09-07 provided an adequate bridge between the late phase 1/ 2 formulations and the phase 3 formulation, both manufactured at Catalent Philadelphia. The initial study product consisted of two netupitant capsules, each containing 150 mg plus a palonosetron 0.5 mg softgel. The subsequent product for phase 3 was the fixed combination capsule containing 300 mg netupitant plus palonosetron 0.5 mg. The reviewers agreed bioequivalence was established in this study.

Study NETU-11-02 provided an adequate bridge between two phase 3 products from two different manufacturing facilities (fixed combination capsule used in development and manufactured in [redacted] vs. commercial site fixed combination product manufactured by HBP in Ireland), i.e., between the two manufacturing sites. Bioequivalence

was established. Dissolution data were also submitted to support bridging. The reviewers found these data further supported bioequivalence. The OSI inspection found the clinical and analytical sites for study NETU11-02 to be satisfactory.

The reviewers also evaluated the dissolution methods and acceptance criteria proposed for both the intermediate and finished fixed combination products.

The Biopharmaceutics reviewers recommended approval. They agreed that the applicant would submit dissolution data from the first five batches of the product following approval as a post approval supplement, and the FDA would reevaluate the netupitant dissolution acceptance criteria.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewers have recommended approval, and I concur. Their labeling recommendations were incorporated, including their recommendation that Akynzeo should have labeling consistent with Pregnancy Category C, based on the netupitant component of this fixed combination product. An increased incidence of external and skeletal abnormalities in rabbit fetuses was observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher (0.2 times the human AUC at the recommended single human dose with each cycle of chemotherapy) during the period of organogenesis. Abnormalities included positional abnormalities in the limbs and paws, and fused sternebrae. 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. The PMHS Maternal Health Team concurred. The reviewers confirmed that the Aloxi product label Section 8.1 Pregnancy Category B remains appropriate.

Netupitant alone was tested in oral toxicity studies of up to 26 weeks in rats and 9 months in dogs. Daily dosing was studied. Netupitant induced phospholipidosis (in liver, lung, and lymphoid tissues) at doses of 10 mg/kg/day or higher in both rats and dogs. The calculated animal to human AUC multiples for netupitant, based on the AUC values associated with exposures to 10 mg/kg/day in both rats and dogs, ranged from 0.4 to 1.8. Oral toxicity studies with the combination of netupitant and palonosetron were performed in rats and dogs for up to 13 weeks. The combination did not produce any additional toxicity as compared with either drug alone. In the one month dog study of netupitant with a 4 week recovery period, phospholipidosis accompanied by inflammation was seen beginning at 15 mg/kg/day (focal liver necrosis was noted in one dog at the 50 mg/kg/day dose). In a dog study of similar duration and recovery period, in which netupitant was combined with palonosetron, hepatic hypertrophy was noted but no necrosis.

The Pharmacology/Toxicology reviewers stated that the "clinical significance of phospholipidosis in these studies is not clear." They noted that animals were dosed daily and human dosing is anticipated to be no more frequent than a dose every 3 weeks, based on the usual scheduling of chemotherapy cycles. The netupitant median half-life in humans (specifically, cancer patients) is 88 hours, so the exposure per 3 week cycle in humans is longer than 24 hours, but is definitely not the daily exposure over multiple weeks that occurred in the animal studies. The available pharmacology/toxicology review of Emend, the currently approved NK-1 inhibitor, does not suggest phospholipidosis is a class effect.

However, in a consult review from Division of Cardiorenal Products' (DCRP) QT Interdisciplinary review team (submitted to IND 73493 on January 26, 2010), a DCRP pharmacologist stated that since another member of the drug class (casopitant) had myocardial necrosis and phospholipidosis observed in nonclinical studies, and hypotension, bradycardia, QT prolongation in nonclinical studies, she raised concern there could be a class effect. She also referred to documented "accumulation" of netupitant and its metabolite in dog myocardium, however, the study was not designed in a way that can identify "accumulation". It appears that she is referring to an increase in myocardial drug levels with increasing dose. On September 22, 2014, Dr. Jacobs provided her review of this issue in a written memo, which stated that there is no evidence of histologic cardiac effects for Akynzeo in any animal study. She concluded that phospholipidosis affecting the heart would be detected by light microscopy and that given the differences in the molecules (netupitant vs. casopitant), a different toxicity profile "is not unexpected". She stated no further nonclinical cardiac studies of netupitant are necessary at this time.

The nonclinical finding of phospholipidosis was considered in evaluating the clinical safety data. See Section 8 Safety of this review; there was no clear safety signal detected associated with netupitant exposure. I further inquired about FDA's experience with how phospholipidosis in nonclinical studies translates into clinical significance in humans. The reviewers stated that Dr. A. Jacobs, the Associate Director in OND IO, concurred that phospholipidosis is a nonspecific finding of uncertain significance. In Dr. Jacobs' September 22, 2014 memo, she stated, "Phospholipidosis commonly occurs with cationic amphophilic drugs of which there are more than 50. Phospholipidosis is not necessarily associated with adverse effects, even when the phospholipidosis persists, and even in the brain." In addition, the reviewer noted that "minimal liver necrosis" in a background of phospholipidosis was detected in only one animal study (oral dosing x 13 weeks in rats), with a margin of 3.4-fold relative to human plasma exposure at the recommended dose. The reviewer noted that there was no liver necrosis noted in the combination studies in animals.

The reviewers confirmed that netupitant did not show mutagenic activity in the Ames test or the in mouse lymphoma cell mutation assay. Netupitant did not significantly increase the frequency of micronucleated polychromatic erythrocytes in bone marrow in the *in vivo* rat micronucleus test. Based on the treatment setting, i.e., intermittent dosing in patients receiving cancer chemotherapy, it was determined a carcinogenicity study should not be required. The decision was based on Executive CAC recommendation/comment. Palonosetron has been subject to a carcinogenicity evaluation. It was positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test. The description of the results of the 104-week carcinogenicity study in mice can be found in the Aloxi product label and will be included in the AKYNZEO label. Palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign/malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma/carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

See Section 10 Pediatrics of this review for a summary of the Pharmacology/Toxicology reviewers' recommendations regarding PREA PMRs.

The Pharmacology/Toxicology and CMC reviewers worked in conjunction to assure that the excipients present in the drug product were adequately qualified, and specifications were appropriate for human safety. The Pharmacology/Toxicology reviewers determined that the excipients identified by CMC for their review were present in amounts that provided reasonable assurance of safety (see Section 3 CMC/Biopharmaceutics). The reviewers entered an addendum review to clarify an error regarding two excipients initially identified as not being present in the FDA Inactive Ingredient Search for Approved Drug Products data base.

5. Clinical Pharmacology

I concur with the Clinical Pharmacology reviewers that there are no outstanding Clinical Pharmacology issues that preclude approval.

An apomorphine challenge study in humans suggested that netupitant plasma concentrations >300 ng/mL were necessary to reduce vomiting relative to placebo. (See Table 4 below for Cmax concentrations of netupitant in healthy subjects.) In the dose finding study, Study 07-07 (key study submitted to support netupitant's efficacy in a setting of cisplatin chemotherapy), there was no significant dose-response relationship for achievement of CR in the delayed phase among the 3 netupitant doses evaluated: 100, 200 and 300 mg. A concentration-response relationship could not be explored because PK was not evaluated in the study.

The median elimination half-life of netupitant in patients with cancer was 88 hours, and 50% and 75% of a radiolabeled netupitant dose was recovered from urine and feces over 120 hours and 336 hours (2 weeks). The majority was recovered in feces (70.7% vs 4% in urine). The fraction of an oral netupitant dose excreted unchanged in urine was <1%. For this reason no dedicated renal impairment study was conducted. The product label will state in Section 8.7 Renal Impairment:

> No dosage adjustment for AKYNZEO is necessary in patients with mild to moderate renal impairment. The pharmacokinetics and safety of netupitant has not been studied in patients with severe renal impairment, although severe renal impairment did not substantially affect pharmacokinetics of palonosetron. The pharmacokinetics for netupitant and palonosetron was not studied in patients with end-stage renal disease requiring hemodialysis. Avoid use of AKYNZEO in patients with severe renal impairment or end-stage renal disease.

The impact of hepatic impairment on netupitant pharmacokinetics was adequately evaluated to support labeling in patients with mild or moderate hepatic impairment. Mean C_{max} increased approximately 30% in both groups, while mean $AUC_{0-\infty}$ increased 56% in mild impairment and 107% in moderate. There were only 2 patients with severe hepatic impairment studied and the C_{max} varied widely between them (63% increase and 463% increase relative to healthy subjects). The product label will state in Section 8.6 Hepatic Impairment:

> No dosage adjustment for AKYNZEO is necessary for patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 8). Limited data are available with

AKYNZEO in patients with severe hepatic impairment (Child-Pugh score >9)/ Avoid use of AKYNZEO in patients with severe hepatic impairment.

Population PK analyses in cancer patients found that C_{max} of netupitant was 35% higher in females than males, but the AUCs were similar. Age did not influence the PK of either netupitant or palonosetron. In dedicated PK studies, the AUC and Cmax of netupitant increased by 25% and 36% in the elderly vs. younger adults. The AUC and Cmax of palonosetron were 37% and 10% higher in the elderly vs. younger subjects.

Table 4 Comparison of Netupitant Systemic Exposure between younger and older subjects after a single AYNZEO dose

Parameter	Young Subjects (22-45 yr)		Elderly Subjects (66-79 yr)	
	N	Mean (SD)	N	Mean (SD)
Cmax [ng/mL]	22	596.4 (233)	12	880.8 (479.2)
AUC_{0-t} [ng.h/mL]	22	17150 (6122)	12	19604 (6747)
$AUC_{0-\infty}$ [ng.h/mL]	22	20039 (8396)	12	24739 (9390)
Vz/F[L]	22	2851 (1633)	12	4101 (5406)
CL/F [L/h]	22	20.5 (10.8)	12	18.7 (12.5)
$T_{1/2}$ [h]	22	101.2 (52.8)	12	129.6 (72.7)

Drug interactions. Neither of the components of this fixed combination product impacted the PK of the other component, i.e., netupitant did not change the PK of palonosetron and palonosetron did not change the PK of netupitant. *In vitro* studies suggested that *in vivo* drug interactions are possible for CYP3A4 enzyme via inhibitory effects of netupitant and its M1 metabolite, while it is unlikely for other CYP enzymes studied *in vitro*. Netupitant is a P-gp and BCRP transporter inhibitor. Palonosetron has been previously shown in *in vitro* studies not to have an impact on these CYP's; however, the effect of palonosetron on CYP2C19 has not been evaluated. There will be a PMC to evaluate netupitant's potential as a P-gp substrate (see below).

With respect to drug interaction clinical studies, I will focus only on the impact of the product on the pharmacokinetics of specific co-administered chemotherapy agents and dexamethasone (drugs metabolized primarily by CYP3A4). Dexamethasone is used concomitantly with NK-1 and 5HT3 inhibitors as part of the antiemetic regimen. Co-administration of Akynzeo and docetaxel resulted in 49% higher mean Cmax and 35% higher AUC of docetaxel. Etoposide's AUC_{0-t} was approximately 21% higher, and the Cmax was not changed. The AUC of cyclophosphamide increased 21% and Cmax was not changed. These data are summarized in the table below, which is reproduced from the Clinical Pharmacology review.

Table5. Docetaxel, Etoposide and Cyclophosphamide Plasma Exposure in Co-administration with Akynzeo (netupitant + palonosetron) or Palonosetron Alone (Reference)

	Cmax ng/ml	AUC0-t h*ng/ml	AUC0-∞ h*ng/ml	Cmax mg/ml	AUC0-t h*mg/ml	AUC0-∞ h*mg/ml	Cmax mg/ml	AUC0-t h*mg/ml	AUC0-∞ h*mg/ml
	Docetaxel with FDC			Etoposide with FDC			Cyclophosphamide with FDC		
n	8	8	6	12	12	9	10	10	10
Mean	3119	5610	5063	18.4	122	111	307	526	533
SD	625	2093	1827	3.5	47.9	21.4	324	408	417
CV (%)	20.1	37.3	36.1	19.1	39.2	19.2	105	77.7	78.2
	Docetaxel with Palonosetron			Etoposide with Palonosetron			Cyclophosphamide with Palonosetron		
n	7	7	3	12	12	10	10	10	10
Mean	2093	3941	4398	17.73	99.3	111	285	476	481
SD	616	1019	1368	2.601	26.5	26.7	334	415	421
CV (%)	29.5	25.8	31.1	14.7	26.7	23.9	117	87.3	87.7

*PK samples were collected up to 24, 36, 48 hr post-dose for etoposide, cyclophosphamide, and docetaxel, respectively.

The clinical meaningfulness of these PK changes was explored by the Clinical reviewers. The docetaxel interaction resulted in the largest changes in chemotherapeutic agent exposure. The Clinical Pharmacology reviewers noted that the changes in docetaxel were consistent with netupitant's classification as a moderate inhibitor of CYP3A4, and the docetaxel product label states that docetaxel dose adjustment is necessary only with co-administration of strong CYP3A4 inhibitors. Co-administration with ketoconazole, a strong CYP3A4 inhibitor, increases docetaxel AUC 120% (2.2 fold). The docetaxel product label says (b) (4) Comparing this to the netupitant interaction data, the magnitude of increase in C_{max} observed in the netupitant study was greater than that observed in the ketoconazole study, however, the impact on docetaxel AUC was markedly greater with ketoconazole compared to netupitant. The Clinical Pharmacology reviewers pointed out that the Drug Drug Interaction Guidance states that designation of inhibition, i.e., strong vs. moderate vs. weak, is based on AUC or CL, not C_{max}.

The clinical trial safety data were explored for evidence that the drug interaction between docetaxel and netupitant impacted safety. The patient numbers are too small to draw definitive conclusions; however, no clear impact on safety was identified. Forty-nine patients were identified who were treated with AKYNZEO and docetaxel. Of those, 19/49 were in a trial that compared Akynzeo to palonosetron (Study 08-18). The remaining 30 were treated in Study 10-29, which compared Akynzeo to aprepitant + palonosetron. In Study 08-18, 19 patients and 13 patients received docetaxel chemotherapy in the Akynzeo and the palonosetron arms, respectively. A numerically higher rate of SAEs was observed in patients receiving palonosetron alone (39%, 5/13) than in the Akynzeo treated patients, (21%, 4/19). In Study 10-29 (comparison of Akynzeo to aprepitant/palonosetron), 5/30 (17%) Akynzeo patients treated with docetaxel had an SAE, compared to 1/5 (20%) of patients in the aprepitant plus

palonosetron arm. The aprepitant label states it is also a moderate CYP3A4 inhibitor, however, it states "oral aprepitant did not influence the pharmacokinetics of docetaxel."

The reviewers also requested analyses of cytopenias based on whether a patient treated with docetaxel was exposed to netupitant. There was no clear evidence of a meaningful impact of the drug interaction, i.e., no persuasive evidence that netupitant resulted in a higher rate of high grade neutropenia or thrombocytopenia when co-administered with docetaxel. Although the rates of Grade 3 and 4 neutropenia were numerically higher in the netupitant group, sample size is too small to support meaningful conclusions. See the tables below, which summarize the hematology data for the docetaxel subgroups in Study 08-18 and Study 10-29.

Table 6: Study NETU-08-18 – Hematology – Grade 3 or 4 changes During Cycle 1 in the Docetaxel treated Subgroup

	NETU/PALO FDC (N=19)		PALO Alone (N=13)	
Parameter	**n**	**(%)**	**n**	**(%)**
Leukocytes: WBC decreased				
Number of patients with result	19		13	
Any severe grade	9	(47.4)	4	(30.8)
Grade 3	1	(5.3)	2	(15.4)
Grade 4	8	(42.1)	2	(15.4)
Neutrophils: neutrophil count decreased				
Number of patients with result	19		13	
Any severe grade	11	(57.9)	5	(38.5)
Grade 3	4	(21.1)	1	(7.7)
Grade 4	7	(36.8)	4	(30.8)
Hemoglobin: anemia				
Number of patients with result	19		13	
Any severe grade	0		0	
Platelets: platelet count decreased				
Number of patients with result	19		13	
Any severe grade	0		0	
Grade 3	0		0	
Grade 4	0		0	

Table 7: Study NETU-10-29 – Hematology – Grade 3 or 4 changes During Cycle 1 in the Docetaxel treated Subgroup

	NETU/PALO FDC (N=30)		Aprepitant/Palo (N=5)	
Parameter	**n**	**(%)**	**n**	**(%)**
Leukocytes: WBC decreased				
Number of patients with result	30		5	
Any severe grade	5	(16.7)	1	(20.0)
Grade 3	4	(13.3)	1	(20.0)
Grade 4	1	(3.3)	0	
Neutrophils: neutrophil count decreased				
Number of patients with result	30		5	
Any severe grade	3	(10.0)	2	(40.0)
Grade 3	1	(3.3)	2	(40.0)
Grade 4	2	(6.7)	0	
Hemoglobin: anemia				
Number of patients with result	30		5	
Any severe grade	0		0	
Platelets: platelet count decreased				
Number of patients with result	30		5	
Any severe grade	0		0	
Grade 3	0		0	
Grade 4	0		0	

The Clinical reviewer presented a pooled analysis of patients exposed to docetaxel across the trials, reproduced below, which doesn't take into consideration the severity of cytopenias or infections. However, the table summarizes the distribution of any SAEs across treatment arm in this subgroup, as well as "serious" diarrhea. There was one case of serious diarrhea in docetaxel exposed patients treated with Akynzeo and none in the other antiemetic arms.

Table 8 SAEs and TEAEs in the Docetaxel chemotherapy subgroup, by treatment arm, across trials.

	Palo IV 0.25 N=13 C=13	Palo OS 0.50 N=37 C=77	FDC N=49 C=196	Apre plus Palo N=5 C=21
Number (%) of pts with at least one SAE	4 (30.8)	5 (13.5)	10 (20.4)	1 (20.0)
Number (%) of pts with any TEAE of interest	2 (15.4)	3 (8.1)	10 (20.4)	-
Anaemia	-	-	5 (10.2)	-
Leukopenia	-	1 (2.7)	7 (14.3)	-
Neutropenia	1 (7.7)	2 (5.4)	6 (12.2)	-
Thrombocytopenia	1 (7.7)	1 (2.7)	4 (8.2)	-
Serious Diarrhoea	-	-	1 (2.0)	-
Infections	1 (7.7)	1 (2.7)	9 (18.4)	-

N = number of patients
C=number of cycles
The percentage is calculated based on N

I also contacted the clinical review group in the Oncology Division that manages docetaxel to confirm that no new safety issue had been identified related to interactions with moderate CYP3A4 inhibitors. The team leader confirmed that there is currently no plan to alter the docetaxel label regarding moderate CYP3A4 inhibitors. The Akynzeo label will state in Section 7.1 Effects of AKYNZEO on Other Drugs:

> *Interaction with chemotherapeutic agents*
> The systemic exposure of chemotherapy agents metabolized by CYP3A4 can increase when administered with AKYNZEO. Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine *[see Clinical Pharmacology)]*. Caution and monitoring for chemotherapeutic related adverse reactions are advised in patients receiving chemotherapy agents metabolized primarily by CYP3A4.

Emend labeling includes dexamethasone dose instructions as part of the Dosage and Administration section because it is part of the overall antiemetic regimen (along with a 5HT3 inhibitor). The Akynzeo efficacy trials included dexamethasone in the antiemetic regimen as well. Like Emend, netupitant increases dexamethasone exposure due to CYP3A4 inhibition. Drug interaction studies determined that the AUC_{0-24} of dexamethasone increased 1.7 fold with coadministration of netupitant. CYP3A4 inhibition persisted after a single netupitant dose for at least 4 days, and the dexamethasone $AUC_{84-\infty}$ was 2.4 higher. Dexamethasone C_{max} increased 1.2 fold on Day1 and 1.7 fold on Day 2 and Day 4. See data summarized in Table 9 below, which is reproduced from the Clinical Pharmacology review. Based on these data, similar to the Emend regimen, the dexamethasone doses administered in the Akynzeo clinical trials were reduced from the usual antiemetic regimen dose to 12 mg (reduced from 20 mg) on Day 1 and to 8 mg once a day (reduced from twice a day) on Days 2-4 (for highly emetogenic chemotherapy). The Dosage and Administration Section of the Akynzeo label will reflect this dexamethasone dosing schedule for cisplatin based chemotherapy. For anthracycline plus cyclophosphamide chemotherapy and non-highly emetogenic chemotherapy, the dexamethasone dose for co-administration will be 12 mg on Day 1 only.

Table 9 Mean Ratio PK Parameters for Dexamethasone with and without concomitant netupitant 300 mg (ratio: with/without)

Day	Pharmacokinetic parameter	Mean Ratio* (%)	90% Confidence Interval* (%)	
			Lower	Upper
Day 1	Cmax (0-24h)	111.0	102.3	120.5
	AUC0-24	171.6	156.7	188.0
Day 2	Cmax (24-36h)	166.3	150.3	184.1
	AUC24-36	243.0	217.7	271.3
Day 4	Cmax (84-108h)	174.9	155.5	196.8
	AUC84-108	238.2	220.7	257.1
	AUC84-inf	243.2	225.7	262.1

Because CYP 3A4 inhibition appeared to persist even by Day 4, and no data were available to document the impact beyond Day 4, the Clinical Pharmacology reviewers requested that the applicant estimate the [I]/Ki for CYP3A4 inhibition by netupitant and its metabolites, beyond Day 4. The estimation suggested that the drug interaction via CYP 3A4 inhibition was less likely on Day 6; however, it could not be entirely ruled out. Based on this, Section 7.1 Effects of AKYNZEO on Other Drugs will state:

> *Dexamethasone*
> A two-fold increase in the systemic exposure of dexamethasone was observed 4 days after single dose of netupitant. The duration of the effect was not studied beyond 4 days. Administer a reduced dose of dexamethasone with AKYNZEO.

In addition, there will be a PMC to evaluate duration of Akynzeo's inhibition of CYP3A4 (see below).

QT evaluation. The Clinical Pharmacology reviewer and QT Interdisciplinary Review Team (IRT-QT) determined there was no significant QTC interval prolongation observed with a combination of netupitant 600 mg and palonosetron 1.5 mg in healthy subjects. (QTIRT consult was entered in DARRTS under IND 73493 in January 2010.) The 600 mg netupitant dose was selected for study based on an assumption that the to-be-marketed dose of netupitant would be 200 mg, i.e., the supratherapeutic dose would be 3-fold higher than the assumed to-be-marketed dose. However, the applicant ultimately chose to develop a higher netupitant dose, 300 mg. Therefore, the supratherapeutic dose studied in the tQT study is 2-fold higher than the to-be-marketed dose. The Clinical Pharmacology reviewers determined that an additional tQT study of a higher netupitant dose (i.e., >600 mg) is not necessary, as the Cmax of the 600 mg dose covers the Cmax observed in patients with moderate hepatic impairment and in healthy subjects coadministered a strong CYP3A4 inhibitor. The upper bound of the confidence interval for the change in QT interval with the 600 mg dose was <10 ms; whereas the upper bound for moxifloxacin 400 mg was 16.3 ms. These data are summarized in the table below, which is reproduced from the Clinical Pharmacology review.

Table 10: Point Estimates and 90% Confidence Intervals for ΔΔQTcF(ms) from tQT Study

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Netupitant/palonosetron (200 mg/0.50 mg)	14	4.4	(1.5, 7.3)
Netupitant/palonosetron (600 mg/1.50 mg)	16	5.9	(2.8, 9.1)
Moxifloxacin 400 mg*	4	13.2	(10.1, 16.3)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 5 timepoints (1, 2, 4, 5, and 6 hours) was 9.2 ms.

Summary. I concur with the Clinical Pharmacology reviewers' labeling recommendations and I concur with their recommendation for the following PMCs:

2769-4 *In vivo* drug interaction study to evaluate the duration of inhibitory effects of Akynzeo (netupitant and palonosetron) on CYP3A4 enzyme activity beyond 4 days after Akynzeo (netupitant and palonosetron) administration.

2769-5 *In vitro* study to evaluate the potential of netupitant to act as a substrate for P-gp transporter in a bi-directional transport assay system.

6. Clinical Microbiology

Not applicable because palonosetron is not an antimicrobial product.

7. Clinical/Statistical-Efficacy

The Clinical and Statistical Reviewers have concluded that the applicant provided substantial evidence of efficacy for the fixed combination product Akynzeo (netupitant plus palonosetron) for the proposed indications for prevention of CINV. The clinical development program was designed with substantive input from FDA to assure there would be adequate evidence to establish the contribution of each component drug to treatment effect. The development program followed what has become a very traditional approach for antiemetic products intended to treat CINV, i.e., separate clinical trials were conducted in the setting of what has been considered HEC and what has been traditionally considered MEC. The Division has requested that trials evaluate efficacy and safety in repeat dosing to support labeling for repeat dosing. The following key trials established the efficacy of Akynzeo, and established the contribution of each of its component drugs to the treatment effect. See Section 2 Background for regulatory history regarding the primary endpoints of key interest to FDA.

Table 11 Overview of Key Trials Providing Efficacy Data for the Netupitant/Palonosetron Fixed Combination (Akynzeo) Program

Trial No.	Design	No. of Patients randomized/treated/FAS	Duration	Indication	Primary Endpoint	Role of Study for efficacy demonstration
NETU-07-07	Double-blind, randomized (1:1:1:1:1) parallel group	PALO oral 136/136/136* PALO + NETU 100 135/135/135* PALO +NETU 200 142/138/137* PALO +NETU 300 143/136/135* Aprepitant +Onda 138/134/-- Total 694/679/543*	Single-cycle	**HEC**	CR Overall phase (0-120 hr) Key endpoint of interest for FDA= CR in delayed phase (25-120 hours)	Key evidence of ***contribution of netupitant to the efficacy*** of Akynzeo in setting of HEC (cisplatin based chemotherapy)
NETU-08-18	Double-blind, randomized (1:1) parallel group	PALO oral 726/725/725 Akynzeo 729/725/724 Total 1455/1450/1449	Single and Multiple cycles	**MEC**$^{\partial}$	CR Delayed phase (25-120 hr)#	Pivotal evidence of FDC efficacy in MEC
NETU-10-29	Double-blind, randomized (3:1) parallel group	Akynzeo 309/308/309 Aprepitant + PALO oral 104/104/103 Total 413/412/412	Multiple cycles	MEC and HEC	Safety	Supportive Evidence of multicycle efficacy in MEC and HEC
PALO-10-01	Double-blind, randomized (1;1) parallel group	PALO **oral** 371/370/369 PALO **IV** 372/369/369 Total 743/739/738	Single-cycle	**HEC**	CR Acute phase (0-24 hr)	Establishes oral palonosetron efficacy in HEC and its contribution to Akynzeo treatment effect in HEC

*For NETU-07-07 the numbers of patients are randomized/number treated/MFAS
Key secondary endpoints: CR acute phase (0-24 hr), overall phase (0-120 hr)
∂ The chemotherapy administered in this study was anthracycline plus cyclophosphamide
Akynzeo= Netupitant/Palonosetron Combination Capsule (palonosetron 0.50 mg/netupitant 300 mg)
Dexamethasone was included in all dose regimens.

Refer to the Statistical and Clinical reviews for more detailed information regarding the FDA's evaluation of the efficacy data from these trials. I will focus on a few key review issues.

Study 07-07 established the contribution of netupitant to efficacy in the setting of cisplatin based chemotherapy. The major efficacy issue was evaluation of the impact of the study conduct issues identified by the applicant at Site 120. This trial was originally designed as a netupitant dose ranging trial to identify the phase 3 dose. When FDA noted this trial had the potential to establish the contribution of the netupitant component of Akynzeo to its efficacy in the setting of cisplatin based chemotherapy, HEC, the applicant further audited the trial sites. Protocol deviations at Site 120 raised concerns that caused the applicant to present the efficacy data from Study 07-07 with and without inclusion of that site. The applicant determined that elimination of Site 120 data did not impact the statistically significant efficacy results favoring the combination in the 300mg + palonosetron 0.5 mg arm relative to palonosetron 0.5 mg. The FDA Statistical reviewer didn't agree and found that when the data were analyzed with methods considered appropriate by FDA, the analysis that excluded Site 120 was not statistically significant favoring the combination. This difference in conclusions prompted multiple sensitivity analyses which produced varying outcomes, some with statistically significant results favoring the combination and some not.

In order to understand the importance of inclusion/exclusion of Site 120 for the purposes of understanding the strength of evidence provided by this trial, the Clinical reviewers requested detailed information on the violations that had caused the applicant's concerns. There were 3 violations in the palonosetron only arm considered major by the applicant and 10 minor. In the netupitant 300 mg plus palonosetron arm, there were also 3 major and 15 minor violations. The Clinical reviewers found that the major violations were related to co-administration of another antiemetic and the minor violations were related to a patient having taken a prior dose of dexamethasone within the study window prior to entry, a period when a patient was not to have received dexamethasone.

The reviewers confirmed with the applicant that these patients with dexamethasone violations had still received the dexamethasone dose they should have received as part of antiemetic therapy. Based on this, these minor violations would not be expected to have a significant efficacy effect. The vast majority of concomitant antiemetic violations were concomitant administration of ondansetron on Day 1 of chemotherapy. I concur with the Clinical reviewers' conclusions that co-administration of another 5HT-3 inhibitor on Day 1 of chemotherapy would not be expected to impact efficacy. Even if it had a theoretical psychological effect on patients, this effect would be expected to be limited to the first 24 hours (prior to the delayed phase, the primary period of interest for the NK-1 component). It is also important to note that there were equal numbers of these violations in the two arms of interest. (There was a numerically higher number of major violations, i.e., 5, in the 200 mg netupitant arm; however this arm was not the focus of the efficacy analysis.)

Ultimately, the reviewers concurred that the full analysis set, without exclusion of Site 120, was most appropriate for efficacy analysis of Study 07-07. This analysis established the efficacy of netupitant in the delayed and acute phases in the setting of cisplatin chemotherapy. The analysis that includes Site 120 will be presented in product labeling (see table below).

Table 12 Proportion of Patients Responding by Treatment group and Phase in Study 07-07

	AKYNZEO 300 mg netupitant/ 0.5 mg palonosetron N=135 %	Palonosetron 0.5 mg N=136 %	p-value*
COMPLETE RESPONSE			
Delayed Phase†	90.4	80.1	0.032
Acute Phase‡	98.5	89.7	0.002
Overall Phase§	89.6	76.5	0.003

*Adjusted p-values for multiple comparisons using Cochran-Mantel-Haenszel test, stratified by gender.
†Delayed phase: 25 to 120 hours post-cisplatin treatment.
‡Acute phase: 0 to 24 hours post-cisplatin treatment.
§Overall: 0 to 120 hours post-cisplatin treatment.

Study 08-18 established the contribution of netupitant to efficacy of Akynzeo in the delayed and acute phases, in the setting of anthracycline plus cyclophosphamide (AC) chemotherapy. The latter has been traditionally designated MEC in previous CINV development plans, including oral palonosetron 0.5 mg. Palonosetron 0.5 mg is a component (in addition to netupitant) of Akynzeo. Therefore, Study 08-18 was adequate to establish the contribution of each component of Akynzeo for this chemotherapy regimen. The efficacy data from Study 08-18 are summarized in the table below.

Table 13: Proportion of Patients Responding by Treatment Group and Phase – Cycle 1 in Study 08-18

	AKYNZEO 300 mg netupitant/ 0.5 mg palonosetron N=724 %	Palonosetron 0.5 mg N=725 %	p-value*
PRIMARY ENDPOINT			
COMPLETE RESPONSE			
Delayed Phase†	76.9	69.5	0.001
MAJOR SECONDARY ENDPOINTS			
COMPLETE RESPONSE			
Acute Phase‡	88.4	85.0	0.047
Overall Phase§	74.3	66.6	0.001

*p-value from Cochran-Mantel-Haenszel test, stratified by age class and region.
‡Acute phase: 0 to 24 hours after anthracycline and cyclophosphamide regimen.
†Delayed phase: 25 to 120 hours after anthracycline and cyclophosphamide regimen.
§Overall: 0 to 120 hours after anthracycline and cyclophosphamide regimen.

Study 10-10 established the contribution of the oral palonosetron 0.5 mg component of Akynzeo to its efficacy in the setting of cisplatin based chemotherapy. This trial was necessary because oral palonosetron does not carry a HEC indication. This noninferiority trial in the setting of cisplatin based chemotherapy (≥70 mg/kg) compared oral palonosetron 0.5 mg to IV

palonosetron 0.25 mg. IV palonosetron 0.25 mg does have an indication for prevention of CINV in the acute phase in the setting of cisplatin based chemotherapy. Noninferiority of oral palonosetron to IV palonosetron was established for the acute phase in this trial. The applicant's delayed phase noninferiority analysis was not considered valid and relevant as the treatment effect of palonosetron IV in the delayed phase has not been established in the setting of cisplatin based chemotherapy. In the oral palonosetron arm, 89.4% of patients achieved a CR in the acute phase compared to 86.2% of patients in the intravenous palonosetron arm, with a difference of 3.21% (99% CI: -2.74% to 9.17%). Non-inferiority of oral palonosetron versus intravenous palonosetron was demonstrated since the lower limit of the two-sided 99% CI for the difference in proportions of patients with CR was greater (i.e., closer to zero) than the pre-defined non-inferiority margin set at -15%.

Efficacy with repeat dosing. I agree with the reviewers that the data from Study 10-29 and the repeat dose data from Study 08-18, support the efficacy of Akynzeo in repeated cycles of chemotherapy.

Special population exploratory analyses. In the course of evaluating the special population subset analyses for purposes of product labeling, it was noted that the applicant had utilized an age cut point of 55 years, which is not the cut off utilized for inclusion in Section 8.5 Geriatric Use. It appeared the applicant had focused on age 55 years for subgroup analysis because publications in the literature report differences in propensity for CINV in individuals younger than 55 years relative to those older. I will summarize the efficacy data by age for each age cut point (55 or 65 years) for Study 08-18, Study 07-07 and Study 10-10 below. There appeared to be a difference in efficacy for older patients in the setting of AC chemotherapy (Study 08-18) compared to younger patients, in both the 55 year and the 65 year cut point analyses. Older patients seemed to demonstrate a lower netupitant treatment effect in the delayed phase, and the diminution appeared to be related to a higher palonosetron delayed phase response in the older patients.

Table 14: Study 08-18 (AC Chemotherapy) Efficacy Analysis by Age: 55 year Cut point Age analysis

	NETU/PALO FDC(N=724)	**PALO alone(N=725)**
Age <55 Years	N=371	N=372
Complete Response Cycle 1 Delayed Phase (25-120 hours)		
Responder, n (%)	279 (75.2%)	232 (**62.4%**)
Difference from PALO alone, %	**12.8%**	
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	313 (84.4%)	295 (79.3%)
Difference from PALO alone, %	5.1%	
Complete Response Cycle 1 Overall Phase (0-120 hours)		
Responder, n (%)	266 (71.7%)	217 (29.9%)
Difference from PALO alone, %	41.8%	
Age >=55 Years		
Complete Response Cycle 1 Delayed Phase (25-120 hours)	N=353	N=353
Responder, n (%)	278 (78.8%)	272 (**77.1%**)
Difference from PALO alone, %	**1.7%**	
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	327 (92.6%)	321 (90.9%)
Difference from PALO alone, %	1.7%	

Complete Response Cycle 1 Overall Phase (0-120 hours)		
Responder, n (%)	272 (77.1%)	266 (75.4%)
Difference from PALO alone, %	-3.7%	

Note: The sponsor indeed conducted the analysis for the delayed phase and the results were the same as shown.

Table 15: Study 08-18 Efficacy Analysis by Age 65 year Cut Point Age analysis:

	NETU/PALO	PALO alone
Age <65 Years	N=608	N=602
Complete Response Cycle 1 Delayed Phase (25-120 hours)		
Responder, n (%)	463 (76.2%)	405 (**67.3%**)
Difference from PALO alone, %	**8.9%**	
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	531 (87.3%)	503 (83.6%)
Difference from PALO alone, %	3.8%	
Complete Response Cycle 1 Overall Phase (0-120 hours)		
Responder, n (%)	446 (73.4%)	386 (64.1%)
Difference from PALO alone, %	9.2%	
Age >=65 Years		
Complete Response Cycle 1 Delayed Phase (25-120 hours)	N=116	N=123
Responder, n (%)	94 (81%)	99 (**80.5%**)
Difference from PALO alone, %	**0.5%**	
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	109 (94.0%)	113 (91.9%)
Difference from PALO alone, %	2.1%	
Complete Response Cycle 1 Overall Phase (0-120 hours)		
Responder, n (%)	92 (79.3%)	97 (78.9%)
Difference from PALO alone, %	0.4%	

Study 07-07: cisplatin based chemotherapy

In contrast, in the setting of cisplatin based chemotherapy, i.e., Study 07-07, there was an apparent difference in efficacy based on age that varied depending on the age cut point used for analysis. When 65 years was the cut point, the dose response in efficacy attributable to netupitant in the delayed phase appeared to be limited to the elderly population. Note that the sample sizes are quite small, particularly in the older age groups in the 65 year cut point analysis. In both analyses (55 and 65 years), there was an apparent difference between the older and younger subgroups in the point estimate for delayed phase complete response (i.e., higher rate in the older than younger subgroup within each cut point analysis). However, this was not seen in the age subgroup exploratory analysis of the delayed phase of Study 10-01 (see later presentation of Study 01-01 age analysis), a trial in which patients were also treated with cisplatin.

Table 16: Study 07-07 Efficacy Analysis by Age: 55 year Cut point Age analysis

	PALO alone (N=136)	PALO+NETU 100 mg (N=135)	PALO+NETU 200 mg (N=142)	PALO+NETU 300 mg(N=143)
Age < 55 Years	N=67	N=63	N=67	N=73
Delayed Phase (25-120 hours)				
Number (%) of Subjects	50 (74.6%)	55 (87.3%)	59 (88.1%)	66 (90.4%)
Difference from PALO alone		12.7%	13.5%	15.8%
Acute Phase (0-24 hours)				
Number (%) of Subjects	58 (86.6%)	59 (93.7%)	58 (86.6%)	71 (97.3%)
Difference from PALO alone		7.1%	0%	10.7%
Overall Phase (0-120 hours)				
Number (%) of Subjects	47 (70.1%)	54 (85.7%)	54 (80.6%)	65 (89.0%)
Difference from PALO alone		15.6%	10.5%	18.9%
Age >=55 Years	N=69	N=72	N=70	N=62
Delayed Phase (25-120 hours)				
Number (%) of Subjects	59 (85.5%)	67 (93.1%)	66 (94.3%)	56 (90.3%)
Difference from PALO alone		7.6%	8.8%	4.8%
Acute Phase (0-24 hours)				
Number (%) of Subjects	64 (92.8%)	67 (93.1%)	69 (98.6%)	62 (100%)
Difference from PALO alone		0.3%	5.8%	7.2%
Overall Phase (0-120 hours)				
Number (%) of Subjects	57 (82.6%)	64 (88.9%)	66 (94.3%)	56 (90.3%)
Difference from PALO alone		6.3%	11.7%	7.7%

Table 17: Study 07-07 Efficacy Analysis by Age: 65 year Cut point Age analysis

	PALO alone	PALO+NETU 100 mg	PALO+NETU 200 mg	PALO+NETU 300 mg
Age < 65 Years	N=116	N=112	N=117	N=115
Delayed Phase (25-120 hours)				
Number (%) of Subjects	91 (78.4%)	101 (90.2%)	106 (90.6%)	102 (88.7%)
Difference from PALO alone		11.7%	12.2%	10.2%
Acute Phase (0-24 hours)				
Number (%) of Subjects	104 (89.7%)	104 (92.9%)	107 (91.5%)	113 (98.3%)
Difference from PALO alone		3%	1.8%	8.6%
Overall Phase (0-120 hours)				
Number (%) of Subjects	87 (75%)	98 (87.5%)	101 (86.3%)	101 (87.8%)
Difference from PALO alone		12.5%	11.3%	12.8%
Age >=65 Years	N=20	N=23	N=20	N=20
Delayed Phase (25-120 hours)				
Number (%) of Subjects	18 (90%)	21 (91.3%)	19 (95%)	20 (100%)
Difference from PALO alone		1.3%	5%	10%
Acute Phase (0-24 hours)				
Number (%) of Subjects	18 (90%)	22 (95.7%)	20 (100%)	20 (100%)
Difference from PALO alone		5.7%	10%	10%
Overall Phase (0-120 hours)				
Number (%) of Subjects	17 (85%)	20 (87%)	19 (95%)	10 (100%)
Difference from PALO alone		2%	10%	15%

Study 10-01: Noninferiority trial in cisplatin based chemotherapy setting.
In the IV palonosetron 0.25 mg vs. oral palonosetron 0.5 mg trial, when the younger age cut point was used there is a sizeable numerical difference between arms favoring the oral dose form in the younger age group relative to the older group. This difference diminished in the analysis that used 65 years as the cut point.

Table 18 Statistical Reviewer's Subgroup Analysis Results for CR in the Acute Phase on FAS Population for Study PALO-10-01

	Oral PALO (N=369)	I.V. PALO (N=369)
Age <55 Years	N=124	N=127
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	107 (86.3%)	98 (77.2%)
Difference from PALO alone, %	9.1%	
Age >=55 Years	N=245	N=242
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	223 (91%)	220 (90.9%)
Difference from PALO alone, %	0.11%	

Table 19 Statistical Reviewer's Subgroup Analysis Results for CR in the Acute Phase on FAS Population for Study PALO-10-01

	Oral PALO (N=369)	I.V. PALO (N=369)
Age <65 Years	N=272	N=281
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	243 (89.3%)	238 (84.7%)
Difference from PALO alone, %	4.6%	
Age >=65 Years	N=97	N=88
Complete Response Cycle 1 Acute Phase (0-24 hours)		
Responder, n (%)	87 (89.7%)	80 (90.9%)
Difference from PALO alone, %	-1.2%	

The following 65 year cut point data from the exploratory analysis of the delayed phase in Study 10-01 provides point estimates of response to oral palonosetron in the delayed phase in the setting of cisplatin based chemotherapy for purposes of comparison to the oral palonosetron delayed phase results from Study 07-07 above. The response rates in the subgroup older than 65 years in Study 10-01 are very similar to its <65 years subgroup, and are similar to the point estimates associated with the <65 years subgroup of Study 07-07 treated with palonosetron alone.

Table 20. Exploratory Subgroup Analysis Results for CR in the Delayed Phase of Study PALO-10-01 using a 65 year cut point

	Oral PALO (N=369)	I.V. PALO (N=369)
Age <65 Years	N=272	N=281
Complete Response Cycle 1 Delayed Phase (25-120 hours)		
Responder, n (%)	208 (76.5%)	212 (75.4%)
Difference from PALO alone, %	1%	
Age >=65 Years	N=97	N=88
Complete Response Cycle 1 Acute Phase (25-120 hours)		
Responder, n (%)	73 (75.3%)	64 (72.7%)
Difference from PALO alone, %	2.5%	

Section 8.5 Geriatric Use of the label will state:

> Of the 1169 adult cancer patients treated with AKYNZEO in clinical studies, 18% were aged 65 and over, while 2% were aged 75 years and over. The nature and frequency of adverse reactions were similar in elderly and younger patients. Exploratory analyses of the impact of age on efficacy were performed in the two trials that compared AKYNZEO to palonosetron *[see Clinical Studies]*. In Study 1 in patients treated with cisplatin chemotherapy, among the patients less than age 65 years, 116 were treated with palonosetron alone and (b) (4) were treated with AKYNZEO. Among the patients 65 years or older, 20 were treated with palonosetron alone and 20 were treated with AKYNZEO. The difference in Complete Response (CR) rates between palonosetron alone and AKYNZEO was similar between the two age groups in both the acute and delayed phases. In Study 2 in patients treated with anthracycline plus cyclophosphamide chemotherapy, among the patients less than age 65 years, 602 were treated with palonosetron alone and 608 were treated with AKYNZEO. Among the patients 65 years or older, 123 were treated with palonosetron alone and 116 were treated with AKYNZEO. The difference in CR rates between AKYNZEO and palonosetron alone (4% in <65 years and 2% in ≥65 years) was similar between the two age groups in the acute phase. In the delayed phase, the difference in CR rates between AKYNZEO and palonosetron alone (9% in <65 years and 1% in ≥ 65 years) was numerically higher in patients <65 years. This difference between age groups in the delayed phase of Study 2 may be explained, in part, by higher CR in the delayed phase associated with palonosetron alone in the older age group (81%) relative to the younger patients treated with palonosetron alone (67%).

Summary.
The applicant has established the efficacy of Akynzeo for acute and delayed phases of CINV. The trials submitted for review establish the contribution of each component to the proposed indication. Palonosetron contributes to prevention of CINV in the acute phase. The netupitant component contributes to prevention of CINV in both the acute and delayed phases.

As discussed in Section 2 Background of this review, in light the changes in designation of doxorubicin plus cyclophosphamide chemotherapy to HEC, the indication will state:

> AKYNZEO 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 is an oral combination of palonosetron and netupitant: palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

8. Safety

The NDA included 1538 patients and healthy volunteers who had been exposed to Akynzeo, including 1169 who had been exposed in the setting of one of 3 active controlled trials. Among those patients, 782 had been exposed to at least 4 cycles, 321 were exposed for at least 6 cycles. (Dr. Snow's review contains a table that states 317 patients were exposed for at least 6 cycles, however, the ISS reflects that 321 patients were exposed to Akyzneo for at least 6 cycles. The applicant clarified that the table in Dr. Snow's review refers to completion of an entire chemotherapy cycle and the ISS counts exposure to Akynzeo at the beginning of the cycle. For this reason the product label will reflect 321.) The maximum number of cycles patients received in Study 08-18 was 8 (n=3). In Study 10-29, the maximum number of cycles of exposure was 14 (n=1). Although these numbers do not represent analyses based on time exposed, e.g., X number treated for 1 year, the product is administered intermittently with chemotherapy cycles, which are usually scheduled on a every 3 or 4 week basis. Section 6 of the Emend product label indicates that the maximum number of exposures in the trials supporting its approval ranged from 4 to 6 cycles. The reviewers identified no safety issues that precluded approval or prompted a recommendation to require a postmarketing safety study/trial (PMR) or a REMS.

A particular challenge in the safety review of antiemetics for CINV is that patients are treated with concomitant chemotherapeutic agents that have significant associated toxicities. For this reason, even numeric imbalances of specific events between the Akynzeo arm and a control arm are difficult to attribute to study drug, as the imbalance could merely reflect a random imbalance in one of many wide ranging toxicities associated with chemotherapeutic agents and/or the underlying malignancy. The applicant proposed to (b) (4) The review team concluded that given the potential differences between the populations studied in the randomized, controlled trials (including underlying malignancy) and the chemotherapy regimens studied in each trial (AC in 08-18; cisplatin in Study 07-07 and Study 10-01), the safety data in the label should be presented separately by trial. In addition, the reviewers recommended that, consistent with FDA Guidance, the (b) (4) should not be the sole basis for inclusion of events. Instead, the reviewers recommended that the events reported at a higher rate in the Akynzeo arm than the control arm (palonosetron in Study 07-07 and Study 10-01) should be reported in the label's Section 6.

Because the product is a fixed combination of netupitant and palonosetron, the review team recommended including the safety data from the noninferiority trial Study 10-10, which only evaluated palonosetron (IV vs. oral).

I will limit my review discussion to two specific safety issues, cardiac safety and hepatic safety data. Refer to the Clinical and CDTL reviews for a more comprehensive summary of the safety data presented in this NDA.

Cardiac Safety. The Agency was aware of nonclinical data in another (different) NK-1 inhibitor development program that demonstrated cardiac necrosis. This was <u>not</u> noted in the

nonclinical studies of netupitant; however, there were nonclinical data available that documented drug levels in the myocardium of dogs. As noted in Section 2 Background of this review, the Division recommended that repeat dosing of Akynzeo should be evaluated in the setting of a control arm, and should specifically be evaluated in the setting of cardiotoxic chemotherapy to permit assessment of a signal of potential additive/synergistic cardiotoxicity.

Study 08-18, was a multicycle study that included doxorubicin chemotherapy. The applicant evaluated baseline ECGs, cardiac ejection fractions and troponin levels. These were repeated at end of study to evaluate for changes and differences between study arms. There was no definitive signal noted. There was no clear difference between arms in cardiac treatment emergent adverse events. See table below, which is reproduced from the Clinical Review.

Table 21. Cardiac treatment emergent adverse events in Study 08-18

	Akyzneo	Palonosetron
	N=197	N=191
Cardiac Disorder		
Arrhythmia	5 (2.5%)	3 (1.6%)
Atrial Fibrillation	1 (0.5%)	0
Cardiac failure	0	1 (0.5%)
Cardiomyopathy	1 (0.5%)	1 (0.5%)
Cytotoxic cardiomyopathy	1 (0.5%)	
Metabolic cardiomyopathy	0	1 (0.5%)
Tachycardia	1 (0.5%)	0

In the multi-cycle study that compared Akynzeo to aprepitant plus palonosetron, Study 10-29, there was also no cardiac signal noted. Treatment emergent events in similar categories to those identified by the Clinical reviewer for Study 08-18 are summarized in the table below, which is derived from the applicant's study report Table 14.3.1.1.2.1.

Table 22. Cardiac treatment emergent adverse events in Study 10-29

	Akyzneo	Aprepitant/palonosetron
	N=308	N=104
Cardiac Disorder		
Atrial Fibrillation	2 (0.6%)	0
Cardiopulmonary failure	3 (1%)	0
Cardiac arrest	1 (0.3%)	0
Myocardial ischaemia	3 (1%)	1 (1%)
Metabolic cardiomyopathy	1(0.3%)	1 (1%)
Tachycardia	5 (1.6%)	3 (3%)
Sinus tachycardia	7 (2.3%)	2 (1.9%)

Evaluation of ECG changes over multiple cycles revealed no evidence of meaningful differences between the two arms. There was a numerically higher rate of sinus tachycardia (25% vs. 21%), ectopic supraventricular rhythm (2% vs. 1 %), premature atrial complexes (12% vs. 10%, first degree AV block (7% vs. 5%), and flat T waves (34% vs. 30%) in the

Akynzeo group in a summary analysis of ECG changes that were noted in at least 1% or greater.

Left ventricular ejection fractions were assessed at baseline and at end of study in Study 08-18. The change from baseline in EF, based on medians from MUGA, was similar between arms:- 4.45% in the Akynzeo arm and -5.0% in the palonosetron arm.

Troponin monitoring was performed in both multi-cycle trials, i.e., Study 08-18 and Study10-29. All patients in Study 08-18 and some patients in Study 10-29 received anthracycline chemotherapy. Troponin levels were obtained during screening for cycle 1 and on days 2 and 6 of each subsequent cycle. If a cTNI level ≥0.12 ng/ml was detected, patients had a cardiovascular functional assessment. If the cTNI was ≥0.5 ng/mL a functional assessment was performed and the patient was withdrawn from study. The following table, reproduced from the Clinical review, is an integrated summary of the troponin data from these two controlled, multi-cycle trials. No difference was noted between Akynzeo and the controls.

Table 23 Proportions of Patients with Documented Troponin Elevations in the Multicycle Controlled Trials – All Cycles.

Troponin	NETU/PALO 300/0.5mg N=1033 n (%)	PALO 0.05mg N=725	Aprepitant+Palo N=104	Total
≥ 0.12 ng/mL and < 0.5 ng/mL	28 (2.7)	17 (2.3)	2 (1.9)	47 (2.5)
≥0.5 ng/mL	5 (0.5)	5 (0.7)	1 (1.0)	11 (0.6)

Ref: Summary Clinical Safety, Table 31, p.129.

The Clinical reviewer noted that most patients who had an elevated troponin level did not have a significant change in cardiac function, defined as change in ejection fraction <10%. There were 6 patients in Study 08-18 who had an elevated troponin and a change in LVEF of ≥10% - 4 treated with Akynzeo and 2 with palonosetron alone. The Akynzeo arm patients were detected at Cycle 6 of chemotherapy or "post withdrawal," while the palonosetron patients were detected at Cycle 5. The largest change occurred in an Akynzeo treated patient, whose ejection fraction (EF) dropped 39% to an EF of 21%. The lowest documented EF in the palonosetron treated patients who had an elevated troponin value was 47%, in a patient whose EF dropped 22%. There was only one patient in the multi-cycle trial NETU10-29 with a significant drop in EF and a concurrent troponin elevation, and this occurred on the aprepitant arm. See the table below, which is reproduced from the Clinical review.

Table 24 Patients with Both Elevated Troponin and Decrease in LVEF of ≥10 in Study 08-18 and Study 10-29.

Study	Arm	Cycle	Measured value (%)	Change from B/L
NETU-08-18	NETU/PALO FDC	6	21	-39
NETU-08-18	NETU/PALO FDC	6	56	-10
NETU-08-18	NETU/PALO FDC	6	50	-20
NETU-08-18	Palo alone	5	47	-22
NETU-08-18	Palo alone	5	54	-14
NETU-08-18	NETU/PALO FDC	Post withdrawal	56	-13
NETU-10-29	Aprep/Palo	Post withdrawal	30	-25

Ref: Reviewer's table

Hepatic safety. Evaluation of liver safety was of particular interest in light of the netupitant non-clinical study findings of phospholipidosis. In her review of laboratory abnormalities in the safety database, the Clinical reviewer stated that there "were no major differences in laboratory findings between treatment groups for hematology or chemistry, as shown in Table 83." That table includes ALT, AST and Alkaline phosphatase across the major trials. The relevant section of the table is reproduced below.

Table 25. Summary of Elevated Transaminases across the randomized controlled trials.

	Netupitant/ Palonosetron 300/0.50 mg (N=1033) n (%)	Palonosetron 0.50 mg (N=725) n (%)	Aprepitant plus Palonosetron (N=104) n (%)	TOTAL (N=1862) n (%)
Number of patients with new laboratory abnormality	159 (15.4)	101 (13.9)	18 (17.3)	278 (14.9)
ALT increased	13 (1.3)	12 (1.7)	–	25 (1.3)
Grade 3	13 (1.3)	12 (1.7)	–	25 (1.3)
AST increased	9 (0.9)	5 (0.7)	–	14 (0.8)
Grade 3	8 (0.8)	5 (0.7)	–	13 (0.7)
Grade 4	1 (0.1)	–	–	1 (0.1)
Alkaline phosphatase increased	4 (0.4)	1 (0.1)	–	5 (0.3)
Grade 3	4 (0.4)	1 (0.1)	–	5 (0.3)

As summarized in the CDTL review, patients were identified in the controlled clinical trials with transaminase and bilirubin elevations that were consistent with drug induced liver injury (DILI). The applicant had a consultant review the cases and that report has been reproduced, nearly in its entirety, in the CDTL review. I have summarized the tabulations of cases from that report, by treatment arm, below. The cases included patients who were exposed to palonosetron alone and Akynzeo (which contains palonosetron as a component). Based on this, it was difficult to attribute a causal relationship with netupitant. The applicant's consultant concluded that it was difficult to distinguish the potential contribution of the antiemetics to these events vs. concomitant chemotherapy, or other concomitant medications.

In Study 07-07 (cisplatin based chemotherapy), there were seven cases of "possible or probable" DILI, as designated by the applicant's expert:

Palonosetron only =1/136 (0.7%)
Palo plus netupitant 100mg, 200mg, or 300mg =5/135; 1/138; 1/136 = 5/410 (1.2%)
Aprepitant plus ondansetron= 1/134 (0.8%)

The following table summarizes the magnitude of elevation of transaminase across the treatment groups, for those elevations that were at least 5 X ULN. With that cut point, the distribution was similar across treatment arms.

	Palonosetron	Netup+Palo	Aprepitant + Ondansetron
At least 5x ULN	1/136 (0.7%)	3 (0.7%)	1 (0.8%)
At least 10X ULN	1/136 (0.7%)	3 (0.7%)	1 (0.8%)

It should be noted that one of the patients who received netupitant 300 mg +palonosetron and experienced a transaminase elevation that exceeded 10X ULN had a normal bilirubin. All decreased, but didn't completely normalize, by day 6 with no further follow up, with the exception of two cases:

One Netup/palo patient, had an increase on Day 6 with no further f/u
One Netup/palo patient had documented resolution on Day 14

In Study 08-18 (AC chemotherapy), there were five cases of "possible or probable" (N=3) and "unlikely" (N=2) DILI, as designated by the applicant's consultant:

Palonosetron only = 4/725 = (0.6%)
Palo plus netupitant = 1/725 = (0.1%)

The two cases considered unlikely were two patients treated with palonosetron alone. They occurred in Cycle 2 or Cycle 3, but there no similar elevations in the patients' subsequent cycles.

The following table summarizes the magnitude of transaminase elevation across the treatment groups, for those elevations that were at least 5 X ULN. With that cut point, the distribution was similar, though numerically higher in the palonosetron only group, between arms.

	palonosetron	Netup+palonosetron
At least 5x ULN	2/725 (0.3%)	1 (0.1%)
At least 10X ULN	1/725 (0.1%)	0

There were two patients flagged by the consultant for evaluation for potential Hy's Law due to bilirubin rising to at least 2 X ULN (one treated with palonosetron only and the other with Akynzeo). The abnormal values in the palonosetron only patient were first observed in Cycle 2 (Day 2 rise with a further increase on Day 6). The values had returned to normal by the start of Cycle 3; however, they increased again to the highest values documented for this patient on Day 2 of Cycle 3. They normalized by Day 6 of that same cycle.

The Akynzeo arm patient flagged for Hy's Law had experienced transaminase and alkaline phosphatase elevations in Cycles 1-3. Levels decreased or normalized in time for each cycle. Levels were normal at the start of Cycle 4, but on Day 2 transaminases increased to over 7 X ULN, bilirubin increased to 1.5 X ULN and alkaline phosphatase increased to 2.3 X ULN. On Day 6 of that cycle, transaminases and alkaline phosphatase decreased slightly; however, bilirubin increased to 2 X ULN. The last documented follow-up laboratory values were ALT 1.4 XULN, AST 2.9 X ULN, Alkaline phosphatase 1.6 X ULN and normal bilirubin. The applicant's consultant pointed out the elevated alkaline phosphatase and ALT/Alk Phos ratio of 3, and said this was "not in accordance of the definition", i.e., Hy's law.

In the 4 patients treated with palonosetron only who had possible/probable DILI, a Day 6 rise was noted in 2 patients with subsequent normalization. There was a Day 2 rise in 1 patient, who had documented subsequent normalization. One patient had a Day 6 rise and no f/u to document improvement.

In Study 10-01, which was a single cycle trial that compared IV palonosetron to oral palonosetron, there were two cases of "possible DILI" identified. Both were on the IV arm and neither was elevated ≥5 X ULN. One was documented on Day 2 and the other on Day 6. There was no follow up of either case to document decline or normalization.

Overall, these events were clustered primarily on Day 2, with some detected at Day 6. Generally, laboratory monitoring post chemotherapy in clinical practice does not include evaluation of transaminases and bilirubin on Day 2 and/or 6 for the chemotherapy drugs that were administered in the trials submitted in this NDA. It is possible that if such frequent monitoring of transaminases and bilirubin were conducted on a routine basis, we would have a clearer picture of what extent these changes are in fact attributable purely to the chemotherapy. A literature search identified reports of DILI associated with cisplatin, VP-16, doxorubicin and cyclophosphamide[2, 3, 4, 5]. Larroquette, et al, summarized the transaminases, bilirubin and alkaline phosphatase from the records of 190 consecutive patients with breast cancer who were treated with doxorubicin, cyclophosphamide and 5-flourouracil. Approximately half received the chemotherapy as adjuvant treatment. The authors reported that 77% of the patients who received their chemotherapy in the adjuvant setting and 82% of those treated for metastatic disease developed abnormalities in "liver function tests" during treatment. Among the patients receiving adjuvant treatment, 35% developed new abnormal aspartate aminotransferase. Similarly, 31% of the patients treated for metastatic disease developed a transaminase abnormality. Total bilirubin increased in 4% of the patients treated with adjuvant chemotherapy, and 2% of patients with metastatic disease developed a new abnormally high bilirubin. Alkaline phosphatase increased in 31% of adjuvant patients and 47% of patients with metastatic disease. The maximum elevation of bilirubin was 2.5 in the adjuvant group and 1.9 in the metastatic disease group. The maximum elevation in transaminase was just over 3 x ULN in the adjuvant group and just over 4 x ULN in the metastatic disease group. They concluded that the abnormalities were a manifestation of drug toxicity. These publications support the applicant's consultant's conclusion that the changes observed in the Akynzeo clinical trials could have been caused by the chemotherapy the patients received.

I concur with the Clinical reviewers that there is no compelling evidence in this safety dataset that netupitant causes DILI. Beside the fact that all patients were also exposed to chemotherapy drugs that could have contributed to the observed laboratory changes, cases were also identified in patients treated only with palonosetron. The Aloxi product label states that elevations of transaminases have been reported in patients treated with palonosetron. OSE reviewers conducted a FAERS search on August 14, 2014 for evidence of reported cases of severe cases liver toxicity associated with antiemetics, including palonosetron, ondansetron, aprepitant and fosapreptitant. The database was searched for reports for severe liver injury/failure using MedDRA Preferred Terms acute hepatic failure, asterixis, chronic hepatic failure, coma hepatic, hepatic encephalopathy, hepatic failure, hepatorenal syndrome, subacute hepatic failure, hepatic necrosis, hepatitis fulminant and liver transplant. The search retrieved

[2] King P and Perry M. The Oncologist 2001, 6:162-176.
[3] Larroquette C, Hortobagyi G, et al. JAMA, Dec 5, 1986: Vol 256, No.21: 2988-2990
[4] Cersosimo RJ. Ann Pharmacother 1993 Apr; 27(4):438-41
[5] Tra A, Housset C, et al. Journal of Hepatology, 1991;12:36-39.

(without removal of duplicates) 72 reports for ondansetron, 4 for aprepitant and 2 for palonosetron. There were no reports for fosaprepitant. Only 2 "suspect cases" were identified – one in the US and one from the UK; both were for ondansetron. They occurred in 1998 and 2002. The OSE reviewer commented that "it is noteworthy that no additional cases have been received in FAERS since 2002." He concluded that there was no new, actionable safety signal identified in this search.

Summary. I agree with the reviewers that there are no safety issues identified in this NDA that preclude approval or necessitate a postmarketing trial/study. The changes in transaminases observed in the clinical trials, which occurred in both the Akynzeo and comparator arms, will be described in product labeling, since the comparator was palonosetron in two of the trials and palonosetron is also a component of Akynzeo.

9. Advisory Committee Meeting

There was no Advisory Committee meeting convened for this NDA as there were no issues that required discussion in an Advisory Committee.

10. Pediatrics

PMHS provided input on the proposed pediatric plan. The Pediatric Review Committee (PeRC) concurred with the division's recommendations regarding the pediatric study plan. The pediatric development of this product is anticipated to be challenging because the product is a fixed combination oral drug, and flexibility of dosing may become necessary if weight based dosing is needed in younger pediatric age groups. The age appropriate formulation may be an IV formulation of netupitant (for patients less than age 6 years, in whom swallowing oral capsules is anticipated to be difficult) administered in addition to the approved pediatric dose of intravenous palonosetron, if an alternative oral combination formulation for this age group cannot be developed (such as a liquid). The following PREA PMRs will be included in the Approval letter:

2769-1 An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with netupitant alone.

Final Protocol Submission:	05/30/2015
Study Completion:	12/30/2015
Final Report Submission:	03/30/2016

2769-2 A PK/PD dose finding study of netupitant to characterize the netupitant PK/PD relationship for complete response in the delayed phase following oral administration of a single dose of netupitant given concomitantly (in separate formulations) with an oral single administration of palonosetron in pediatric cancer patients ages 0 to17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission: 11/01/2015
Study Completion: 04/30/2018
Final Report Submission: 09/30/2018

2769-3 An adequate, well-controlled, double-blind, randomized study to evaluate the safety and efficacy of a dose of the netupitant/palonosetron fixed combination compared to standard therapy in pediatric cancer patients ages 0 to 17 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission: 04/30/2019
Study Completion: 12/31/2021
Final Report Submission: 04/30/2022

11. Other Relevant Regulatory Issues

Financial Disclosures. The Clinical reviewer stated that the applicant provided sufficient documentation to show that there was no financial arrangement with clinical investigators whereby the value of compensation could affect the outcome of the studies. Because Study 07-07 was not originally intended to be a key study supporting the efficacy and safety of Akynzeo, the applicant attempted to locate investigator to obtain financial disclosure information. They were not able to locate all the investigators and subinvestigators. The Clinical reviewer evaluated documentation of the applicant's efforts to locate all reviewers and determined they had acted with due diligence to obtain the information required.

OSI. OSI was unable to inspect the Ukrainian sites initially selected for inspection because of travel restrictions related to political unrest in the region. Six clinical investigator sites and the applicant were inspected. The clinical sites included a Hungarian site, two Polish sites, a Russian site and two sites in India. OSI conducted a sponsor inspection to evaluate compliance with sponsor responsibilities, including selection and oversight of contract research organizations (CROs), monitoring, financial disclosure and quality assurance, as per OSI procedures for a new molecular entity.

In the inspection of the sponsor, OSI inspector reviewed the Trial Master Files, with special attention to Ukrainian sites that could not be inspected due to regional unrest. These included sites from Study 08-18, Study 10-29 and Study 07-07. Inspection of the files for Study 07-07 included records for Site 120, which the applicant had reported as having "multiple major audit findings, ranging from failure to meet eligibility criteria and administration of prohibited medications to inconsistencies between source data and CRFs." OSI found that Site 120 issues included not transmitting ECGs by phone, errors in timing of ECGS and vital signs, and temperature issues in

transport of drug supply. They noted there was some shift of values between pages in the NCR pages for the visual analog scale. (The visual analog scale was not a key endpoint for labeling.)

The OSI reviewer concluded the issues at Site 120 were isolated in nature. The monitoring reports and QA audits of NETU 07-07 revealed no evidence of other non-compliant PIs or under reporting of AEs. Otherwise the oversight appeared adequate. The studies appeared to have been conducted adequately and the OSI reviewer determined that the data generated by the studies appear acceptable in support of the indications.

Controlled Substance Staff review. The CSS reviewers concluded that the data submitted in the NDA supported that Akynzeo has no potential for abuse or dependence. The applicant proposed to eliminate Section 9.0 from the product label, consistent with the Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, and CSS ultimately concurred.

12. Labeling

I have addressed the major labeling issues and how they were resolved in the earlier Sections of this review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval for indication of 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. The indication will state that the product is an oral combination of palonosetron and netupitant and that the palonosetron prevents nausea and vomiting during the acute phase, and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.

- Risk Benefit Assessment- I concur with the reviewers that the risk benefit ratio for Akynzeo, a fixed combination of palonosetron and netupitant is favorable. The applicant has provided substantial evidence of efficacy for the CINV indication, and the trials submitted establish the contribution of each drug in the combination to the treatment effect. No safety issue was identified that precluded approval, and there was no issue identified that necessitated a PMR study/trial as a condition of approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None necessary.

- Recommendation for other Postmarketing Requirements and Commitments
  PREA applies to this NDA. See Section 10 Pediatrics for the PREA PMRs. In addition, the Clinical Pharmacology reviewers have recommended two post marketing commitments. See Section 5 Clinical Pharmacology.

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/s/

DONNA J GRIEBEL
09/26/2014